AMERICAN UNIVERSITY OF BEIRUT

GLYCEMIC INDICATORS AND MENTAL HEALTH SYMPTOMS: RESULT FROM THE GREATER BEIRUT AREA CARDIOVASCULAR COHORT

by
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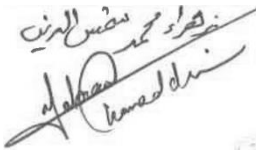

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ABSTRACT

OF THE THESIS OF

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Title: Glycemic Indicators and Mental Health Symptoms: Results from the Greater Beirut Area Cardiovascular Cohort

Background: Mental health disorders are a growing public health priority; with the most common being depression and anxiety. These conditions also present high and complex comorbidity with diabetes; however, the exact mechanisms underlying their co-occurrence remain unknown.

Objective: This study aims to address the more direct links between metabolic indices (HbA1c and fasting blood glucose) and depression and anxiety symptoms in a community sample of middle-aged Lebanese adults.

Methods: The project is based on a secondary data analysis of the Greater Beirut Area Cardiovascular Cohort (GBACC). The GBACC sample was first examined in 2014 (n=501) and a five-year follow-up wave was completed in 2019 (n=198). Sociodemographic, lifestyle, medical, and biological data were collected at both waves and mental health was assessed only at the follow-up study examination. We investigated associations between glycemic indicators and continuous mental health scores using piecewise regression models to identify specific ranges of glycemic indicators where associations might potentially be different. Regression models were adjusted for Sociodemographic, lifestyle, and health characteristics.

Results: In bivariate analysis, there was a pattern for associations between higher FBG levels in 2014, having diabetes in 2014 and more depression and anxiety symptoms measured five years later. Graphical representations and piecewise regression models showed that there are different associations between glycemic indices in the diabetic/clinical versus non-diabetic range: Among participants with <126 mg/dl FBG range, higher baseline (2014) FBG levels were associated with lower depressive (beta=-0.093, 95%CI= [-0.0177, -0.009]; p=0.03) and anxiety symptoms (beta=-0.095, 95%CI= [-0.1763, -0.0147]; p=0.02). In contrast, among participants with FBG levels ≥ 126 mg/dl *FBG*, higher FBG levels in that range were significantly associated with higher anxiety symptoms (beta=0.054; 95%CI= 0.007, 0.101; p=0.02). Higher 2014 FBG levels in the ≥126 mg/dl range showed a trend -but not significant- for higher depressive symptoms. Although not significant, HbA1c levels in 2014 showed similar patterns of associations with negative associations with mental health symptoms in the below 6.5% range (beta= -1.436, 95%CI= [-3.477 0.604]; p=0.16) for depression and (beta= -1.526, 95%CI= [-3.520,0 .467];p= 0.133) for anxiety symptoms
.

Conclusion: Our results showed that FBG levels are associated with worst mental health symptoms only in the clinical/diabetic range, and not in the normal range. Results also suggests the presence of delayed or longer-term associations, with baseline FBG and diabetes status being associated with depression and anxiety symptoms assessed five-years later. Together these findings highlight the importance of clinical and pathological changes in glycemic indicators for mental health and motivate further research into the diabetes-mental health co-morbidity.

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CHAPTER 1

BACKGROUND

Mental health disorders are a growing public health priority, affecting up to one billion people globally, 80% of which 76 in Low- and Middle-Income Countries (LMIC)[2]. Depression was considered the second most disabling condition according to the Global Burden of Disease (GBD) in 2019 and anxiety was considered the eighth [3]. According to a WHO report, the lost productivity from depressive and anxiety disorders costs the global economy $1 trillion USD annually[5]. This burden was largely exacerbated during the COVID-19 pandemic. According to a 2020 Lancet review, due to the pandemic, there was an additional 53.2 million and 76.2 million cases of anxiety and major depressive disorders, constituting a prevalence increase of 25.6% and 27.6%, respectively [6]. In Lebanon, due to several cascading adversities over the past two years, mental health is increasingly a priority concern given the documented impact of stressful experiences and environments on mental health and well-being [7].

Both worldwide and local trends and contexts call for a better understanding of the development and risk trajectories of mental health disorders; however, the exact mechanisms underlying depression and anxiety remain unclear. This gap in knowledge regarding underlying mechanisms can be explained by the multifactorial nature of these disorders, wherein genetic, environmental, social, and biological factors have been implicated in their development. One important biological mechanism that have been linked to depression and anxiety concerns disruptions in endocrinology and metabolic pathways [3, 8]. The implication of endocrionologic and metabolic pathways is mainly supported by the observed high co-occurrence of mental health and Type 2 Diabetes Mellitus (T2DM) [9]. Type II Diabetes is another disease that is globally important for

its high occurrence worldwide and potentially severe consequences[10]. According to the International Diabetes Federation (IDF), 425 million people had diabetes in 2017 and this number is anticipated to climb to 629 million by 2045 [11]. Depression is two times higher in diabetic population compared to the general population [3]. Also, a patient with diabetes is 1.5 times more likely to develop severe anxiety than a non-diabetic person [12-14].

Given their prevalence and their impact on daily functioning and health, there is a pressing need to better understand the complex comorbidity between mental health illnesses and diabetes; and, one approach that can be particularly helpful in these efforts is to investigate the more direct links between mental health symptoms and the biological building blocks of diabetes. [12]. Indeed, a number of studies show associations of both glycated hemoglobin A1c (HbA1c) and fasting blood glucose (FBG) with mental health, further motivating research on how biological pathways implicated in diabetes may also impact mental health [15, 16]. Specifically, elevated HbA1c and FBG levels have been linked to higher anxiety levels and depressive symptoms; these associations are thought, at least partially, to arise due to the role which substandard blood glucose levels plays in damaging blood vessels and causing neuropathy [15, 17]. In a recent meta-analysis of 147 studies, the overall prevalence of depression was high with an average 28.3% in samples with high mean HbA1c levels of 8% [3]. Despite considerable research on the co-morbidity between diabetes and mental health diseases, findings regarding their relationship as well as the relation of diabetes indicators with depression and anxiety remain inconclusive, particularly with regards to the temporality of the relationship. This can be explained by the fact that most of the studies that investigated this association are cross-sectional studies done in a diabetic

population [15]. Moreover, data have supported both directions of this relationship [18]. Indeed, some studies showed that higher levels of baseline depressive symptoms were associated with subsequent higher levels of HbA1c, whereas others reported that higher baseline HbA1c values were associated with 18% increased risk of probable depression [15]. Examining the role of elevated HbA1c and FBG levels as a risk for depression and anxiety requires longitudinal data, which can help in examining changes in these indicators' levels. Studies on these associations in mid-life are particularly informative as the metabolic and cardiovascular changes in this time window are critical in the development of chronic diseases.

CHAPTER 2

DEPRESSION

2.1. Epidemiology of Depression

Depression is one of the most common mental illnesses in the world having a substantial impact on people's functional status and health-related quality of life and contributing greatly to the Global Burden of Disease (GBD) [19, 20]. The number of DALYs caused by depression have accounted for 1.85% of all DALYs worldwide [19]. In 2019, it was considered a leading cause of disability as it affects around 300 million persons around the world [19].

Depression prevalence ranges widely, from 3 to 17 percent, depending on the sociodemographic characteristics of each country. However, depression showed discrepancies between the developed and developing countries and this might be explained by the incapability of some countries to adequately safeguard populations' rights and standards of living and to meet the needs of the vulnerable in terms of prevention and treatment [20]. According to a study published by the WHO in 2015, 80% of depression burden worldwide was reported among people living in low- and middle-income countries. Factors related to this high prevalence of depression in LMICs include adverse social factors, such as gender inequalities, social insecurity, lower educational levels, and poverty [17], the absence of mental health policy and lack of resources and budgets for mental health programs [21]. For instance, there is a lack of mental health policy in 41% of world countries, and that proportion mostly include low-middle income countries(LMIC) where four of five people having severe mental health don't receive effective treatment [21, 22].

In Lebanon, a middle-income country located in the middle east, depression was the most prevalent mental health disorder with an estimated prevalence of 9% among its adult population in the year of 2008[23]. And, this burden has been worsening. El Ahmadieh et al. estimated a prevalence of depression of 17.3% among a population of 510 Lebanese older adults in Beirut Greater Area in 2014 [24]. It is also important to contextualize these findings within the current realities of the country. In the past three years, the country has been facing numerous interacting crises, including the COVID-19 pandemic, the Beirut Blast and, a severe economic crisis – ranked among the top 3 most severe crises of this century by the World Bank [7]. At the end of 2020, the UN reported that 82% of the Lebanese people live in poverty[25]. In the context of the ongoing hardship and crisis, the social and economic threats to well-being and mental health are perpetually growing.

2.2. Definition and Characteristics of Depression

Depression, otherwise known as major depressive disorder, is characterized by an assortment of mood-related symptoms involving persistent sadness, changes in weight, sleep disturbance, decisiveness and self-worth [3]. It is also characterized by lack of motivation, fatigue, and impaired appetite [20]. Depression, similar to other mental health disorders, is clinically diagnosed based on a clinical interview and mental health examinations [26]. According to the Diagnostic and Statistical Manual of Mental disorders, fifth edition, an individual must have experiencing at least five of the following, during the same two-week period: depressed mood most of the day, nearly every day; diminished interest or pleasure in daily activities; significant weight or appetite changes; slowing down of thought and decreased physical movement; fatigue

or loss of energy; feelings of worthlessness or excessive/inappropriate guilt; limited ability to concentrate or think; recurrent suicidal or death ideation. For clinical diagnosis, these symptoms must be causing significant distress or impairment in daily functioning; at least one of the symptoms should be either depressed mood or loss of interest or please. Findings from cross-sectional studies have been strikingly inconsistent, both in terms of the high-risk age group and in terms of age specific rates of depression [27]. Current evidence suggests that depression can happen at any age starting from the adolescence, early adulthood, and reaching older age [20]. Presence of depressive symptoms or distress is usually associated with poor adherence to anti-depressive medication, unhealthy eating diet with low exercise rate, which in turn increases the possibility of medical complications reaching mortality[18]. Psychological, biological, environmental and lifestyle and life changes, and genetic factors have been linked to the risk of developing depression [20]. Depression is also associated with the occurrence of other severe health problems including diabetes, hypertension, stroke, and dyslipidemia [28, 29]. Medically ill people have been found to have elevated depressive symptoms especially if they don't adhere to any treatment program [28].

2.3. Pathophysiology of Depression

The exact pathophysiology of depression is still not fully understood. Several mechanisms have been proposed to explain its development. One proposed mechanism focuses on deficiency of monoamine as a driving factor in depression. According to the monoamine-deficiency theory, the central nervous system's lack of the

neurotransmitters serotonin, norepinephrine, or dopamine is the underlying pathophysiological cause of depression[30].

Serotonergic pathways are the most investigated biological pathway in relation to depression [31]. The main support for their involvement in depression comes from studies of tryptophan depletion. The amino acid tryptophan is a precursor of serotonin and studies have shown that a tryptophan deficiency result in a decrease in the production of central serotonin, which in turn leads to abnormally reduced central serotonergic system function and the onset of depressive symptoms among at-risk participants (e.g., participants with a personal or family history of depression) [30]. However, a recent comprehensive systematic review entailing 17 studies showed that there is no convincing evidence about the serotonin pathway and its role in depression, which raises questions about the monoamine deficiency theory [32] and calls for more evidence on the role of neurotransmitters' processes.

Another mechanism implicated in the development of depression is the Hypothalamic-Pituitary-Adrenal axis (HPA) Dysregulation [33]. Indeed, one often reported finding among depressed patients is the activation, with elevated cortisol and corticotrophin-releasing hormone[34]. This HPA deregulation in depression and in stressful life events is also often proposed as the link between the co-occurrence of depression and diabetes[33], given the role of HPA axis deregulation in the etiology of metabolic disorders [35]. A vicious cycle of mental and physical problems is created by these hormonal dysregulations leading to a variety of metabolic and circulatory abnormalities that characterize diabetes and that are also often seen in depressed individuals [35]. The main strength of this theory is the widely recognized role of early and recent stress

experiences as a risk factor for mental disorders. However, it is challenged by the absence of consistent evidence regarding antidepressant effects of drugs targeting the HPA axis [30].

Depression is considered as a pro-inflammatory state and a growing body of evidence has been putting forward the role of inflammation markers in the development of depression[36].In fact, according to this theory, the over expression of pro inflammatory cytokines, along with the significant up regulated levels of inflammatory markers as TNF-α, IL-6, and C- creative protein(CRP) play a role in the development of depression; this is also a hypothesis proposed to explain the high co-morbidity between depression and physical illnesses such as diabetes and metabolic and inflammation diseases [33, 37]

As summarized above, hypothesized mechanisms implicated in depression intersect with different physiological processes. With the limited conclusive evidence on these mechanisms, investigations that identify the biological building blocks of depression are highly needed and can have important implications for prevention, treatment, and management of this prevalent and burdensome mental health condition.

CHAPTER 3

ANXIETY

3.1 Epidemiology of Anxiety

Anxiety Disorders are also classified among the most prevalent and disabling mental disorders [38]. It was estimated by the Global Burden of Diseases that anxiety contributed to 26.8 million disability-adjusted life years in 2010 [39]. The incidence, as well, has been increasing every year reaching 45.82 million in 2019 [40]. While numerous research efforts have concentrated on depression, for its implications on economy, social life, and health care policy, significantly less have addressed anxiety [39]. The recognition of this increase in the burden of anxiety and the implication of not treating this illness has been motivating more research on the disease in the past decade [39] . In Lebanon, anxiety, was found to be the most common mental health disorder with a prevalence of 16.7% among the general population according to a ministry of public health 2020 report [41]. Usually, people who have experienced war-related trauma are twice as likely to experience an anxiety disorder[41].

3.2. Definition and Characteristics of Anxiety

Anxiety disorders are defined by an excess in multifocal worry focusing on variety of things including finances, family, health, and the future, in addition to debilitating fear that prevents productivity [42]. The term “generalized anxiety disorder” is used interchangeably to express a chronic anxiety [40]. According to the DSM-V, a person is diagnosed with GAD with the following criteria: (i) having a minimum of 6 months of excessive anxiety and worry; (ii) difficulty and challenges in controlling the worry; (iii) the anxiety and worry are associated with at least three of the following six

symptoms: restlessness or a feeling of being keyed up or “on edge,” being easily fatigued, having difficulty concentrating, irritability, muscle tension, and sleep disturbance; (iv) the anxiety, worry or physical symptoms cause significant impairment in daily life; (v) the disturbance is not due to the physiological effects of a substance or medical condition, and (vi) the disturbance is not better accounted for by another mental disorder [43]. The average age of starting anxiety varies greatly across populations so there is no specific age where generalized anxiety disorders occur at, where some people may experience it in childhood, most start in early adulthood, and another peak of incident cases take place in older adulthood along with other chronic physical conditions [44]. In general, it has been consistently reported that females have a higher rate of anxiety [45].

