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The Inflammatory Exposome of Major Depressive Disorder in an Egyptian Sample

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Graduate Studies

The Inflammatory Exposome of Major Depressive Disorder in an Egyptian Sample

A THESIS SUBMITTED BY

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Declaration of Authorship

I, Reem Deif, declare that this thesis titled, "The Exposome of Major Depressive Disorder in an Egyptian Sample" and the work presented in it are my own. I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University.
- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
- I have acknowledged all main sources of help.
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself.

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Abstract

Major depressive disorder (MDD) has been recognized as a global public health concern affecting the lives of 264 million people with increasing prevalence worldwide. Inspired by the exposomic research, this study aims to investigate the dynamic and complex interplay between different demographic, lifestyle, environmental factors and bimolecular factors that are potentially involved in the pathology of MDD in a sample of Egyptian adults living in Cairo. This is in an attempt to acknowledge the biological underpinnings of MDD without underestimating the role of environmental influences. The context of Egypt provides richness to the current study given the national transition from an agricultural society, to a more industrialized one. The sample included 107 adults from both genders between the ages of 18 and 50. Convenience sampling was used to recruit participants from different social and community platforms. Participants were excluded on the basis of having comorbid psychotic or neurodegenerative disorders, terminal conditions and cognitive disabilities that might interfere with their clinical presentation. A comprehensive questionnaire was developed and then refined to collect demographic, psychosocial, lifestyle and environmental data in addition to a mini mental state examination (MMSE). Additionally, the Arabic version of the Beck Depression Inventory-II (BDI-II) was used to assess the severity of depressive symptoms and to generate a symptoms profile. The translated Mini International Neuropsychiatric Interview (MINI 7.0.2) was used to diagnostically differentiate between participants with MDD and healthy controls in addition to identifying cases of past episodes and recurrent episodes of MDD. Participants were also required to give blood samples for the examination of a wide range of biomarkers that are theoretically expected to be linked with MDD. These included EGF, FGF-2, FGF-9, FGF-21, FGF-22, IFN-γ, IGF-1, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, TNF-α , VEGFC, and VEGFD in addition to complete blood parameters. Statistical analysis were conducted including basic descriptive testing, correlational testing and mediation analysis. Results show several significant correlations between different inflammatory and neurotrophic biomarkers. Significant correlations were also established between different

lifestyle factors and MDD outcomes and different biomarkers and MDD outcomes. Some biomarkers (namely, EGF, FGF-2, FGF-21, FGF-9, IGF-1, IL-1β, IL-17, IL-6, TNF-α , VEGFD, WBC, MCH and RBC) showed symptom-specific correlations. More in-depth analysis revealed the mediational effect of a few biomarkers between some risk factors and MDD outcomes. However, some challenges limit the generalizability of the findings including the sample size, the cross-sectional study design and the use of peripheral rather than central biomarkers. In conclusion and despite its limitations, this study offers valuable insights about the complexity of MDD in an Egyptian sample combining psychosocial, environmental and biomolecular data. Such findings highlight the pressing need for a more personalized approach in the study of MDD and other psychiatric disorders. It shows real potential of investing in precision mental health research for the development and enhancement of personalized intervention and prevention strategies.

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Contents

List of Figures/Images/Sound Files

List of Tables

List of Abbreviations

BDI-II	**Beck Depression Inventory-2**
DSM-5	**Diagnostic and Statistical Manual of Mental Disorders-5**
BDNF	**Brain-derived neurotrophic factor**
EGF	**Epidermal growth factor**
FGF-2	**Fibroblast growth factor 2**
FGF-9	**Fibroblast growth factor 9**
FGF-21	**Fibroblast growth factor 21**
FGF-22	**Fibroblast growth factor 22**
HCT	**Hematocrit**
HGB	**Haemoglobin**
ICD	**International Classifications of Diseases**
IFN-γ	**Interferon gamma**
IGF-1	**Insulin-like growth factor 1**
IL-1β	**Interleukin 1**
IL-2	**Interleukin 2**
IL-4	**Interleukin 4**
IL-6	**Interleukin 6**
IL-8	**Interleukin 8**
IL-10	**Interleukin 10**
IL-17	**Interleukin 17**
LYMPH	**Lymphocytes**
MCH	**Mean corpuscular haemoglobin**
MCHC	**Mean corpuscular haemoglobin concentration**
MCV	**Mean corpuscular volume**
MDD	**Major Depressive Disorder**
mhGAP	**WHO's mental health Gap Action Programme**
MINI	**Mini International Neuropsychiatric Interview**
MMSE	**Mini Mental State Examination**
MXD	**Mixed cell count**
NEUT	**Neutrophils**
PLT	**Platelets**
PUFAs	**Omega-3 polyunsaturated fatty acids**
RBC	**Red blood cells**
TNF-α	**Tumor necrosis factor alpha**
VEGFC	**Vascular endothelial growth factor C**
VEGFD	**Vascular endothelial growth factor D**
WBC	**White blood cells**
WHO	**World Health Organization**