Although many studies have addressed the risk-factors for anxiety at the later age stage, the results appeared to be heterogeneous [27]. However, female sex, lower socioeconomic status, and exposure to childhood traumas such as physical and sexual abuse, violence, and poor parenting styles are consistently reported as consistent and well established risk factors for anxiety [44].

3.3. Pathophysiology of Anxiety

Similar to depression, the exact pathophysiology of anxiety remains unknown with various sources of data and evidence implicating several biological processes in the manifestation of the illness. Patients with generalized anxiety disorder are more likely to develop additional mental health conditions and physical health problems, such as inflammatory bowel disease, chronic pain syndromes, and chronic obstructive pulmonary disease [44]. Some other studies also link anxiety to metabolic and cardiovascular

diseases, namely diabetes and high blood pressure. Together these findings suggest a role of inflammation and hypothalamic–pituitary–adrenal (HPA) axis processes in the development of anxiety [38]. It has been documented that experimentally induced stress produces inflammation reaction [46]. Moreover, chronic stress often creates alterations in the hypothalamic–pituitary–adrenal (HPA) axis and in the immune system that have been linked to both the development and manifestation of depression and anxiety [47]. Under normal circumstances, the HPA axis functions to control inflammatory reactions; persistent hyperactivity of the HPA axis may attenuate the anti-inflammatory effects of glucocorticoids, leading to increased inflammation. Similar anxiety-inducing effects may also result from immunological alterations brought on by age, chronic illness, and disease, however, unlike depression, studies which addressed thoroughly the relation between anxiety disorders and endocrine and inflammation processes are limited [38].

3.4. Relationship between Anxiety and Depression: Common Symptoms and Risk Factors

Anxiety and depression disorders often co-occur [38]. They also share common symptoms mainly: sleep disturbance, restlessness, fatigue, and difficulty in concentrating [48]. Approximately, over half of individuals with depressive disorder usually experience anxiety [49]. Taking into consideration that they are moderately heritable, anxiety and depressive disorders share common genetic risks, as for example neuroticism, which may be a potential endophenotype playing a role in the existence of common susceptibility genes for depression and anxiety[50]. There are also other shared non-genetic risk factors that are linked to the development of anxiety and depression, these include age, sex, experiencing traumatic events and childhood

adversities, lower educational and socioeconomic level, and current stress exposure [18, 27, 51]. Both conditions have also been associated with behavioral factors, such as smoking and reduced physical activity, as well as other physical illnesses. Duration of chronic diseases was significantly associated with anxiety and depressive disorders [52]. Depression and anxiety are prevalent in patients with cardiovascular diseases (CVD) and associated with higher levels of morbidity and mortality in those patients [29, 53] . BMI, a diabetes and CVD risk factor, is linked to higher rates of depression and anxiety[18]. Individuals showing higher anxiety and depression levels have higher BMI values [38, 54]. The similarities in symptoms, common risk factors, and genetic causes are proposed to explain the high co-occurrence of anxiety and depression disorders.

CHAPTER 4

DIABETES, ANXIETY, AND DEPRESSION

4.1. Epidemiology of Diabetes

Diabetes mellitus is a highly prevalent chronic medical condition that causes a wide range of complications [9]. Obesity, steady decline in beta-cell insulin release, and insulin resistance all contribute to the development of diabetes affecting older people more than any other age group [16]. Diabetes is characterized by unstable glycemic control, specifically high levels of blood sugar that causes serious complications in the body organs of the patient over time [55]. Fasting blood glucose (FBG) and HbA1c are the standard markers for the diagnosis and management of diabetes. . In 2010, the American Association of Diabetes as well as the WHO recommended that an HbA1c level of 6.5% and higher to be a diagnostic criterion for diabetes, highlighting the importance of laboratory quality assessment to ensure the accuracy of measurements[56]. For FBG, levels of 99 mg/dl or lower are considered in the normal range; values between 100 to 125 mg/dl indicate pre-diabetes status while values of 126 mg/dl or higher indicate diabetes [10]. The presence of FBG≥126 mg/dl OR HbA1c≥6.5% are the diagnostic criteria of diabetes. HbA1c is generally considered as a better indicator for the diagnosis and longer term monitoring of diabetes, given that HbA1c captures the cumulative glycemic history of the preceding three to four months [57]. Untreated and uncontrolled diabetes often leads to long-term adverse health problems such as heart and kidney diseases, foot problems, retinopathy, and stroke [14, 24]. To overcome this and maintain glycemic control, patients with diabetes must follow a lifelong therapeutic self-management routine [58].

Globally, Diabetes is the seventh leading cause of death [59]. Further, it is a growing health concern for its increasing prevalence and incidence globally over time. The International Diabetes Federation (IDF) estimated that 425 million people were diagnosed with DM in 2017[24]. It is expected that this number will increase to 592 million cases by 2035 [55] and 629 million by 2045 with the majority of cases occurring in low- and middle-income countries [24]. However, the numbers are exceeding the expectations. It was found that 80% of the 425 million patients with diabetes worldwide reside in the Middle East and North Africa (MENA) region [24, 60]. Lebanon, a small country in the Arab world, stood on the high side of the region with a reported prevalence of 15% in a community sample in the Greater Beirut Area in 2014 [10]. In the follow-up study done in 2019, the Greater Beirut Area Cardiovascular Cohort study reported an incidence of 17.2 per 1000-person year in this Lebanese sample, which is higher than the reported value in other countries and which is in line with the higher diabetes prevalence in the MENA region [1]. Several factors are proposed to explain this elevated diabetes prevalence in the Arab World, including obesity, life style factors (unhealthy eating habits, level of physical activity, and smoking status), and genetic predisposition [24]. It has also been explained by the population aging, increased urbanization, and nutritional transition that MENA countries have been facing [61]. These high rates also contribute to increases in diabetes related complications, resulting in a significant economic burden for individuals, families, and health care systems [55].

4.2. Diabetes and Comorbidities

Diabetes often occurs with mental health problems such as related distress, poor sleep quality, anxiety, and depression; this co-morbidity has been reported to result in poorer glycemic control and reduced quality of life [9, 58]. According to a meta-analysis compiling over 42 studies and 21,351 patients with diabetes, the prevalence of depression in this population was 11% to 31% [24]. Additionally, other studies showed that quarter to third of patients with diabetes experience doubling and tripling depression rates compared to the general population [9, 58]. People with diabetes are 2 times more likely to have comorbid depressive disorder than healthy individuals as reported in prospective, retrospective, and meta-analyses studies [13, 14, 62, 63]. A large body of evidence has consistently showed that depression is associated with an increased risk of morbidity and mortality in people with diabetes, and that depression may have a harmful impact on adherence to glucose-lowering treatments [17].Anxiety is also one of the most prevalent comorbidities of people with diabetes with a prevalence ranging from 22 to 75% [55]. Patients having diabetes are 1.5 times more likely to have elevated anxiety symptoms, compared to nondiabetics [62]. The lifetime prevalence of anxiety disorders also appeared to be 20% higher among diabetic people [14].

4.3 Glycemic Indicators and Mental Health Outcomes

Because they are both influenced by biological, social, and psychological factors, diabetes and co-occurring psychiatric diseases may interact in a complicated and bidirectional manner [58]. Depression is thought to increase the risk of developing diabetes and conversely, diabetes may increase the risk of depression [64]. A wide

range of studies reported a link experiencing symptoms of anxiety and depression and blood glucose levels variation [9, 14, 17, 64]. However, many studies also report contradictory results of no association between depression and glycemic indicators [62].

HbA1c and fasting glucose levels (FBG) are the main indicators in monitoring and treating diabetes, with HbA1c being the primary indicator given its higher stability and ability to capture cumulative glycemic levels of the previous 2-3 months[31, 57]. A cohort by Fisher et al. to evaluate the association of HbA1c with depression and anxiety over time in a diabetic population showed a significant link between depressive disorders and HbA1c,where higher levels of HbA1c was associated with elevated levels in depression, however, no association between HbA1c and anxiety was observed[65]. Conversely, there was a study done by Belhara and Segar reported significant positive correlation between anxiety scores in patients having diabetes with each of FBG and HbA1c levels suggesting that uncontrolled diabetes might be a predictor of the occurrence of major mental health disorders [66]. However, other studies fail to find this association [67, 68].

CHAPTER 5

RESEARCH GAP AND AIMS

5.1. Research Gap

While the co-morbidity between diabetes and both depression and anxiety is often reported, the literature reveals inconsistent findings pertaining to the association between glycemic indicators themselves and depression or anxiety [15, 20]. Some studies revealed a significant association of depression and anxiety with glycemic indices [9, 17, 64] while others showed positive associations that do not reach statistical significance [66, 69]; in some cases this could be explained by the sample size [62]

The relationship of diabetes and glycemic indices with depression or anxiety is thought to be a bidirectional association [35]. However, most of the studies investigating these relationships ae cross-sectional, and thus were not able to assess changes – rather than onetime assessment – of glycemic indices and to make inference on temporality or longer-term associations between diabetes indicators and anxiety and depression [17, 28]. Moreover, to this date, it remains unclear whether how glycemic indicators, the biological building blocks of diabetes, are related to mental health symptoms. Understanding this more direct relationship can help in elucidating whether glycemic deregulations and diabetes-related processes are a predictor or a consequence of the development of depression and anxiety.

Further, to the best of our knowledge, there is no study that assessed the association of FBG, HbA1c with mental health outcome in the general population, and most evidence come from studies focusing on diabetic or pre-diabetic populations [15], wherein glycemic indicators have already shifted to the more extreme and clinical ranges.

It is important to investigate the continual range of glycemic indicators, to better identify how relationships with mental health symptoms occur along the normal-to-pathological glycemic range[70]. For that, investigations of middle-aged sample can provide an added advantage to explore a time window where diabetes risk is changing[70].

5.2. Research Aims

Our study aims to address this need for investigations in mid-life on the earlier links between metabolic indices (HbA1c and fasting blood glucose) with depression and anxiety in Lebanese adults.

The study will answer the following questions:

1. Is there a cross-sectional association between glycemic indices (fasting glucose and HbA1c) and mental health symptoms, specifically depression and anxiety in middle-aged Lebanese adults?
2. Are prior levels of glycemic indices (fasting glucose and HbA1c) related to subsequent mental health symptoms, specifically depression and anxiety, in middle-aged Lebanese adults?
3. Are changes in levels of glycemic indices (fasting glucose and HbA1c) over 5 years in mid-life related to mental health symptoms, specifically depression, and anxiety in middle-aged Lebanese adults?

CHAPTER 6

METHODS

6.1. Study Design, Sampling and Data Sources

This project is based on a secondary data analysis of the Greater Beirut Area Cardiovascular Cohort study. The study includes two waves of data collection, the baseline wave was conducted in 2014 and enrolled 501 adult men and women from the Greater Beirut Area. The baseline study examination was conducted between March and May 2014. Participants aging 18 and above living in Beirut and its suburban were eligible to participate. Pregnant women, dialysis patients, subjects with intellectual inability to understand the study and to provide informed consent were excluded[10].Both study waves were approved by the Institutional Review Board of the American University of Beirut, and all participants provided written informed consent at both study waves.

The sampling strategy was random multi-stage cluster sampling based on area probability within Beirut and its suburbs. It was followed by a systematic random sampling to select the family, starting within the district, reaching neighborhood then household. At the household level, a primary adult respondent was selected based on the most recent day of birth [71].

6.2 Follow-up Study Design and Process

The follow-up study wave was conducted 5 years later. From February to May 2019. The study contacted all participants who had consented at baseline to be re-contacted for future follow-up waves and who provided contact information (n=486) except for 8 subject who were no longer eligible to participate in the study; 198

completed the study follow-up examination. Of the 478 who were eligible to partake in the follow-up study, 36.1% were not successfully reached because of wrong phone numbers and 17.9% did not answer; 17.5% were too busy, 15.7% were not interested, 8.9% were too ill, and 3.9% had moved/traveled. For the 198 participants in the 2019 examination, a follow up visit was scheduled at the Nutrition and Food Science (NSFC) department at the American University of Beirut, similarly to baseline. At both study waves, participants were instructed to come after a 10 hours fast for the blood exams. Data collection, as detailed below were conducted via standardized protocols in a confidential manner by trained and CITI certified interviewers; data collection at both the baseline and follow-up examinations followed same data collection protocols and procedures.[1]

6.3. Data Collected

The data collection occurred through face to face interviews with the participants; in addition, anthropometric and lab measures were collected. The follow-up wave constituted of a repeated assessment of all measures assessed at baseline; the data collected is described below and in following sections, we describe in more details the measures that were specifically relevant for this project.

Demographic and socioeconomic: gender; area of residence; marital status (categorized as married, single, or other being separated/divorced/ widowed); education (categorized as no schooling/primary school, intermediate, secondary/technical, or university); occupation; crowding index (defied as the average number of people per room, excluding kitchen and bathroom; and income bracket per family (categorized as (USD per month): less than 600, 600-999.9, or more than 1000 USD[10].

Lifestyle habits***:*** ***dietary intake:***(using a validated 80-item culture-specific semi-quantitative Food Frequency Questionnaire (FFQ); physical activity (using the short version of the International Physical Activity Questionnaire (IPAQ); smoking (with current defined as any daily smoking, regardless of the number of cigarettes); alcohol intake (defined as any intake); and caffeine intake. Sleep was assessed using the Berlin questionnaire for obstructive sleep apnea and the Epworth Sleepiness scale (ESS)[10].
Medical history: Family history, medication intake, and all chronic illnesses (diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, cancer, and thyroid disease). Specific diabetes-related questions included whether the participants have been previously told by a doctor or health professional that they had diabetes. If the answer was yes, then enquiry about the duration and management was recorded [1].
Anthropometric measures: weight and height; waist circumference (using a standardized method; body composition (using bio impedance analyzer (In body Composition Analyzer). Blood pressure was obtained twice, and the average was recorded to the nearest millimeter of mercury. Body mass index (BMI) (kg/m^2) was calculated and categorized according to the World Health Organization classification for overweight and obesity. (5) Laboratory measures: fasting plasma glucose (FPG), hemoglobin A1C (HbA1c), serum creatinine, lipid profile, C-reactive protein (CRP), insulin, thyroid stimulating hormone (TSH), 25-hydroxyvitamin D, and urinary micro albumin to creatinine ratio (ACR). Insulin resistance was calculated using the homeostasis model of assessment of insulin resistance (HOMA-IR)[10].
Lab assays: 15 ml of blood and urine were obtained. 5 ml of whole blood were split into two tubes; frozen for future studies, and the other refrigerated and sent on the same day for HbA1c measurement. A finger stick glucose was obtained as well at the same time

as the laboratory tests. HbA1c was performed by High-performance liquid chromatography (HPLC). Fasting plasma glucose FPG was analyzed by enzymatic method, Serum and Urine Creatinine by the Jaffe rate method. Urine micro albumin; TSH, and vitamin D were also measured. Levels of triglycerides, HDL-C, and total cholesterol were measured using enzymatic colorimetric method, and of LDL-C using Coupled Classic precipitation. CRP was measured by Immunoturbidimetry assay[10].

6.4. Concepts and Measurements:

6.4.1 Outcomes of Interests

The outcomes of interest, depression and anxiety symptoms were only assessed in the follow-up wave.

6.4.1.1 Depressive Symptoms

Depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9), a widely used instrument used for assessing depression severity levels among adults. The scale includes 9 self-reported items that assesses the existence and severity of major depressive disorders in the past two weeks [72]. It contains the following questions: During the past 2 weeks how often you have been bothered by any of the following problems (i) Little interest or pleasure in doing things; (ii) Feeling down, depressed, or hopeless; (iii) Trouble falling or staying asleep, or sleeping too much; (iv) Feeling tired or having little energy; (v) Poor appetite or overeating; (vi) Feeling bad about yourself; (vii) Trouble concentrating on things, such as reading the newspaper or watching television; (viii) Moving or speaking so slowly that other people could have noticed - Or the opposite being so fidgety or restless that you have been moving around a lot more than usual; (xi) Thoughts that you would be better off dead, or of hurting

yourself. The frequency of experiencing each item is ranked on a 4-point Likert scale ranging from 0 to 27. The score for PHQ-9 was computed by summing the scores of each question item; higher scores indicate more depressive symptoms. The scale is shown to have high internal consistency (Cronbach's alpha between .86 and. 88)[73] and high test reliability (Cronbach's alpha between .84 and .95) [72, 74] . Scores of 10 and more suggest the presence of depression [14] this cut-off was used in this study to categorize participants as with and without elevated depressive symptoms. The PHQ-9 was administered as part of the mental health module in the GBACC follow-up survey by trained interviewers in face-to-face interviews conducted in a private setting.

6.4.1.2. Anxiety Symptoms

Anxiety symptoms were assessed using the Generalized Anxiety Disorder -7 (GAD-7) scale, a reliable and valid instrument used for assessing presence and severity of anxiety symptoms [75]. The GAD-7 is based on DSM-IV criteria [72]; it is self-reported, and includes 7 items, with each item ranked in frequency on 4-point Likert scale from 0 to21. GAD-7 was administered as part of the mental health module in the GBACC survey at follow-up and contains the following questions: During the past 2 weeks how often you have been bothered by any of the following problems (i) Feeling nervous, anxious or on edge; (ii) Not being able to stop or control worrying; (iii) Worrying too much about different things; (iv) Trouble relaxing; (v) Being so restless that it is hard to sit still; (vi) Becoming easily annoyed or irritable; (vii) Feeling afraid as if something awful might happen. The score for GAD-7 was computed by summing the scores of each question item, with higher scores indicating higher anxiety symptoms. The GAD-7 exhibits excellent internal consistency (Cronbach's alpha

between .89 and.92) [74-76]. Scores greater than or equal to 10 are considered a positive screen for generalized anxiety disorder [14]. Participants in this cohort were also categorized according to this threshold into having or not having elevated anxiety symptoms. Both PHQ-9 and GAD-7 were adapted and validated in Lebanon and Arab speaking communities [72] and the validated versions were used for data collection.

6.5. Main Exposure Variables: Glycemic Indicators

This study investigated two glycemic indicators as the primary exposures: Fasting blood glucose (FBG) and glycosylated hemoglobin A1c (HbA1c).

FBG and HbA1C measures at each wave were examined in the analysis continuously; we also generated variables that reflect change in these indicators over 5 years between baselines and follow-up, it's the difference between HbA1c/FBG in 2014 and HbA1c/FBG in 2019. In addition to glycemic indicators, we also examined diabetes status. At both baseline and follow-up, we classified probably diabetes cases, based on the American Diabetes Association (ADA) guidelines which requires the following: FBG > =126 mg/dl or HbA1c >= 6.5% or self-reported diabetes, or taking anti-diabetic medication [1]. Finally, family history of diabetes was self-reported and categorized into presence of family history of diabetes (if any one of participant's mother, father, or siblings had diabetes) versus no family history of diabetes.

6.6. Socio - Demographic Characteristics and Other Covariates

The following covariates were selected to be adjusted for, based on an extensive literature review of factors that are consistently associated with anxiety, depression and

diabetes and that can be on common causal pathways. Those covariates include both sociodemographic and health related indicators.

Sociodemographic data included age (continuous variable), sex (men/women), and educational attainment. Educational attainment was reclassified, at the baseline and follow up examination, into higher (secondary/technical/university degree) and lower educational attainment (no education/primary or intermediate school) to facilitate analysis and because an investigation of the original categories with the outcomes of interest supported this grouping.

BMI (kg/m^2), was generated according to its formula weight (kg)/height ^2 at both study waves (2014 and 2019).

Smoking has often been associated with depression, with reports of higher depression prevalence among smokers and of people with elevated depressive symptoms being more likely to smoke and to find smoking cessation more challenging [45]. Current smoking was included in the analysis as an independent variable. Smoking was assessed at both study waves, based on whether participants reported being current daily smokers (yes/no)[77].

Physical activity was treated as categorical variable and generated based on IPAQ scores at the two study examinations. The scores were classified into low, moderate and high according to the IPAQ scoring cut-offs [21].

Participants self-reported whether they have been ever told by a doctor or healthcare professional that they have high blood pressure (hypertension: yes/no) at both study visits. We also considered the following co-morbidities that are relevant for both mental health disorders and diabetes: Presence of coronary heart disease (CHD) was determined, at both study waves, based on self-reporting the occurrence of at least

one of the following conditions: a heart attack, cardiac catheterization or coronary heart bypass surgery. Dyslipidemia also was self-reported at both study waves, based on having been told by a doctor or health care professional diagnosis of raised cholesterol or triglycerides. Cancer, thyroid, and stroke were also considered and were based on self-reports by participants at both study waves.

For these medical comorbidities, we further created a variable summarizing the count of chronic diseases based on the sum of the presence of chronic diseases of interest: Stroke + dyslipidemia + CHD + cancer + thyroid Disease), ranging from 0 to 5, with higher values indicating more comorbidities; this variable was created for each of the study waves to take into account the number of chronic diseases and to facilitate analysis as the prevalence of some disorders was low in our sample.

6.7. Missing Data

At the follow-up wave, three observations had missing lab measurement of FBG as well as one observation missing 2019 BMI value. Two observations had missing data on 2019 educational level and two had missing data for 2019physical activity. Given that the missing values are very minimal in the study, the total 198 cases were considered for the analysis and no observations were removed.

6.8. Data Analysis

Data were analyzed using STATA 13 software version. Descriptive statistics were performed in order to examine the variability and the distribution of the outcome variables (depression and anxiety) and the main exposure variables (HbA1c and FBG). Correlations between each of the main exposures (HbA1c and FBG) and between the

outcomes themselves were conducted using Pearson correlation. Depression and anxiety symptoms were treated as continuous variables as total scores of the PHQ-9 and GAD-7 scales, respectively. We also examined the presence of elevated mental health symptoms by creating binary variables indicating the presence of elevated depression and anxiety symptoms (yes/no) based on the cut-off scores of the PhQ-9 and GAD-7 respectively.

First, we checked the existence of association of covariates of interest with each of the binary outcomes of interest (depression and anxiety); we examined associations with both cross-sectional values of the covariates (i.e., 2019 values) and prior values of covariates (baseline, 2014 values). To achieve this, chi-square tests was used for categorical covariates: sex, education (2014 and 2019), diabetic status (2014 and 2019), hypertension (2014 and 2019), dyslipidemia (2014 and 2019), cancer (2014 and 2019), stroke (2014 and 2019), thyroid disease (2014 and 2019), currently smoking (2014 and 2019), and physical activity according to the IPAC scores (2014 and 2019). On the other side, t- test was used with the continuous variables which are: Age (2014 and 2019), HbA1c (2014 and 2019 in addition to the 5 years change), and FBG (2014 and 2019 in addition to the 5 years change). This test was performed to assess whether there was a significant difference among each of the elevated depression (yes/no) or elevated anxiety (yes/no) groups over the continuous covariates of interest. Prior to performing t-test, and aiming to check for the assumptions of the test, Levene's test was used also to check the equality of variances between people having elevated depression/anxiety and not having it. Another component of the bivariate analysis included looking at depression and anxiety symptoms continuously. Linear regression models were

performed to assess relationships with PHQ-9 and GAD-7 scores with the main exposure variables: FBG and HbA1c at both (2014 and 2019, and change over 5 years).

For the main associations of interest (glycemic indicators and mental health outcomes), we first investigated their relationship graphically, examining for the relationships of each of the main exposure variables HbA1c and FBG, at both baseline and follow-up, with depressive and anxiety symptoms. As detailed below, the Locally Weighted Scatterplot Smoothing Plots - Lowess plots- identified points in the range of HbA1c and FBG levels at which the relationships between these indicators and mental health outcomes changed, and these points corresponded to the diabetic cut-offs for both indicators (namely 6.5% for HbA1c and 126 mg/dl for FBG). Accordingly, for the regression analysis, we used segmented linear piecewise regression, a type of analysis that is efficient for scenarios od different associations across the range of the predictor variables; this method thus allowed us to partition the glycemic indicators' levels into two intervals (the normal and clinical ranges), based on the threshold that appeared in Lowess plots.

For the adjusted analysis, we built models adding gradually more covariates to assess the adjusted association between PHQ-9 and GAD-7 continuous scores and each of the main independent variables separately. First, we included basic adjustment for age and sex; in the second set of models, we added adjustment for more primary confounders: educational levels, BMI, smoking status, and hypertension; finally, we also included adjustment for number of chronic diseases, family history of diabetes, and physical activity. Models were built for each glycemic indicator (FBG and HbA1c) and for each of the baseline and follow-up values of these predictors, thus assessing cross-sectional association with mental health and relationship of prior levels of these

indicators with mental health symptoms 5 years later. We used the covariates values that correspond to the year of the primary predictor in the model (e.g., 2014 values for 2014 FBG). Regression coefficients (Betas) and 95 confidence intervals were reported. The threshold for statistical significance was 5%. For each outcome, same analysis was repeated for the binary outcome classification (elevated symptoms yes/no) using logistic regression models (Appendix). Across all analysis, FBG and HbA1c levels were analyzed separately, given their high correlation and given the interest in detecting associations with each of these indicators.

6.9. Ethics

Original study was reviewed by the IRB, the continual study was approved on October 12, 2021. The IRB protocol number that was assigned to the study is BIO-2018-0386.The data used for the secondary analysis was de-identified data.

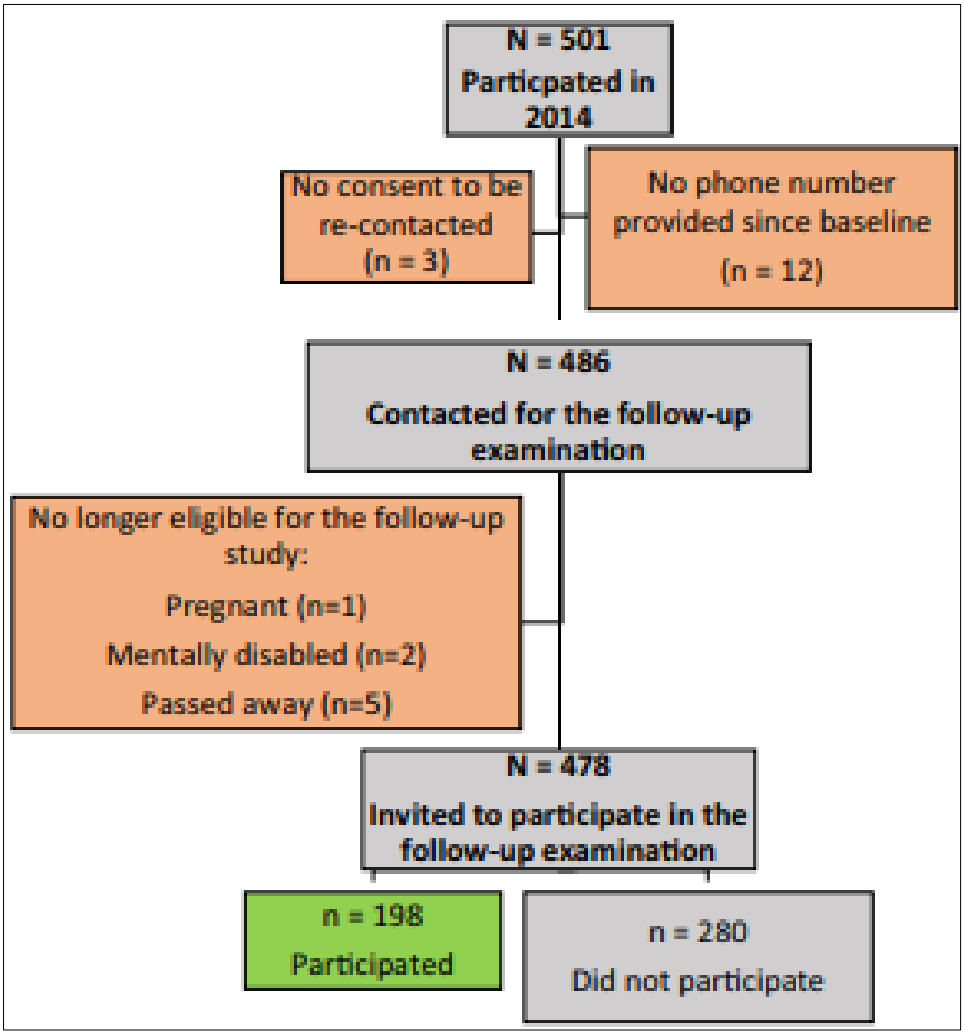

Figure 1. Response Rate Flow Diagram [1]

CHAPTER 7

RESULTS

This chapter presents the statistical analysis starting with descriptive analysis of the study sample of 198 middle aged adults, followed by normality tests performed on the continuous outcomes, the bivariate analysis and multivariable regression models conducted to estimate the association of glycemic indicators with depression and anxiety symptoms.