List of Symbols

α	alpha
β	beta
γ	gamma

Chapter 1

Introduction

1.1 Background

Depression, clinically recognized as major depressive disorder (MDD), stands as a major health concern affecting the lives of more than 264 million people worldwide and contributing significantly to the disability and global burden of disease. With a rapidly increasing prevalence, it has become one of the priorities covered by WHO's mental health Gap Action Programme (mhGAP) and a call has been made for "a comprehensive, coordinated response to mental disorders at the country level" in the 2013 World Health Assembly resolution (World Health Organization, 2020). By the year 2030, epidemiological projections expect depression to be the third highest cause of disease burden in low-income countries and the second highest in middle-income countries (Mathers & Loncar, 2006). Within the context of Egypt, and according to the most recent National Survey for Mental Health surveying a total of 22,000 households representative of each governorate, prevalence of mood disorders was estimated to be 3.1% and MDD was the most prevalent disorder accounting for 41% of all psychiatric conditions making it in itself a public health concern (General Secretariat of Mental Health & Addiction Treatment, 2017). Unlike global epidemiological trends showing a rapid increase in the prevalence of most psychiatric disorders, there has been a significant decline in the prevalence of mood disorders compared to findings from the 2009 National Survey of Prevalence of Mental Disorders in Egypt, which estimated the prevalence to be 6.43% (Ghanem et al., 2009). However, such a variation should be approached with caution given the differences in the methodological complexity and the sample size (14,640 individuals in 2009 as opposed to 22,000 households in 2017) giving more credibility to the 2017 findings.

Given the polythetic nature of most psychiatric disorders, including MDD, meaning that diagnosed patients may have both similar and different symptoms of the same disorder (Olbert et al., 2014), different clusters of depressive symptoms should be considered in light of

the current study instead of merely differentiating between patients with MDD versus healthy controls. This is also due to the clinical inaccuracy of labelling someone as overall "healthy". Generally speaking, symptoms of depression may manifest affectively/emotionally, cognitively, behaviorally, and/or somatically, and exploring different subtypes of depression has been an appealing area of inquiry for many researchers and clinicians to better understand the etiology and clinical presentation of depression. Affective symptoms include mood disturbances such as feelings of sadness, apathy, loss of pleasure, loss of interest, anxiety, crying, and guilt (Beck et al., 1979). Previously referred to as pseudo-dementia (Kiloh, 1961), cognitive symptoms of depression include poor attention and concentration, language difficulties, and decision-making difficulties (Fehnel et al., 2013). Behavioral symptoms may include social withdrawal, substance use, and impulsivity (US National Institute of Mental Health, 2023). Finally, somatic symptoms of depression include sleep problems, appetite disturbance, fatigue and poor energy (Kapfhammer, 2006).

Different theories have attempted to conceptualize depression from different biopsychosocial perspectives. Extensive research has been conducted on the genetic determinants of depression, including twin studies and gene knockouts, but much less on the gene-environment interaction that is potentially involved in its pathology (Dunn et al., 2015). In 1973, the concept "endophenotype" was proposed by Gottesman and Shields in an attempt to link different psychiatric symptoms (i.e.: affective, cognitive, behavioral) with specific genetically-determined phenotypes. The more modern idea of "neuropattern" was then introduced and showed relevant success in clinical outcomes of MDD including better diagnosis and the provision of treatment based on the neuropattern of patients (Bergemann et al., 2019). Additionally, some genes have been shown to underlie the pathology of depressive symptoms through the up regulation of the hypothalamic-pituitary-adrenal (HPA) axis as a form of cortical dysfunction (Gandal et al., 2018).