7.1. Sample Characteristics

The characteristics of the study participants are shown in Table 1. The 2014 and 2019 measures of the glycemic indicators, health-related characteristics, and life style variables are reported. Mean age was 51.5 years (SD=13.38), 64.14% of the sample were women and 63.45% had lower educational attainment at follow-up. In the sample, 40% were currently smokers and average BMI of the sample was 30.43 kg/m^2 (5.90) indicating a trend of obesity at follow-up. Regarding health indicators, 61% of the sample didn't have any chronic disease in 2014 while in 2019, 45.45% didn't have any chronic disease, 37.37% had one, and 15.66% had two diseases as shown in Table 1. The most frequent diseases that were reported in 2014 were dyslipidemia (25.76%) and thyroid disease (12.12%). In 2019, the most prevalent diseases were also dyslipidemia (40.91%) and hypertension (35.35%). Cancer and stroke were persistent over the 5 years with low prevalence of 2.53% and 1% respectively at both years. (Table 1).

In 2014, 21% of the sample had diabetes. The prevalence was higher at the follow-up wave, reaching 30.3% in 2019. This was accompanied with the elevation in the levels of

FBG and HbA1c. In 2019, the average of FBG and HbA1c levels of the sample was 5.95% (1.31%) and 117.62 mg/dl (39.76) respectively compared to 5.9 %(1.15%) and 109.08 mg/dl (29.52) in 2014.

7.2. Distribution of the Outcome Variable

The outcome variables in this project were considered both categorically and continuously, to permit a more comprehensive overview of their associations with glycemic indicators. The histogram along with the normal plot showed approximately normal distribution, slightly positively skewed (Fig.2, Fig 3). The normality plot of both variable show that most of the data lie at the best-fitted model with slight deviation at the tails (Fig 4, Fig 5).

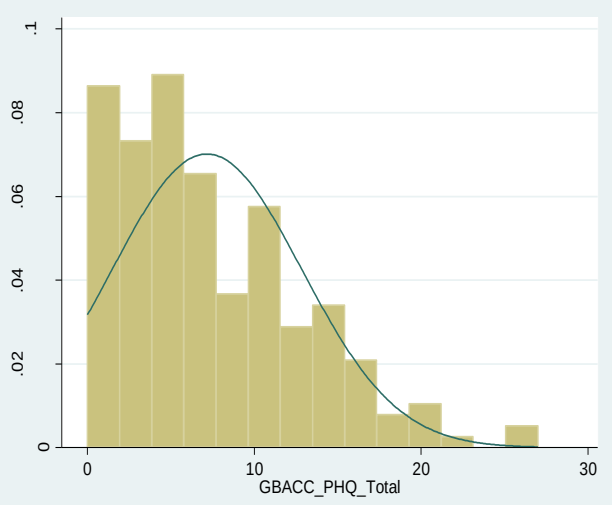

Figure 2. Histogram showing Normality Plot of PHQ-9 Scores

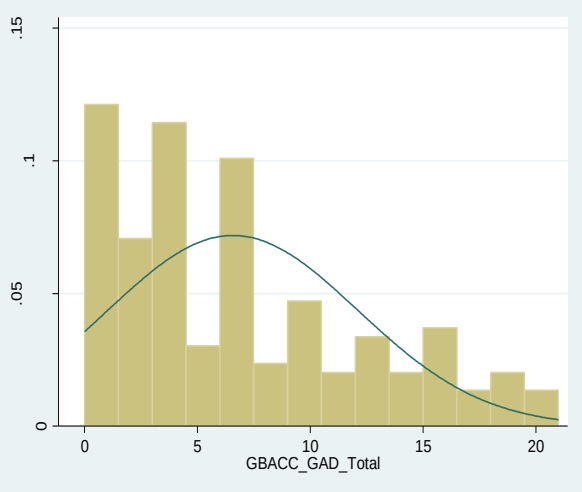

Figure 3. Histogram showing Normality Plot of GAD-7-Scores

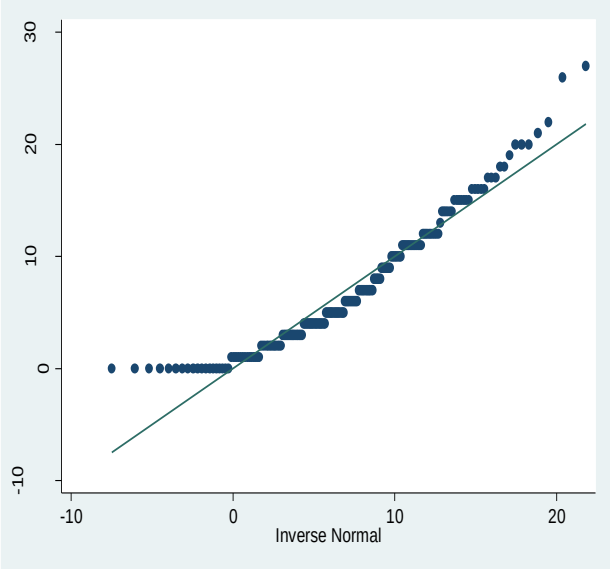

Figure 4. Q-Q plots of PHQ-9 Scores

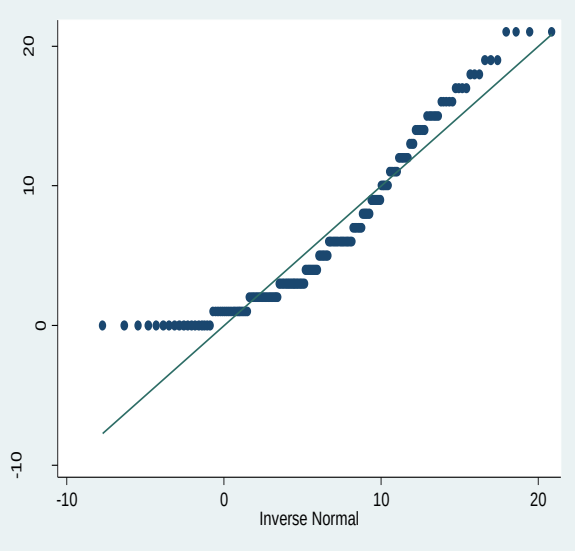

Figure 5. QQ plots of GAD-7 Scores

Table 2 shows that 32.3% and 26.8% of participants had elevated depression and anxiety symptoms respectively. The average anxiety score was 6.67 (SD=5.55). The average Depression score was 7.16 (SD=5.68) (Table 2). It's important to mention that depression and anxiety are significantly associated (Chi-Square, p-value=0.000) and they comorbid each other where in our sample 41 participant (20.7%) had both depression and anxiety (Supplementary Table 1). The PHQ-9 and GAD-7 scores show a significant and high correlation as well (ρ = 0.69) (Supplementary Table 2).

Table 1. Descriptive analysis of socio-demographic factors, health-related characteristics, and physical activity of the Greater Beirut Area Cardiovascular Cohort sample at baseline and five-year follow up (n=198)

Variables		Categories	*n* (%) or Mean ±SD	Missing n
Socio-Demographic Characteristics				
Age (years)	**2014**		46.96 ± 3.31	0
Age (years)	**2019**		51.56 ± 13.38	0
Sex		*Female*	127 (64.14)	0
Education	**2014**	*Higher*	59 (29.95)	0
Education	**2019**	*Higher*	71 (36.22)	2
Diabetes Characteristics and Indicators				
FBG (mg/dl)	**2014**		109.08±29.52	0
FBG (mg/dl)	**2019**		117.62± 39.76	3
HbA1c (%)	**2014**		5.90 ±1.15	0
HbA1c (%)	**2019**		5.95±1.31	0
Diabetes ¥	**2014**	*Yes*	43 (21.27)	0
Diabetes ¥	**2019**	*Yes*	60 (30.30)	0
Family History of DM		*Yes*	107 (54.04)	0
Lifestyle and Health Characteristics				
BMI(kg/m^2)	**2014**		30.00±5.85	0
BMI(kg/m^2)	**2019**		30.43±5.90	1
Hypertension	**2014**	*Yes*	38 (19.19)	0
Hypertension	**2019**	*Yes*	72 (35.35)	0
Dyslipidemia	**2014**	*Yes*	51(25.76)	0
Dyslipidemia	**2019**	*Yes*	81(40.91)	0
Coronary Heart Disease	**2014**	*Yes*	17(8.59)	0
Coronary Heart Disease	**2019**	*Yes*	30(15.15)	0
Stroke	**2014**	*Yes*	2(1.01)	0
Stroke	**2019**	*Yes*	2(1.01)	0
Cancer	**2014**	*Yes*	5 (2.53)	0
Cancer	**2019**	*Yes*	5(2.53)	0
Thyroid disease	**2014**	*Yes*	24 (12.12)	0
Thyroid disease	**2019**	*Yes*	27 (13.64)	0
Nb. Of chronic diseases	**2014**	*0*	117 (59.09)	0
		1	66 (33.33)	
		2	13 (6.57)	
		3	1 (0.51)	
		4	1 (0.51)	
Nb. Of chronic diseases	**2019**	*0*	90 (45.45)	0
		1	74 (37.37)	
		2	31 (15.66)	
		3	3 (1.52)	
Currently Smoking	**2014**	*Yes*	78(39.39)	0

Currently Smoking	**2019**	*Yes*	80(40.40)	0
Physical activity levels	**2014**	*Low*	92 (46.46)	
		Moderate	73 (36.87)	0
		High	33 (16.67)	
Physical activity levels	**2019**	*Low*	104(52.79)	
		Moderate	70(35.53)	1
		High	23(11.68)	

Table 2.

¥ A person is considered having diabetes if FBG ≥ 126 mg/dl **or HbA1c ≥ 6.5% or taking diabetic medication.**

Mental health characteristics of the Greater Beirut Area Cardiovascular Cohort

		n (%) or Mean ±SD	***Missing , n***
Elevated depressive symptoms	*Yes*	*64 (32.3%)*	*0*
Depression total scores		*7.16±5.68*	*0*
Elevated anxiety symptoms	*Yes*	*53 (26.8%)*	*0*
Anxiety total scores		*6.67±5.55*	*0*

(assessed at follow-up; n=198)

7.3. Correlation among Glycemic Indicators

Table 3 shows the correlation matrix of the 4 main exposure variables. HbA1c and FBG showed positive, strong, and significant correlation at both waves of measurement, in 2014 (ρ = 0.81) and 2019 (ρ = 0.84). Stable correlation in time were observed for each of the main exposures: HbA1c in 2014 was strongly correlated with follow-up HbA1c levels in 2019 (ρ = 0.79). FBG in 2014 also was correlated with FBG in 2019 levels (ρ = 0.69).

Table 3. Correlation matrix of main exposure variables in 2014 and 2019.

Variables	**FBG 2014**	**FBG 2019**	**HbA1c2014**	**HbA1c 2019**
FBG 2014	1			
FBG 2019	0.69*	1		

HbA1c 2014	0.81*	0.67*	1	
HbA1c 2019	0.71*	0.84*	0.79*	1

Table 4. Table showing the associations of the mental health outcomes along with the main glycemic indicators and covariates.

		Depression		P-value	Anxiety		P-value
		No	Yes		No	Yes	
		Mean±sd or n	Mean±sd or n		Mean±sd or n	Mean±sd or n	
Socio-Demographic Characteristics							
Age mean(sd)		50.76 ±13.60	53.23±12.86	0.2180§	51.18 ±13.34	52.6 ±13.57	0.5151§
Sex	*Male*	59	12	0.00*	61	10	0.00*
Education	*Higher*	59	13	0.00*	56	16	0.31
Diabetes Characteristics and Exposure indicators							
FBG 2014		105.85±21.28	115.84±41.25	0.07§	106.70± 24.1	115.47±40.47	0.94§
FBG 2019		113.8 ± 33.29	125.52±50.11	0.09§	116.19± 3.16	121.55±6.21	0.44
HBA1C 2014		5.79 ± 0.08	6.125 ±0.18	0.106§	5.85±0.087	6.03 ±0.192	0.40§
HBA1C 2019		5.84 ±1.09	6.18±1.65	0.14§	5.948 ±1.31	5.984 ±1.31	0.86§
Change in FBG¶		1.540 ± 5.061		0.76§	-3.551± 4.382		0.44§
Change in HbA1c¶		0.010±0.12		0.93§	-0.13±0.126		0.29§
Diabetes 2014	*Yes*	21	22	0.00‡*	28	15	0.17‡
Diabetes 2019	*Yes*	37	23	0.22‡	45	15	0.71‡
Covariates: Lifestyle and Health Characteristics							
BMI 2014		29.48± 4.93	31.10 ±7.33	0.11§	29.98± 5.48	30.06 ±6.79	0.681§
BMI 2019		29.92±5.22	31.51 ± 7.03	0.10§	30.32 ±0.47	30.74 ± 0.90	0.681§
Hypertension 2014	*Yes*	22	16	0.15‡	25	13	0.24‡
Hypertension 2019	*Yes*	46	26	0.38‡	47	25	0.06‡
Dyslipidemia 2014	*Yes*	32	19	0.38‡	36	15	0.62‡
Dyslipidemia 2019	*Yes*	45	36	0.00*	55	26	0.15‡
Coronary Heart Disease 2014	*Yes*	11	6	0.78‡	13	4	0.75‡
Coronary Heart Disease 2019	*Yes*	17	13	0.16‡	22	8	0.98‡
Stroke 2014	*Yes*	0	2	0.04*‡	1	1	0.46‡
Stroke 2019	*Yes*	1	1	0.59‡	1	1	0.46‡
Cancer 2014	*Yes*	2	3	0.18‡	3	2	0.49‡

Cancer 2019	*Yes*	0	5	0.00*	2	3	0.09‡
Thyroid disease 2014	*Yes*	14	10	0.29‡	13	11	0.02*‡
Thyroid disease 2019	*Yes*	15	12	0.14‡	13	14	0.00*‡
No. Of chronic diseases 2014		0.44±0.64	0.63±0.76	0.09§	0.46±0.65	0.62±0.79	0.17§
No. Of chronic diseases 2019		0.58±0.69	1.04 ± 0.86	0.00*§	0.64±0.75	0.98 ± 0.79	0.00*§
Current Smoking 2014	*Yes*	53	25	**0.94‡**	62	16	0.10‡
Current Smoking 2019	*Yes*	56	24	0.57‡	62	18	0.26‡
Physical activity levels 2014	*Moderate*	51	19	0.35‡	58	12	0.08‡
	High	17	6		15	8	
Physical activity levels 2019	*Moderate*	53	20	0.179‡	55	18	0.199‡
	High	18	15		20	13	

¶ ***Change*** in FBG = FBG in 2014 – FBG in 2019 - ‡ Chi-Square Test - § t-test

7.4. Bivariate Analysis

The results of the bivariate analyses of the two outcomes of interest with each of the glycemic indicators and covariates are presented below.

7.4.1. Association of Elevated Depressive Symptoms with Sample Characteristics

Error! Reference source not found.Starting with the elevated depressive symptoms (yes/no) binary outcome, all socio-demographic characteristics except age were associated with elevated symptoms (Table 4). Women were more likely to have elevated depressive symptoms compared to men (p value< 0.01); people with lower educational attainment had higher proportion of elevated depression symptoms than those with higher educational attainment (p value<0.01).

Over the investigated chronic diseases, only dyslipidemia (n= 44, p-value< 0.01) in 2019 was significantly associated with higher proportion of elevated depressive

symptoms. There were too few participants with a cancer or stroke history so we could not robustly estimate associations with mental health outcomes of interest. People with elevated depressive symptoms were more likely to have more chronic diseases in 2019 (p-value<0.01).

7.4.2. Association of Elevated Anxiety Symptoms with Sample Characteristics

Socio demographic characteristics were not associated with anxiety except for gender. According to table 3, women had higher prevalence of elevated anxiety symptoms than men (p-value< 0.05). Participants with thyroid disease in 2014(p-value =0.02) and 2019(p-value <0.01) also were more likely to report anxiety symptoms. People with elevated anxiety symptoms were more likely to have more chronic diseases in 2019 (p-value<0.01) (Table 4).

7.4.3. Bivariate Analysis of Continuous Depression and Anxiety Scores with Sample Characteristics

Table 5 presents the Error! Reference source not found.bivariate analysis using the continuous depression and anxiety scores (PHQ-9 and GAD-7 scores). The statistical significance of the associations with regard to socio-economic factors was consistent with the binary outcomes' results. Women had higher depression and anxiety scores; participants with higher educational level had 2.39 lower PhQ-9 (p-value <0.01). This trend also appeared with the anxiety scores (p value= 0.10).

Higher BMI and higher hypertension positively tracked with depressive scores, although these associations did not reach statistical significance. Having a higher number of chronic illnesses was associated with more depressive symptoms: as the chronic diseases count increases by one, the PHQ-9 increases by 1.61 units (CI = [0.474

2.755]). Anxiety scores also increased by 0.9 for each additional chronic disease, according to the 2019 diagnosis (p value=0.07).

7.4.4. Bivariate Analysis of Continuous Mental Health Scores and Glycemic Indicators

Depressive symptoms in 2019 were not associated with FBG or HbA1c levels measured in the same year (p>0.3) nor with the change in blood glucose levels between 2014 and 2019. Similarly, anxiety symptoms were not associated with concomitant FBG and HbA1c levels (p>0.47). However, prior glycemic indicators measured in 2014 were related to both mental health outcomes: higher FBG levels in 2014 were associated with higher depressive and anxiety symptoms (beta=0.024, CI= [-0.002, 0.051], p-value=0.072) (beta=0.035, CI= [0.009, 0.060], p-value=0.009. Higher 2014 HbA1c levels also showed a trend of being associated with more depressive symptoms but without reaching statistical significance (Beta=0.532, CI= [-0.158, 1.223], p-value=0.130). Finally, diabetes status in 2014 was associated with higher depression (Beta=2.110, CI= [0.195, 4.026], p-value=0.031*****) and nearly significant with anxiety symptoms (Beta=1.647, CI= [-0.223, 3.52], p-value=0.08*****) (Table 5).

Table 5. Linear bivariate regression models of the main outcomes (depressive and anxiety symptoms) with glycemic indicators and with socio-demographic, lifestyle, and health characteristics at 2014 and 2019.

			Depression (PHQ-9) Scores			Anxiety (GAD-7) Scores			
			Beta	**CI**	**P-value**	**Beta**	**CI**		**P-value**
Socio-Demographic Characteristics									
Age	**2014**		0.025	[-0.034 0.085]	0.398	-0.003	[-0.060	0.057]	0.954
Age	**2019**		0.024	[-0.035 0.084]	0.422	-0.002	[-0.061	0.056]	0.927

Sex		*Female*	3.589	[2.001 5.177]	0.000*****	2.690	[1.108	4.271]	0.000*****
Education	**2014**	*Higher*	-2.150	[-3.877 - 0.423]	0.015*****	-1.271	[-2.973	0.430]	0.142
Education	**2019**	*Higher*	-2.382	[-4.025 - 0.738]	0.005*	-1.504	[-3.110	0.101]	0.066#
Diabetes Characteristics and Exposure indicators									
FBG	**2014**		0.024	[-0.002 0.051]	0.072#	0.035*	[0.009	0.060]	0.009*****
FBG	**2019**		0.009	[-0.009 0.029]	0.329	0.007	[-0.012	0.027]	0.473
HbA1c	**2014**		0.532	[-0.158 1.223]	0.130	0.460	[-0.214	1.135]	0.180
HbA1c	**2019**		0.126	[-0.490 0.742]	0.687	0.135	[-0.467	0.738]	0.661
Change in FBG¶			0.008	[-0.018 0.036]	0.535	0.024	[-0.003	0.051]	0.084#
Change in HbA1c¶			0.702	[-0.286 1.690]	0.163	0.538	[-0.430	1.507]	0.274
Diabetes	**2014**	*Yes*	2.110	[0.195 4.026]	0.031*****	1.647	[-0.223	3.52]	0.085#
Diabetes	**2019**	*Yes*	0.509	[-1.228 2.247]	0.564	-0.556	[-2.251	1.139]	0.519
Covariates: Lifestyle and Health Characteristics									
BMI	**2014**		0.095	[-0.041 0.231]	0.170	0.017	[-0.116	0.151]	0.798
BMI	**2019**		0.090	[-0.045 0.230]	0.190	0.012	[-0.120	0.145]	0.853
Hypertension	**2014**	*Yes*	1.916	[-0.094 3.928]	0.062#	1.312	[-0.659	3.284]	0.191
Hypertension	***2019***	*Yes*	1.165	[-0.489 2.818]	0.166	0.980	[-0.635	2.595]	0.233
No. Of chronic diseases	**2014**		1.614	[0.474 2.755]	0.006*****	0.636	[-0.495	1.767]	0.269
No. Of chronic diseases	**2019**		2.100	[1.111 3.088]	0.000*****	0.903	[-0.096	1.901]	0.076#
Currently Smoking	**2014**	*Yes*	0.177	[-1.458 1.813]	0.831	-0.920	[-2.511	0.670]	0.255
Currently Smoking	**2019**	*Yes*	-0.397	[-2.024 1.231]	0.631	-0.726	[-2.313	0.859]	0.367
Physical activity levels	**2014**	*Moderate*	-0.813	[-2.574 0.948]	0.364	-0.386	[-2.089	1.317]	0.665
		High	0.355	[-1.920 2.636]	0.759	2.126	[-0.078	4.330]	0.059#
Physical activity levels	**2019**	*Moderate*	-1.315	[-3.003 0.372]	0.126	-1.341	[-3.013	0.329]	0.115
		High	-0.456	[-2.971 2.059]	0.721	1.187	[-1.302	3.677]	0.348

7.4.5. Graphical representation of the association between continuous depression and anxiety symptoms and glycemic indicators:

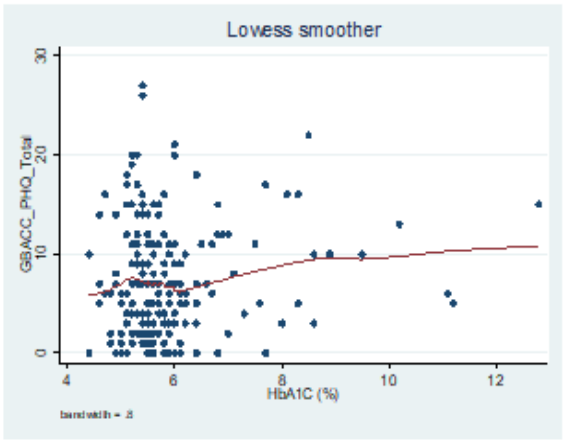

Figure a. PHQ-9_HBA1C 2014

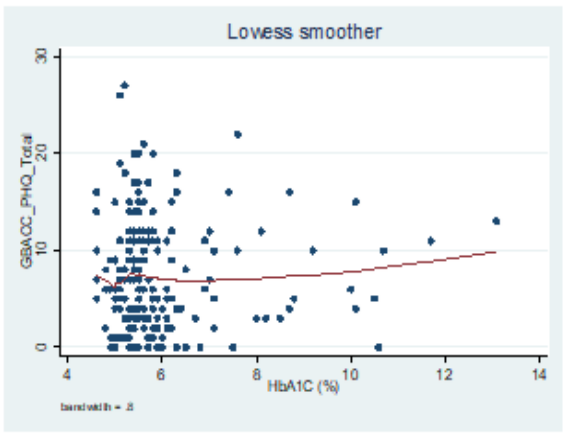

Figure b. PHQ-9__ HBA1C 2019

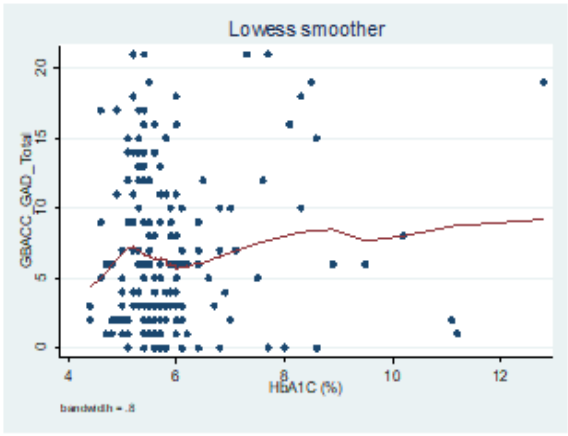

Figure c. GAD-7_ HBA1C 2014

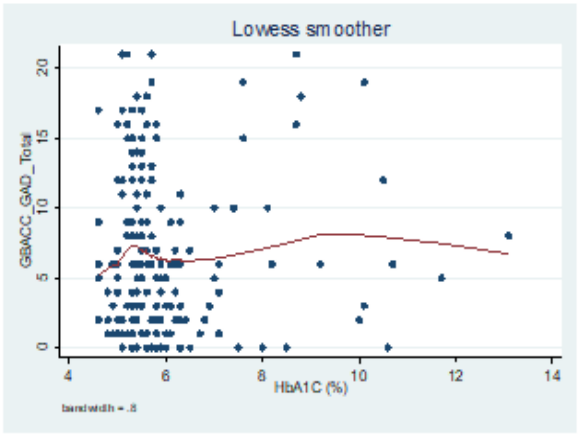

Figure d. GAD-7_ HBA1C 201

Figure 6. Lowess plots of depression and anxiety scores with 2014 and 2019 HbA1c levels.

Figure 6 represents 4 Lowess plots of the association of baseline and follow-up HbA1c with each of the depression (PhQ-9) and anxiety (GAD-7) scores. The graphs suggest a change in the association, wherein above 6.5% HbA1c value, a positive linear trend between HbA1c and mental health scores is more apparent, whereas below 6.5%, the association either follows a plateau or no clear patterns of association. Figure 7 displays the plots of continuous depression and anxiety scores across FBG 2014 and 2019 levels. A similar trend is observed wherein the associations are different before

and after values of FBG=126 mg/dl. The fact that we observed these trends for both glycemic indicators and for both outcomes of interest motivated to conduct segmented piecewise regression separating the ranges of <126 mg/dl and >==126 mg/dl for FBG and <6.5% and >=6.5% for HbA1c.