To further understand the biological underpinnings of depression in a more precise way, research has made substantial efforts in examining the neural circuits associated with the manifes-

tation of different affective states. The beginnings included hypotheses about the role of several disruptions in the reward system circuits in predicting the severity of depressive symptoms and cognitive deficits in patients in MDD. (Gong et al., 2017). Another more sophisticated approach involved the identification of specific biotypes of depression arguing for the inclusion of several, rather than single, pathological mechanisms. Some biotypes that have been examined include rumination, anxious avoidance, negative bias, threat dysregulation, anhedonia, context insensitivity, inattention and cognitive dyscontrol. Such biotypes are not only hypothesized to differ pathologically, but also in terms of targeted treatments that are proved to be effective with each of these biotypes (Williams, 2016).

As much as the manifestations of MDD is heterogeneous in terms of clinical symptoms, their association with certain neurobiological factors is also highly diverse (Milaneschi et al., 2020). In this regard, the reliance on the categorical diagnosis of depression rather than the clinical presentation of depression may underestimate the findings. Instead, the adoption of network analyses to better understand the link between various neurobiological factors, including inflammatory proteins, and depression has been recommended towards a more personalized approach of mental health through personalized treatment selection models (Cohen & DeRubeis, 2018).

But despite all advances, the attempts of translational research have not succeeded in establishing objective laboratory measures to diagnose MDD or identify at-risk individuals yet (Daria et al., 2020). The examination of the impact of different exposures on the development of depressive symptoms, on the other hand, has received comparatively less attention. In this regard, there exists a need for a better understanding of the roles of different exposures, whether environmental or psychosocial. Such knowledge is crucial for demonstrating these factors as "modifiable" risk factors and trying to incorporate them into evidence-based interventions. This is based on the assumption that the accurate identification of modifiable risk factors may improve mental health outcomes on different levels (Guloksuz et al., 2018).

Following a long history of stigma, mental health has finally been recognized as a global health concern, thanks to the everyday advancements in research, documentation and practice that are showing the high disease and disability burdens of various mental health problems. In clinical settings, current evidence contradicts the notion of "the typical patient in need of the one-size-fits-all treatment". This underscores the pressing need for more personalized approaches to treatment that deal with individuals as whole, with all their complex dynamics, rather than symptoms and diagnoses. In other words, this created a major paradigm shift towards *precision mental health.* According to Bickman, Lyon, & Wolpert (2016), *precision mental health* is conceptually defined as a data-driven approach that identifies the needs, preferences and prognosis of an individual based on evidence generated from continuous assessment, monitoring and feedback. This approach ultimately aims to deliver specially-tailored prevention and intervention mental health strategies to the at-risk individuals. Precision psychiatry is a field that is concerned with addressing such issues through a focus on enhancing prevention, diagnosis, and treatment of psychiatric disorders through identifying clinical subgroups in relation to specific disorders, identifying subgroups that may benefit from specific interventions, assessing the effectiveness of different interventions with different subgroups, and identifying risk and protective factors for remission, relapse and vulnerability (Fernandes et al., 2017). The precision approach is supported by the recommendations of the former director of the National Institute of Mental Health who called for an integrative approach for managing biopsychosocial data in relation to risk and vulnerability of individuals (Insel, 2015). One pivotal area that contributes to the continued development of precision mental health is research in the exposome of psychiatric disorders in an attempt to unravel the link between environmental exposure and disease outcomes dissecting mechanisms mediating between them.

1.2 Defining the Exposome

Conceptually, the exposome comprises both internal and external factors that an organism is exposed to at every level starting from the cell level till the larger macrosystem throughout the lifetime. The internal exposome includes elements such as body composition, metabolism, hor-

mones, oxidative stress, ….etc. The external exposome, on the other hand, comprises all environmental factors that might have an influence on an organisms' functioning such as pollution, radiation, infections, and lifestyle behaviors. On a broader scale, the exposome also includes the political, socioeconomic and psychological factors surrounding an individual and influencing him/her from a systems perspective. Put together, these domains give a holistic portrayal of the exposome (Wild, 2012).