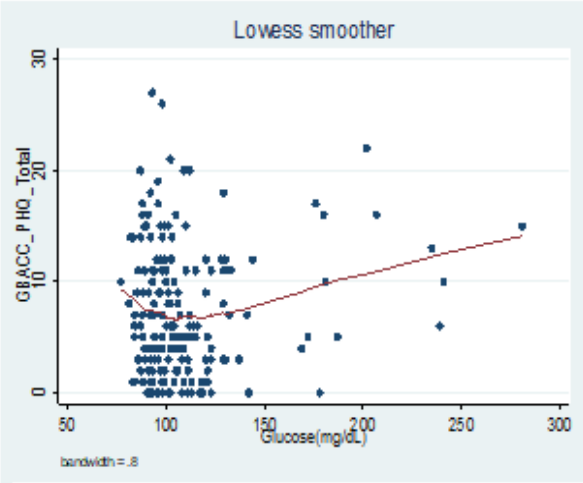

Figure a. PHQ-9__ FBG 2014

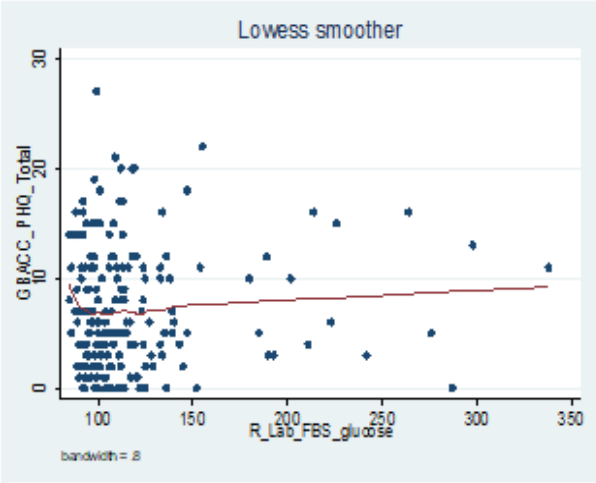

Figure b. PHQ-9__ FBG 2019

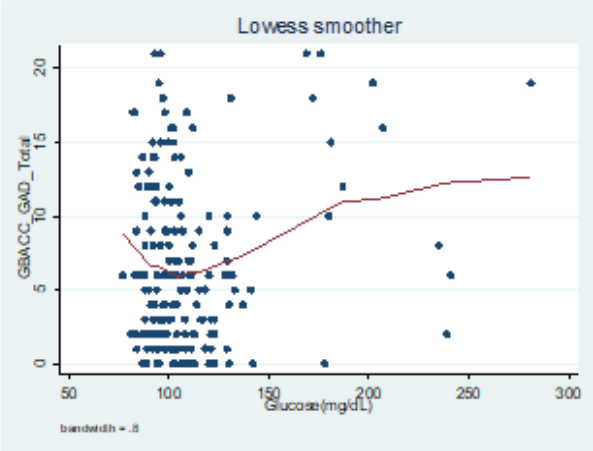

Figure c. GAD-7__ FBG 2014

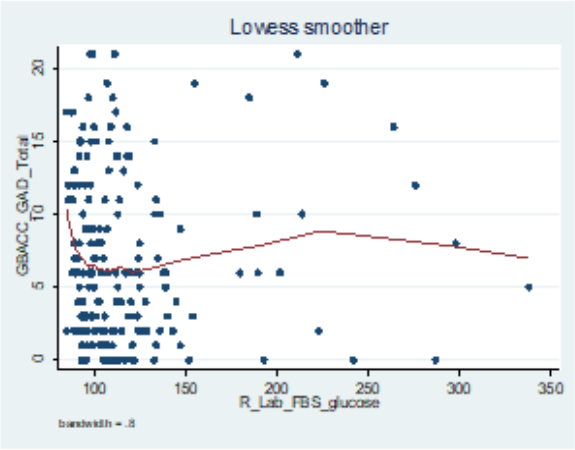

Figure d. GAD-7__ FBG 2019

Figure 7. Lowess plots of depression and anxiety scores with 2014 and 2019 fasting blood glucose levels.

7.5. Multivariable Association of Depressive and Anxiety Symptoms with Glycemic Indicators:

7.5.1. Piecewise Regression Analysis of Glycemic Indicators and Continuous Anxiety and Depression Symptoms - Unadjusted

Table 6. Unadjusted piecewise regression analysis of continuous depression and anxiety scores with 2014 and 2019 FBG and HbA1c levels.

Variables		**Depression (PHQ-9) Scores**			**Anxiety (GAD-7) Scores**		
		Beta	**Conf. Int.**	**p-value**	**Beta**	**Conf. Int.**	**p-value**
FBG 2014	*< 126*	-0.09*3*	[-.0177 -0.009]	0.030*	-0.095	[-.1763 -.0147]	0.021*
	≥126	0.038	[-0.011 0.087]	0.126	0.054	[0.007 0.101]	0.026*
FBG 2019	*< 126*	-0.017	[-0.101 0.066]	0.684	-0.048	[-0.131 0.035]	0.255
	≥126	0.013	[-0.019 0.045]	0.436	0.018	[-0.014 0.050]	0.268
HbA1c 2014	*< 6.5*	-1.436	[-3.477 0.604]	0.167	-1.526	[-3.520 0 .467]	0.133
	≥6.5	0.429	[-0.911 1.770]	0.528	0.488	[-0.821 1.798]	0.463
HbA1c 2019	*< 6.5*	-0.989	[-3.204 1.226]	0.380	-1.617	[-3.773 0.538]	0.141
	≥6.5	0.525	[-0.688 1.738]	0.395	0.587	[-0.593 1.769]	0.328

***significant if p-value <0.05**

7.5.2. Piecewise Regression Analysis of Glycemic Indicators and Continuous Anxiety and Depression Symptoms - Adjusted for Age and Sex

Table 7. Age and sex adjusted piecewise regression analysis of continuous depression and anxiety scores with 2014 and 2019 FBG and HbA1c levels

Variables		Depression (PHQ-9) Scores			Anxiety (GAD-7) Scores		
		Beta	**Confidence Int.**	**p-value**	**Beta**	**Confidence Int.**	**p-value**
FBG 2014	*< 126*	-0.091	[-0.178 -0.007]	0.035*	-0.082	[-.1670 .0013]	0.050*
	≥126	0.034	[-0.013 0.081]	0.155	0.052	[0.005 0 .098]	0.029*
	Age	0.031	[-0.029 0.092]	0.313	-0.003	[-0.063 0.056]	0.897
	Sex	3.290	[1.722 4.867]	0.000*	2.371	[0.826 3.916]	0.003*
FBG 2019	*< 126*	-0.006	[-0.092 0.078]	0.876	-0.034	[-0.121 0.051]	0.428
	≥126	0.013	[-0.017 0.044]	0.380	0.018	[-0.013 0.050]	0.242
	Age	0.016	[-0.04 0.077]	0.600	-0.000	[-0.062 0.062]	0.998
	Sex	3.377	[1.782 4.971]	0.000*	2.534	[0.917 4.151]	0.002*
HbA1c 2014	*< 6.5*	-1.749	[-3.847 0.349]	0.102	-1.482	[-3.571 0.613]	0.165
	≥6.5	0.439	[-0.847 1.725]	0.500	0.516	[-0.767 1.801]	0.428
	Age	0.029	[-0.034 0.092]	0.372	-0.002	[-0.065 0.062]	0.957
	Sex	3.448	[1.861 5.035]	0.000*	2.560	[0.976 4.144]	0.002*
HbA1c 2019	*< 6.5*	-1.281	[-3.528 0.965]	0.262	-1.617	[-3.853 0.619]	0.155
	≥6.5	0.527	[-.6377 1.691]	0.373	0.617	[-0.542 1.776]	0.295
	Age	0.028	[-.0335 .0912]	0.364	0.003	[-0.058 0.065]	0.917
	Sex	3.559	[1.942 5.176]	0.000*	2.672	[1.062 4.282]	0.001*

***significant if p-value <0.05**

7.5.3. Piecewise Regression Analysis of Glycemic Indicators and Continuous Anxiety and Depression Symptoms - Adjusted for Lifestyle and Health Characteristics

Tables 6, 7, 8, and 9 represent the results of unadjusted and adjusted segmented piecewise linear regression analysis of depression and anxiety scores with the four main exposures HbA1c at 2014, HbA1c at 2019, FBG at 2014 and FBG at 2019, while

controlling gradually for potential confounders. Confounders were adjusted accordingly to their value at each of the 2014 and 2019 analysis.

Associations were detected between FBG levels in 2014 and depression and anxiety scores measured five years later, in the unadjusted piecewise regressions (Table 6): In the <126 mg/dl non-diabetic FBG range, higher FBG levels were associated with lower depressive (beta=-0.093, 95%CI= [-0.0177, -0.009]; p=0.03); and anxiety scores (beta=-0.095 ,95%CI=-0.1763, -0.0147; p=0.02); in the diabetic ≥ 126 mg/dl *FBG* range, higher FBG levels were significantly associated with higher anxiety symptoms (beta=0.054; 95%CI= 0.007, 0.101; p=0.026) (Table 6). Higher 2014 FBG levels in the ≥126 mg/dl range showed a non-significant trend for higher depressive symptoms. Similar associations were observed in models adjusted for age and sex (Table 7) and following further adjustment for educational attainment, BMI, current smoking, hypertension (Table 9) and family history of diabetes, number of chronic disease, and physical activity (Table 9). FBG levels in 2019 were not associated with mental health scores. With regards to HbA1c, there was a similar trend for 2014 HbA1c levels, with negative associations with mental health symptoms in the below 6.5% range and positive association in the above 6.5% range; these results are similar to the FBG results, however they did not reach statistical significance. Following adjustments for lifestyle and health indicators in Tables 8 and 9, the negative association between 2014 HbA1c and depressive symptoms (beta= -1.91, 95%CI= [-4.21, 0.293]; p= 0.089) and between 2019 HBA1c levels and both depression (beta= -1.940, 95%CI= [-4.311,0.430]; p=0.108) and anxiety symptoms (beta= -1.833, 95%CI=[-4.528,0.590]; p= 0.137) in the below 6.5% range were more apparent (Table 9) .

Additional exploratory analysis: Despite the limited number of participants for this sub-group analysis, we explored in sensitivity analysis the potential role of treatment and duration of diabetes among participants with diabetes (and thus for whom this self-reported information was available). We found that among participants with diabetes, those who were on medication in 2014 or 2019 did not have different mental health scores (except for a trend for higher anxiety scores among those on medication) than untreated participants with diabetes. Analysis of diabetes duration showed that there was no association among participants with diabetic between duration and mental health outcomes in 2014 but that longer disease duration in 2019 was associated with higher depression and anxiety scores, in line with our conclusion of a longer-term/cumulative form of association (Supplementary Tables 8 and 9).

Table 8. Piecewise regression analysis of continuous depression and anxiety scores with 2014 and 2019 FBG and HbA1c levels, adjusted for age, sex, educational attainment, body mass index, smoking, and hypertension

Variables			**Depression (PHQ-9) Scores**				**Anxiety (GAD-7) Scores**			
			Beta	**Conf. Interval**		**P value**	**Beta**	**Conf. Interval**		**P value**
FBG	**2014**	*< 126*	-0.111	[-0.199	-0.023]	0.013*	-0.092	[-0.179	-.0005]	0.038*
FBG	**2014**	*≥126*	0.039	[-0.008	0.087]	0.103	0.055	[0.008	0.102]	0.022*
Age	**2014**		0.020	[-0.041	0.082]	0.517	-0.007	[-0.068	0.053]	0.815
Sex	**2014**	*Female*	3.132	[1.512	4.752]	0.000*	2.146	[0.539	3.752]	0.009*
Education	**2014**	*Higher*	-1.536	[-3.248	0.175]	0.078	-1.137	[-2.834	0.559]	0.188
BMI	**2014**		0.005	[-0.136	0.147]	0.938	-0.076	[-0.217	0.064]	0.285

current smoking	**2014**	*Yes*	0.692	[-0.907	2.293]	0.394	-0.598	[-2.184	0.988]	0.458
Hypertension	**2014**	*Yes*	1.588	[-0.570	3.747]	0.148	1.390	[-0.749	3.530]	0.202
FBG	**2019**	***< 126***	-0.025	[-0.113	0.063]	0.569	-0.041	[-0.130	0.046]	0.354
FBG	**2019**	***≥126***	0.014	[-0.017	0.045]	0.378	0.017	[-0.014	0.049]	0.274
Age	**2019**		0.017	[-0.046	0.080]	0.591	-0.006	[-0.070	0.056]	0.832
Sex	**2019**	*Female*	3.054	[1.391	4.717]	0.000*	2.459	[0.786	4.132]	0.004*
Education	**2019**	*Higher*	-1.939	[-3.617	-0.261]	0.024*	-1.479	[-3.167	0.207]	0.085
BMI	**2019**	*Smoker*	-0.004	[-0.147	0.138]	0.952	-0.053	[-.1970	.0909]	0.468
current smoking	**2019**	*Yes*	-0.046	[-1.647	1.554]	0.955	-0.542	[-2.152	1.068]	0.507
Hypertension	**2019**		0.447	[-1.310	2.205]	0.616	1.012	[-.7555	2.780]	0.260
HbA1c1	**2014**	*< 6.5*	-2.062	[-4.243	0.119]	0.064	-1.456	[-3.650	0.737]	0.192
HbA1c2	**2014**	*≥6.5*	0.447	[-0.837	1.732]	0.493	0.519	[-0.773	1.811]	0.429
Age	**2014**		0.021	[-0.043	0.085]	0.524	-0.006	[-0.071	0.058]	0.845
Sex	**2014**	*Female*	3.337	[1.703	4.970]	0.000*	2.316	[0.674	3.960]	0.006*
Education	**2014**	*Higher*	-1.544	[-3.280	0.191]	0.081	-1.185	[-2.930	0.560]	0.182
BMI	**2014**		0.030	[-0.117	0.178]	0.687	-0.049	[-0.199	0.098]	0.509
current smoking	**2014**	*Yes*	0.627	[-0.994	2.249]	0.446	-0.761	[-2.392	0.870]	0.359
Hypertension	**2014**	*Yes*	0.909	[-1.224	3.042]	0.402	0.895	[-1.250	3.041]	0.412
HbA1c	**2019**	*< 6.5*	-2.089	[-4.430	0.251]	0.080	-1.974	[-4.296	0..348]	0.095
HbA1c	**2019**	*≥6.5*	0.469	[-0.703	1.642]	0.431	0.486	[-0.677	1.649]	0.411
Age	**2019**		0.031	[-0.033	0.096]	0.347	-0.002	[-0.066	0.063]	0.953
Sex	**2019**	*Female*	3.125	[1.444	4.807]	0.000*	2.522	[0.854	4.190]	0.003
Education	**2019**	*Higher*	-1.927	[-3.630	-0.225]	0.027*	-1.324	[-3.013	0 .365]	0.124

BMI	**2019**		0.039	[-0.108	0.187]	0.597	-0.027	[-0.174	0.119]	0.713
current smoking	**2019**	*Yes*	-0.194	[-1.828	1.439]	0.814	-0.579	[-2.200	1.042]	0.482
Hypertension	**2019**	*Yes*	0.593	[-1.193	2.380]	0.513	1.060	[-0.712	2.833]	0.239

*** significant if p-value <0.05**

Table 9. Piecewise regression analysis of continuous depression and anxiety scores with 2014 and 2019 FBG and HbA1c levels, adjusted for sociodemographic, lifestyle, and health indicators.