Different methodological approaches can be employed to study the exposome of different health outcomes. For example, blood samples can be used to generate data on metabolomics and genomics, environmental assessments offer an image about levels of exposure to toxicants and other chemicals, and questionnaires and self-reports give information about personal and lifestyle factors. However, a multi-omics approach that integrates different domains of the exposome remains the best approach to be adopted in exposomic studies, while still acknowledging the practical limitation of any methodology of not being able to fully encompass the whole exposome with all its complexities across the lifespan.

It is also important to reflect on the dynamic nature of the exposome, not only in terms of changing locations, but also in terms of temporal variation. In other words, the same individual has different exposures at different points of time. This means that, although not methodologically practical, a study of lifetime exposures requires either sequential assessments of cross-sectional exposures across the lifespan of an individual (Wild, 2012) or a continuous, longitudinal study design.

1.3 Research on the Internal Exposome of Depression

Below are some findings derived from research investigating the internal factors linked with depression in light of two conceptualizations of depression; namely, the inflammation hypothesis and the neurotrophic hypothesis.

Inflammation: From an inflammatory perspective, depression can be formulated as a pro-inflammatory condition marked by changes in levels of various inflammatory biomarkers (Dinan, 2009). Similarly, models of immune activation has shown to be able to induce depressive

symptoms (Clarke et al, 2009) and, therefore, the idea of "cytokine-association depression" has been studied (Lotrich, 2015). Additionally, some reviews suggest a link between depression and inflammation based on a symptom-specific pattern. For example, one review of 21 studies reported an association between inflammation with only somatic symptoms of depression (Majd, Saunders, & Engeland, 2020). Such findings supports the hypothesis of symptom-specificity of inflammation in depression (Milaneschi et al., 2021).

To add more complexity, research supports the influence of psychosocial stressors on different biological and physiological processes such as inflammation. For instance, one meta-analysis demonstrated a link between social isolation and increased inflammation suggesting social isolation as a stressor affecting immune functioning (Smith et al., 2020). This underscores the need to not only study the biological underpinnings of disease outcomes, but also the interaction between environmental and biological factors. More specific literature is presented below regarding biomarkers that are examined in this study:

Interleukin 1 Beta (IL-1β): Mixed results have been found with regards to IL-1β including case control studies that found no significant association between the severity of depression and IL-1β (Nahar et al., 2023). On the other hand, one meta-analysis demonstrated that IL-1β was significantly higher in elderly depressed patients (Ng, 2018).

Interleukin 2 (IL-2): IL-2 has shown to reduce depression-like behaviors and normalize neurotransmitter levels in an animal model (Huang et al, 2022). In humans, one study demonstrated the up-regulation of IL-2 receptors in patients with MDD compared to healthy controls (Maes et al., 1990). A more recent research suggested a link between low baseline levels of IL-2 and remission following treatment (Atake, et al., 2022). Contrary to such findings, another study demonstrated an increase in levels of IL-2 following treatment suggesting the protective rather than the pathological influence of IL-2 in relation to MDD (Wang et al., 2022).

Interleukin 4 (IL-4): IL-4 has shown to be able to decrease depressive-like behaviors though the regulation of neurotransmission and the inhibition of IL-1β-induced neural changes (Park et al.,

2015). Similar results were demonstrated in another animal model suggesting IL-4 as a regulator of depressive-like behaviors (Wachholz et al., 2017). In addition to this, IL-4 showed an increase following treatment in patients with MDD (Oktenli et al., 2008) and, interestingly, demonstrated specificity in differentiating between patients with MDD and patients with bipolar depression (Lu et al., 2023). As having promising treatment potential, intranasal administration of IL-4 in mice with depressive-like symptoms supported its antidepressant-like effects through the modulation of both neuroinflammation and oxidative stress (Smaniotto et al., 2023). One explanation of the regulatory function of IL-4 might be the mechanism of action by which it stimulates brain-derived neurotrophic factor (BDNF)-dependent neurogenesis in response to chronic stress in specific brain areas and therefore, reducing the risk of depressive-like symptoms (Zhang et al., 2021).