Variables			**Depression (PHQ-9) Scores**				**Anxiety (GAD-7) Scores**			
			Beta	**Conf. Interval**		**p-value**	**Beta**	**Conf. Interval**		**p-value**
FBG	**2014**	*< 126*	-0.120	[-0.207	-0.032]	0.008*	-0.099	[-0.186	-0.012]	0.026*
FBG	**2014**	*≥126*	0.041	[-0.006	0.088]	0.087	0.055	[0.008	0.102]	0.021*
Age	**2014**		-0.001	[-0.066	0.062]	0.954	-0.009	[-0.074	0.054]	0.761
Sex	**2014**	*Female*	2.91	[1.286	4.541]	0.001*	1.986	[0.365	3.606]	0.017*
Education	**2014**	*Higher*	-1.62	[-3.342	0.091]	0.063	-1.089	[-2.790	0.620]	0.210
BMI	**2014**		0.005	[-0.137	0.147]	0.942	-0.066	[-0.208	0.075]	0.355
Current smoking	**2014**	*Yes*	0.870	[-0.731	2.471]	0.285	-0.400	[-1.990	1.194]	0.621
Hypertension	**2014**	*Yes*	0.888	[-1.347	3.124]	0.434	1.262	[-0.964	3.489]	0.265
Family History of DM	**2014**	*Yes*	-0.090	[-1.637	1.456]	0.908	0.140	[-1.399	1.680]	0.857
No. Of chronic diseases	**2014**		1.501	[0.237	2.766]	0.020*	0.474	[-0.784	1.734]	0.458
Physical activity levels	**2014**	*Moderate*	-1.153	[-2.820	0.519]	0.175	-0.659	[-2.324	1.006]	0.436
		High	0.406	[-1.740	2.553]	0.709	1.974	[-0.163	4.113]	0.070

FBG	**2019**	*< 126*	-0.020	[-.1086	0.067]	0.647	-0.031	[-0.121	0.058]	0.494
FBG	**2019**	*≥126*	0.009	[-.0218	0.041]	0.543	0.013	[-0.018	0.045]	0.409
Age	**2019**		0.007	[-.0566	0.071]	0.828	-0.006	[-0.071	0.058]	0.844
Sex	**2019**	*Female*	2.788	[1.091	4.485]	0.001*	2.421	[0.692	4.149]	0.006*
Education	**2019**	*Higher*	-1.655	[-3.349	0.037]	0.055	-1.223	[-2.943	0.501]	0.163
BMI	**2019**		-0.005	[-.1484	0.137]	0.942	-0.051	[-0.196	0.094]	0.490
Current smoking	**2019**	*Yes*	-0.288	[-1.894	1.317]	0.724	-0.690	[-2.325	0.944]	0.406
Hypertension	**2019**	*Yes*	-0.083	[-1.908	1.740]	0.928	0.942	[-.9147	2.800]	0.318
Family History of DM	**2019**		-0.031	[-1.636	1.573]	0.969	0.450	[-1.183	2.085]	0.587
No. Of chronic diseases	**2019**	*Yes*	1.425	[0.271	2.580]	0.016*	0.413	[-0.762	1.588]	0.489
Physical activity levels	**2019**	*Moderate*	-1.134	[-2.841	0.573]	0.192	-1.219	[-2.955	0.519]	0.168
		High	-0.379	[-2.879	2.119]	0.765	0.526	[-2.019	3.071]	0.684
HbA1c	**2014**	*< 6.5*	-1.91	[-4.120	0.293]	0.089	-1.269	[-3.496	0.956]	0.262
HbA1c	**2014**	*≥6.5*	0.517	[-0.769	1.804]	0.429	0.536	[-0.762	1.834]	0.416
Age	**2014**		-0.003	[-0.071	0.064]	0.921	-0.012	[-0.080	0.056]	0.736
Sex	**2014**	*Female*	3.11	[1.471	4.766]	0.000*	2.139	[0.477	3.801]	0.012*
Education	**2014**	*Higher*	-1.65	[-3.406	0.090]	0.063	-1.160	[-2.924	0.602]	0.196
BMI	**2014**		0.022	[-0.125	0.170]	0.763	-0.049	[-0.198	0.100]	0.518
Current smoking	**2014**	*Yes*	0.739	[-0.887	2.365]	0.371	-0.624	[-2.264	1.016]	0.454
Hypertension	**2014**	*Yes*	0.211	[-2.014	2.440]	0.851	0.774	[-1.473	3.021]	0.498
Family History of DM	**2014**	*Yes*	0.209	[-1.363	1.783]	0.793	0.522	[-1.064	2.109]	0.517

No. Of chronic diseases	**2014**		1.431	[0.143	2.719]	0.030*	0.426	[-0.872	1.725]	0.518
Physical activity levels	**2014**	*Moderate*	-0.925	[-2.630	.7790]	0.285	-0.482	[-2.202	1.236]	0.580
		High	0.292	[-1.904	2.488]	0.793	1.927	[-0.287	4.142]	0.088
HbA1c	**2019**	*< 6.5*	-1.940	[-4.311	0.430]	0.108	-1.833	[-4.258	0.590]	0.137
HbA1c	**2019**	*≥6.5*	0.297	[-0.860	1.456]	0.613	0.302	[-0.882	1.486]	0.615
Age	**2019**		0.013	[-0.051	0.077]	0.687	-0.004	[-.0702	0.061]	0.890
Sex	**2019**	*Female*	2.732	[1.048	4.415]	0.002*	2.400	[0.679	4.121]	0.007*
Education	**2019**	*Higher*	-1.591	[-3.273	.0912]	0.064	-1.064	[-2.784	0.656]	0.224
BMI	**2019**		0.015	[-.1289	.1604]	0.830	-0.038	[-.1867	0.109]	0.605
Current smoking	**2019**	*Yes*	-0.363	[-1.971	1.245]	0.657	-0.673	[-2.317	0.971]	0.420
Hypertension	**2019**	*Yes*	-0.163	[-1.980	1.653]	0.859	0.864	[-.9932	2.723]	0.360
Family History DM	**2019**		0.325	[-1.267	1.917]	0.688	0.692	[-.9359	2.320]	0.403
No. Of chronic diseases	**2019**	*Yes*	1.510	[.35401	2.667]	0.011*	0.445	[-.7372	1.628]	0.458
Physical activity levels	**2019**	*Moderate*	-1.124	[-2.823	0.574]	0.193	-1.266	[-3.003	0.470]	0.152
		High	-0.661	[-3.167	1.845]	0.603	0.267	[-2.296	2.830]	0.837

***significant if p-value <0.05**

CHAPTER 8

DISCUSSION

8.1. Main Findings

The current study aimed to assess the relationship of glycemic indicators with depression and anxiety scores in a Lebanese community-based sample of middle aged adults. In our sample, 32% of respondents had elevated depression symptoms and 26% had elevated anxiety symptoms, which are higher than previously reported prevalence in other studies (which were in 11-17% range)[24], highlighting the importance of research on mental health in Lebanon .

Our study revealed novel findings regarding the association of glycemic indices and mental health. One important finding in this study is that the association between FBG levels and mental health symptoms seems to be differential across the normal to clinical range of 2014 FBG levels, wherein only increases in FBG levels in the 126 mg/dl and above range were significantly associated with worsening depression and anxiety scores. Conversely increases in FBG levels, as long as they were in the below 126 mg/dl range were not associated with worst mental health scores. A similar trend was observed for HbA1c levels but it only came close to statistical significance for the below 6.5% range showing negative associations with mental health outcomes. This finding sheds the light of the importance of having glycemic indicators in the clinical range and worsening of glycemic indicators in the clinical range for mental health outcomes. The results of associations of FBG levels in the ≥126 mg/dl range are in line with other findings. According to a study done in New York that included 249 participants, a sample size that is close to ours, diabetic patients showed a positive and significant correlation between

fasting blood glucose levels and PHQ-9 depression scores [78, 79]. Another study conducted in an Indian health care center among diabetic patients also showed agreement with our result, where anxiety was positively significantly associated with FBG according to the HADS scale[66]. We note that very limited number of studies depended on FBG as an indicator for glycemic control whereas HbA1c is highly studied. Yet, evidence support the role of FBG in diabetes diagnosis. For example, according to a study done by Ghazanfari et al. FBG was found to be more reliable than HbA1c in identifying diabetic and non – diabetic people[80].

We also note that associations of HbA1c with mental health outcomes followed the same trend of negative relationships with mental health scores in the non-clinical/diabetic HbA1c ranges and that larger samples are needed to confirm no associations with mental health in the clinical/diabetic range. Some studies found that HbA1c is associated with depression [17, 54, 64, 81, 82] and anxiety[66] in diabetic people. Whereas other studies found no association [69, 79, 83]. A study done among 514 participants in Iran didn't find association between poor glycemic control (high HbA1c values) and depression in diabetic people (OR = 1.11, 95% CI = 0.87-1.57) [84]. Yet, most of these studies are cross – sectional. One longitudinal study over 5 years follow up period, conducted in a sample of 3762 D2TM patient and another 3-year longitudinal study that aimed – as a secondary purpose – to investigate the relation between glycemic control and depression among adolescents showed that the relationship between depression and HbA1c was not significant after adjustment for confounders [83, 85]. Similarly, our results suggest no relationship between HbA1c and anxiety and depression, however they emphasize that future studies will benefit from looking at the normal-to-pathological ranges of HbA1c to better delineate particularities of this relationship.

In sum, our results show that increases in FBG and HbA1c levels were not linked to worst mental health, as long as the glycemic values did not reach the clinical diabetes threshold. These findings can have important public health and clinical implications, as they suggest that it's not the gradual/cumulative increase of glycemic indices that is problematic but rather entering the disease/pathological stage. Further, the associations were observed directly with glycemic indicators (irrespective of diabetes status or treatment), suggesting that non-diabetic FBG and HbA1c levels (either naturally or controlled) may not impact mental health negatively. We should take into consideration the fact that depression and anxiety has been linked to poor glycemic control, poor adherence to treatment regimens and bad dietary habits, and management of those will ultimately affect the mental health status of the diabetic individuals [18, 62, 81]. Future studies with larger samples and with repeated assessments of both glycemic measures and mental health outcomes can help us in better understanding their complex relationships and their interplay through the role of adherence and success of treatment.

Another important finding of this study is the association of the 2014 diabetes-related measures with mental health scores, which seems more apparent than the 2019 diabetes-related measures, assessed at same time as the mental health scores. Diabetes status and FBG levels in 2014 showed the stronger associations with mental health outcomes. This could suggest a delayed or cumulative response between glycemic indicators and mental health outcomes, and that the relationship of higher glycemic levels and mental health does not appear instantly. This can be seen as a reasonable interpretation when taking into consideration that diabetes is a chronic disease which is not caused by a single agent, but by a complex interaction of several factors, and which entails important biological consequences. Further, diabetes duration was associated with risk of depression in

previous studies [18, 63] . Another potential explanation for the difference between the results of this study and the results from other studies is that our results' lack of significance might be due to the small sample size. However, even if significant associations were only observed at one time, both HBA1C and FBG were highly correlated across time (Supplementary Table 3), highlighting the stability of these indicators and raising the question of why some relationships will be observed at a specific time-point. Our analysis was limited by the one measurement of mental health and the absence of assessments at baseline, so we cannot exclude reverse causality and that higher previous glycemic indices might have been observed among people with a prior mental health problem.

8.2. Strength and Limitations

To the best of our knowledge and after an extensive literature review, this is the first study that address the relationship of mental health conditions with the normal to clinical range of glycemic indices in a community sample. All the reviewed published studies were limited to specific samples with existing comorbidities (people with cardiovascular problems, diabetic 1 and 2, hypertensive, dialysis patients). In addition, this study is a prospective study with repeated assessments of glycemic indicators using rigorous and standardized data collection methods, whereas most previous studies relied on a one-time assessment of glycemic measures. In addition, the time interval between the two study waves, which was of 5 years, allowed assessment of glycemic indices and their relationships with mental health over a longer-term period.

Our study also includes several limitations. First, the high drop-out rate, wherein 303 participants in the baseline wave were lost to follow-up. According to a study on the same cohort, there was no major difference between the responders and non-responders, [1]. It is also important to note that the primary cause for loss to follow-up was due to the inability to contact because of the change in their contact information. This suggests that, despite the reduction in sample size, the follow-up sample was still representative of the baseline sample and that the drop-out did not cause major systematic differences and selection bias in the follow-up sample. However, the drop in sample size could have hindered the detection of smaller magnitude associations and doing more specific sub-group analysis (e.g., controlled diabetes versus uncontrolled diabetes). Further, the study sample remains a selective sample, in the sense that it is recruited from the capital and its surroundings, and thus is not be representative of the general population in Lebanon. Another important limitation is that the study included only one follow-up wave and importantly one assessment of mental health, making it difficult to rule out reverse causality as discussed above. However, the lack of cross-sectional association between mental health and glycemic indices in 2019 suggest that it is possible that similarly mental health in 2014 would not be related to the 2014 glycemic indices. This would support the suggestion that the associations of FBG and diabetes with mental health might be more delayed and prolonged in time. Our results advocate for longitudinal studies with several repeated assessments of both glycemic and mental health measures are needed to better describe their temporal and longitudinal associations. It is also possible that the mental health data included measurement errors, given their subjective nature. Moreover, most of the other chronic diseases were self-reported, leaving the likelihood of undiagnosed or unknown prior occurrences of disease and of residual confounding bias. Finally, stress

and traumatic exposures (whether previous such as war exposures or current) were not assessed in the study and not adjusted for. These exposures are important in the Lebanese context and might have influenced both mental health and the occurrence of chronic diseases. It's important to note that the mental health outcomes were collected in 2019 hence before the economic collapse, the covid-19 pandemic and the Beirut blast, which can have larger impact on the mental health of Beirut and Lebanon residents.

CHAPTER 9

CONCLUSION, RESEARCH SIGNIFICANCE AND PUBLIC HEALTH IMPLICATION

In conclusion, this present work on the relationship of glycemic indicators and depression and anxiety symptoms in a community-based middle-aged samples shed the light on several important particularities of these associations. Namely, findings revealed that adverse associations with higher glycemic levels and mental health are not observed in the normal range of these indicators, but rather only in the clinical/diabetic range of FBG. Results also suggest the presence of delayed or longer-term associations rather than cross-sectional associations. These results have important implications for research, wherein they strengthen the rationale for longitudinal investigations of the relationship between glycemic indicators (HbA1c / FBG) and mental health disorders by using 5-years follow-up assessments of glycemic indices and mental health and by informing these investigations to include participants across the continuum of these indicators to confirm the differences observed between the below and above clinical ranges. Such studies can provide a more systematic and comprehensive evidence regarding the direct relationships of diabetes processes and mental health and can unravel the mechanisms of their co-morbidity and their temporal associations.