Interleukin 6 (IL-6): One large meta-analysis suggested a statistically significant link between an increase in levels of IL-6 and the diagnosis of depression (Osimo et al, 2020). It has shown to have protective properties against neuronal anomalies, especially in the CA1 hippocampal region, linked with depression in an animal model. This has been demonstrated through its role in suppressing oxidative stress and neuronal death (Wang et al., 2019). Such findings support the idea that depression is pathologically marked by neuronal injury and neuronal death in some specific brain regions (Dean & Keshavan, 2017). On the other hand, levels of expression of IL-6 have shown to increase by the action of antidepressants (Wang et al., 2019), and one meta-analysis was able to demonstrate a negative correlation between levels of IL-6 and depressive symptoms following antidepressant treatment (Hiles et al., 2012). However, contradicting findings regarding IL-6 have been demonstrated in other studies suggesting a link between up regulation of serum IL-6 and depression (Maes et al., 2014, Lotrich, 2015) and between higher levels of IL-6 and both the chronicity and severity of depressive symptoms (Lamers et al., 2019). In one study of patients with depression, IL-6 did not have an association with the categorical diagnosis of MDD; however, it showed a significant positive correlation with the somatic and cognitive

symptoms of depression including poor appetite, sleep problems, and mood problems (Manfro et al., 2022).

Interleukin 8 (IL-8): In one randomized controlled trial, IL-8 has been suggested as having a protective role in depression reducing the risk of inflammation-associated depressive mood (Kruse et al., 2022) and lowering the severity of depressive symptoms (Kruse et al., 2021). As a predictor of treatment response, research also suggests that IL-8 shows a significant decrease in response to antidepressant treatment in case of positive response to treatment, unlike cases of no response to treatment where no significant change in IL-8 is noted (Guan et al., 2022).

Interleukin 10 (IL-10): Research shows that a decrease in IL-10 marks the onset and the increase of symptoms of depressive symptoms (Oglodek, 2022). This finding is confirmed by another study showing significantly lower levels of IL-10 in patients with a faster onset of depressive symptoms (Buspavanich et al., 2021). Therapeutically, the administration of antidepressants has shown to have the potential of increasing levels of IL-10 (Kubera et al., 2001; Lee et al., 2020). On the other hand, one meta-analysis failed to establish a link between IL-10 and depression compared to other biomarkers (Dowlati et al., 2010). This indicates the presence of contradicting findings on this biomarkers, like others, where there is still a lack of substantial research .

Interleukin 17 (IL-17): In animal models, IL-17 has shown to induce depressive-like behaviors (Nadeem et al., 2017). Similarly, patients with depression have more serum IL-17 than healthy controls (Davami et al., 2016). Such findings have been demonstrated in specific clinical populations such as postpartum mothers suggesting a positive correlation between IL-17 and the risk of postpartum depression (Min et al., 2022). High levels of IL-17 were also correlated with poor response to antidepressant treatment (Nothdurfer et al., 2021).

Tumor necrosis factor alpha (TNFα): One large meta-analysis suggested a statistically significant link between an increase in levels of TNFα and the diagnosis of depression (Dowlati et atl., 2010; Osimo et al, 2020) and its severity (Das et al., 2021). As a predictor of treatment response,

research also suggests that elevated baseline levels of TNF-α are associated with poor treatment outcomes (Benedetti et al., 2021).

Interferon-Gamma (IFN-γ): IFN-γ has shown to be negatively correlated with depression (Daria et al., 2020). On the other hand, high levels of IFN-γ were reported in cases of post-COVID depression (Lorkiewicz & Waszkiewicz, 2021). In terms of treatment response studies, research shows a significant link between high levels of baseline IFN-γ before treatment and poor treatment outcomes (Husain et al., 2023).

Growth factors: An alternative hypothesis of depression has been proposed building on the neurotrophic hypothesis which conceptualizes depression in terms of pathological alternations of growth factor proteins. What is significant about growth factors is that they are involved in both healthy biological processes including healing and abnormal processes including cancer (Stone et al., 2023).