A better understanding of this complex co-morbidity between diabetes and mental health disorders can have significant implications for these highly prevalent and burdensome conditions, ranging from improving their prevention, management, and consequences. Advancing this knowledge can aid in developing two-dimension strategies that can help manage diabetes and mental health simultaneously, which can be important

in low-resource settings like in Lebanon and where both these conditions are prevalent. Our work also brings forward important hypothesis regarding the clinical course of glycemic indices, as only the clinical range was associated with depression and anxiety symptoms, advocating for prioritizing medical and lifestyle prompt treatment for diabetes and glycemic control to better improve the consequences and mental health co-morbidities for patients with diabetes [86] .

APPENDIX

Supplementary Table 1.Table showing the significance difference in between both glycemic indicator FBG and HbA1c at each time points 2014 and 2019.

Variables	Mean	Std. Dev	Confidence Interval	p-value
FBG 2014	109.2718	29.713	[105.075 113.468]	0.0001*
FBG 2019	117.625	39.763	[112.009 123.241]	
HbA1c2014	5.909	1.159	[5.745 6.072]	0.3995
HbA1c2019	5.958	1.311	[5.773 6.143]	

Supplementary Table 2. Association between depression and Anxiety

		Depression		p-value
		No	Yes	
Anxiety	**No**	122	23	0.000*
	Yes	12	41	

Supplementary Table 3. Correlation matrix of main outcomes

Variables	PHQ-9 Scores	GAD-7 Scores
PHQ-9 Scores	1	
GAD-7 Scores	0.738*	1

Supplementary Table 4. Unadjusted logistic regression analysis of depression and anxiety with 2014 and 2019 FBG and HbA1c levels

Variables		Depression(yes/no)			Anxiety(yes/no)		
		OR	Conf. Interval	p-value	OR	Conf. Interval	p-value
FBG2014	*< 126*	.970	[.9371 1.004]	0.092	0.956	[.9199 .9940]	0.024*
	>126	1.012	[0.992 1.032]	0.222	1.014	[.9951 1.034]	0.142
FBG2019	*< 126*	1.007	[0.975 1.041]	0.634	.9837	[.9497 1.018]	0.359
	>126	1.006	[.994 1.018]	0.271	1.004	[.9924 1.016]	0.469
HbA1c2014	*< 6.5*	0.645	[0.309 .3477]	0.244	0.526	[.2414 1.149]	0.107
	>6.5	1.320	[.8409 2.075]	0.227	1.179	[.7619 1.824]	0.459
HbA1c2019	*< 6.5*	.8714	[.4025 1.886]	0.727	.4220	[.1781 .9999]	0.050
	>6.5	1.246	[.8559 1.815]	0.251	.9645	[.6336 1.468]	0.886

Supplementary Table 5. Multiple logistic regression analysis for PHQ-9 Scores and GAD-7 Scores as the outcomes and FBG and HbA1c as main exposure at two study waves 2014 and 2019 adjusting for age and sex

Variables		Depression(yes/no)			Anxiety(yes/no)		
		OR	Conf. Interval	P value	OR	Conf. Interval	P value
FBG2014	< 126	0.966	[0.930 1.003]	0.079	.953	[0.914 0.993]	0.025*
FBG2014	≥ 126	1.012	[0.990 1.034]	0.270	1.014	[0.993 1.035]	0.177

Sex		3.229	[1.554	6.708]	0.002*	2.896	[1.327	6.318]	0.008*
Age 2014		1.015	[0.989	1.043]	0.242	1.012	[0.985	1.041]	0.371
FBG2019	**< 126**	1.009	[0.975	1.045]	0.585	.984	[0.948	1.022]	0.409
FBG2019	**≥ 126**	1.007	[0.995	1.020]	0.239	1.004	[0.992	1.017]	0.433
Sex		3.360	[1.623	6.954]	0.001	2.931	[1.353	6.348]	0.006*
Age 2019		1.008	[0.983	1.035]	0.499	1.009	[0.982	1.036]	0.481
HbA1c2014	**< 6.5**	0.501	[0.217	1.159]	0.107	0.420	[0.173	1.016]	0.034
HbA1c2014	**≥ 6.5**	1.310	[0.803	2.137]	0.278	1.149	[0.733	1.802]	0.944
Sex		3.420	[1.648	7.095]	0.001	3.175	[1.457	6.921]	0.004*
Age 2014		1.015	[0.988	1.042]	0.273	1.011	[0.984	1.040]	0.339
HbA1c 2019	**< 6.5**	0.851	[0.365	1.987]	0.711	0.378	[0.136	1.051]	0.062
HbA1c 2019	**≥ 6.5**	1.318	[0.882	1.969]	0.177	1.014	[0.644	1.597]	0.949
Sex		3.362	[1.619	6.980]	0.001	3.084	[1.423	6.681]	0.004*
Age 2019		1.011	[0.986	1.036]	0.383	1.014	[0.987	1.041]	0.291

Supplementary Table 6. Multiple logistic regression analysis for PHQ-9 Scores and GAD-7 Scores as the outcomes and FBG and HbA1c as main exposure at two study waves 2014 and 2019 adjusting for adjusted for age, sex, educational attainment, body mass index, smoking, and hypertension

Variables		**Depression(yes/no)**				**Anxiety(yes/no)**			
		OR	**Conf. Interval**		**P value**	**OR**	**Conf. Interval**		**P value**
FBG2014	***< 126***	0.959	[0.921	0.998]	0.043*	0.950	[0.910	0.993]	0.024*
FBG2014	***≥126***	1.013	[0.990	1.036]	0.253	1.016	[0.994	1.038]	0.148
Sex		3.109	[1.455	6.642]	0.003*	2.564	[1.148	5.727]	0.022*
Age 2014		1.012	[0.985	1.039]	0.382	1.011	[0.983	1.040]	0.429
Education		0.515	[0.235	1.128]	0.097	0.672	[0.302	1.496]	0.331
BMI		1.018	[0.959	1.080]	0.551	0.965	[0.906	1.028]	0.272
Smoking		1.260	[0.631	2.514]	0.512	0.657	[0.313	1.378]	0.267
Hypertension		1.288	[0.517	3.206]	0.586	1.750	[0.671	4.560]	0.252
FBG2019	***< 126***	0.999	[.963	1.036]	0.967	0.985	[0.947	1.025]	0.472
FBG2019	***≥126***	1.009	[.995	1.023]	0.170	1.005	[0.992	1.018]	0.387
Sex		2.822	[1.330	5.988]	0.007*	2.996	[1.309	6.853]	0.009*
Age 2019		1.008	[0.982	1.036]	0.521	1.002	[0.974	1.031]	0.865
Education		0.395	[0.185	.8446]	0.017*	0.644	[0.298	1.393]	0.264
BMI		1.015	[0.958	1.077]	0.597	0.980	[0.921	1.043]	0.537
Smoking		0.952	[0.482	1.883]	0.890	0.737	[0.358	1.517]	0.408
Hypertension		0.923	[0.438	1.944]	0.834	1.974	[0.910	4.283]	0.085

HbA1c2014	***< 6.5***	0.336	[0.125	0.901]	0.030*	0.385	[0.138	1.072]	0.068
HbA1c2014	***≥6.5***	1.080	[0.642	1.817]	0.770	1.01	[0.626	1.653]	0.946
Sex		3.204	[1.500	6.846]	0.003*	2.838	[1.276	6.312]	0.011*
Age 2014		1.014	[0.986	1.042]	0.323	1.011	[0.983	1.041]	0.449
Education		0.533	[0.244	1.162]	0.114	0.707	[0.321	1.556]	0.389
BMI		1.027	[0.967	1.091]	0.375	0.976	[0.917	1.039]	0.447
Smoking		1.198	[0.602	2.383]	0.605	0.625	[0.301	1.296]	0.207
Hypertension		0.977	[0.401	2.380]	0.959	1.23	[0.496	3.049]	0.656
HbA1c 2019	***< 6.5***	0.659	[0.243	1.788]	0.413	0.314	[0.103	0.952]	0.041*
HbA1c 2019	***≥6.5***	1.375	[0.831	2.273]	0.215	0.994	[0.612	1.617]	0.982
Sex		2.820	[1.329	5.981]	0.007*	2.979	[1.305	6.800]	0.010*
Age 2019		1.011	[0.984	1.038]	0.441	1.008	[0.980	1.037]	0.576
Education		0.42	[0.198	0.892]	0.024	0.671	[0.310	1.453]	0.312
BMI		1.025	[0.966	1.088]	0.419	0.991	[0.931	1.056]	0.784
Smoking		0.921	[0.466	1.823]	0.814	0.715	[0.345	1.480]	0.366
Hypertension		0.914	[0.437	1.913]	0.812	1.895	[0.877	4.098]	0.104

Supplementary Table 7. Multiple logistic regression analysis for PHQ-9 Scores and GAD-7 Scores as the outcomes and FBG and HbA1c as main exposure at two study waves 2014 and 2019 adjusting for sociodemographic, lifestyle, and health indicators.

		Depression(yes/no)				**Anxiety(yes/no)**			
Variables		**OR**	**Conf. Interval**		**P-value**	**OR**	**Conf. Interval**		**P-value**
FBG 2014	< 126	0.953	[0.914	0.995]	0.027*	0.945	[0.902	0.989]	0.015*
FBG 2014	≥126	1.014	[0.991	1.037]	0.234	1.017	[0.995	1.039]	0.136
Age 2014		1.009	[0.980	1.039]	0.553	1.009	[0.979	1.041]	0.544
Sex	Female	2.915	[1.341	6.339]	0.007*	2.368	[1.043	5.374]	0.039*
Education2014	Higher	0.506	[0.225	1.138]	0.099	0.645	[0.282	1.477]	0.299
BMI 2014		1.02	[0.960	1.084]	0.526	0.967	[0.906	1.031]	0.305

Smoking 2014	Smoker	1.392	[0.685	2.829]	0.360	0.694	[0.325	1.481]	0.345
Hypertension 2014	Yes	1.153	[0.435	3.054]	0.775	1.617	[0.578	4.520]	0.360
Family History	Yes	1.008	[0.505	2.012]	0.983	1.141	[0.550	2.367]	0.723
No. Of chronic diseases 2019		1.421	[0.831	2.433]	0.200	1.364	[0.783	2.375]	0.273
Physical activity levels 2019	Moderate	0.733	[0.344	1.563]	0.422	0.933	[0.423	2.055]	0.863
	High	2.095	[0.848	5.179]	0.109	2.195	[0.866	5.567]	0.098
FBG 2019	< 126	1.000	[0.963	1.039]	0.989	0.99	[0.951	1.029]	0.608
FBG 2019	≥126	1.008	[0.994	1.022]	0.284	1.003	[0.989	1.016]	0.694
Sex 2019		2.603	[1.184	5.722]	0.017	2.894	[1.229	6.816]	0.015*
Age	Female	1.004	[0.976	1.032]	0.788	1.002	[0.973	1.032]	0.875
Education 2019	Higher	0.429	[0.196	0.939]	0.034*	0.784	[0.352	1.743]	0.550
BMI 2019		1.017	[0.957	1.080]	0.594	0.982	[0.921	1.045]	0.569
Smoking 2019	Smoker	0.868	[0.429	1.755]	0.693	0.661	[0.313	1.395]	0.278
Hypertension 2019	Yes	0.709	[0.319	1.576]	0.399	1.818	[0.793	4.169]	0.158
FamilyHistory		1.000	[0.496	2.016]	0.999	1.275	[0.606	2.682]	0.522
No. Of chronic diseases 2019	Yes	1.911	[1.172	3.115]	0.009*	1.442	[0.869	2.392]	0.157
Physical activity levels 2019	Moderate	0.67	[0.316	1.421]	0.296	0.424	[0.186	0.967]	0.041*
	High	0.637	[0.205	1.977]	0.435	1.053	[0.361	3.071]	0.924
HbA1c1 2014	< 6.5	0.346	[0.124	0.965]	0.089	0.384	[0.133	1.110]	0.077
HbA1c2 2014	≥6.5	1.092	[0.645	1.851]	0.429	1.006	[0.617	1.642]	0.981
Age 2014		1.010	[0.980	1.041]	0.921	1.008	[0.978	1.040]	0.607
Sex 2014	Female	2.976	[1.376	6.439]	0.000*	2.624	[1.164	5.912]	0.020*
Education	Higher	0.513	[0.230	1.143]	0.063*	0.671	[0.299	1.508]	0.334
BMI 2014		1.027	[0.966	1.092]	0.763	0.975	[0.915	1.040]	0.441
Smoking14	Smoker	1.296	[0.641	2.620]	0.371	0.64	[0.304	1.348]	0.240
Hypertension 2014	Yes	0.835	[0.320	2.183]	0.851	1.09	[0.410	2.897]	0.864
Family History		1.219	[0.610	2.434]	0.793	1.357	[0.661	2.785]	0.406
No. Of chronic diseases 2014	Yes	1.391	[0.814	2.378]	0.030*	1.319	[0.764	2.278]	0.321
Physical activity levels 2014	Moderate	0.792	[0.372	1.683]	0.285	1.014	[0.467	2.201]	0.971
	High	1.992	[0.806	4.924]	0.793	1.93	[0.770	4.835]	0.161
HbA1c1 2019	< 6.5	0.533	[0.177	1.601]	0.262	0.248	[0.072	0.856]	0.027*
HbA1c2 2019	≥6.5	1.323	[0.805	2.174]	0.269	0.892	[0.537	1.483]	0.660
Age 2019		1.006	[0.978	1.034]	0.700	1.009	[0.979	1.039]	0.563
Sex	Female	2.462	[1.111	5.453]	0.026*	2.947	[1.239	7.008]	0.014*
Education	Higher	0.429	[0.196	0.941]	0.035*	0.762	[0.339	1.710]	0.509

BMI19		1.022	[0.961	1.086]	0.488	0.98	[0.918	1.047]	0.554
Smoking2019	Smoker	0.826	[0.405	1.681]	0.597	0.57	[0.262	1.239]	0.156
Hypertension	Yes	0.692	[0.312	1.533]	0.364	1.882	[0.803	4.411]	0.146
No. Of chronic diseases 2019		1.131	[0.563	2.272]	0.730	1.566	[0.731	3.356]	0.248
Family History	Yes	1.902	[1.166	3.104]	0.010*	1.539	[0.916	2.586]	0.104
Physical activity levels 2019	Moderate	0.883	[0.420	1.856]	0.743	0.35	[0.151	0.809]	0.014
	High	0.656	[0.209	2.061]	0.470	0.801	[0.262	2.448]	0.697

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