Epidermal growth factor (EGF): A significant disease-dependent increase in EGF has been demonstrated in MDD in a 2-year follow-up study of adolescents and young adults (Skibinska et al., 2021). Another study was able to show decreased levels of EGF following mindfulness and cognitive-behavioral therapy as psychotherapeutic interventions and that it was associated to response to treatment (Memon et al., 2017). Contrary to such findings, low levels of EGF have been observed in patients with MDD compared to healthy controls in other studies (Sohan et al., 2023; Tian et al., 2012).

Vascular endothelial growth factors C and D (VEGFC; VEGFD): One study aimed to examine the role of growth factor proteins in inpatients with treatment-resistant depression specifically (Pisoni, 2018). Blood analysis was done to compare between patients and healthy controls examining serum biomarkers and patients were assessed at admission and discharge following inpatient treatment. Findings suggested that, compared to healthy controls, patients had lower serum levels of BDNF and VEGFC. Additionally, and compared to patients who showed im-

provements in symptomatology, higher levels of VEGFD and lower levels of VEGFC predicted treatment resistance in non-responders.

Insulin-like growth factor 1 (IGF-1): Given its high levels in depressed patients than healthy controls as shown in some meta-analyses, IGF-1 has been suggested as a clinical biomarker for depression (Chen et al., 2020; Tu et al., 2016) and also as having antidepressant-like effects (Duman et al., 2009). High levels of IGF-1 in depressed patients has been shown to be responsible for the link between depression and cognition specifically (Ali et al., 2020, Tu et al., 2016) and another study demonstrated a significant correlation between IGF-1 levels and the pathogenesis of hypothymia, anxiety, and cognitive disturbances (Levada et al., 2020). Such links are explained in terms of the effect of IGF-1 on the hypothalamus-pituitary-adrenal axis and, therefore, the underlying pathophysiology of MDD (Weber-Hamann et al., 2009). This is because it affects essential neural processes such as synaptic plasticity and neurogenesis (Szczęsny et al., 2013).

Fibroblast growth factor 2 (FGF-2): In animal models of depression, FGF-2 has shown to be down regulated (Ji et al., 2014) and to be upregulated following treatment (Maragnoli et al., 2004). Similarly, serum levels of FGF-2 (He et al., 2014) and postmortem examination of brains of patients with MDD revealed low levels of expression (Evans et al., 2004). On the other hand, in one meta-analysis, peripheral FGF-2, rather than central, was significantly linked with depression (Wu et al., 2016). Another study demonstrated an increase in FGF-2 in patients with MDD (Nobis et al., 2020).

Fibroblast growth factor 9 (FGF-9): FGF-9 has been shown to be a modulator of negative affect that is significantly linked with higher incidence of depression (Aurback et al., 2015). In one study of postmortem brains, levels of FGF-9 showed significant up regulation in patients with MDD (Evans et al., 2004).

Fibroblast growth factor 21 (FGF-21): FGF-21 has shown to be inversely correlated with depressive severity, but only in males (Liu et al., 2017). This has been confirmed by another animal model illustrating the effect of FGF-21 on inhibiting the inflammatory pathway and therefore reducing depressive-like symptoms (Wang et al., 2020). In another study, the opposite was found suggesting higher levels of FGF-21 in patients with MDD than healthy controls (Mason et al., 2022).

Fibroblast growth factor 22 (FGF-22): FGF-22 is inversely correlated with depression and has shown to increase in response to treatment (Xu et al., 2017). In animal models, FGF-22-knockout mice displayed depressive-like behaviors (Williams et al., 2016).

Besides the inflammation and the neurotrophic hypotheses, other findings have been reported in research, yet receiving less scholarly attention. These are summarized below.

Iron status: In one study of children with transfusion-dependent thalassemia and comorbid depression, results showed an association between iron overload and consequent inflammation and the development of depressive symptoms. The blood biomarkers measured included iron, ferritin, and transferrin saturation percentage (Al-Hakeim et al., 2020).

Prenatal development: Highlighting the significance of prenatal exposure, a study by Conradt and colleagues (2013) showed that infants born to mothers who experienced depression during pregnancy had higher levels of methylation of placental *NR3C1*, and, on the behavioral and physical levels, poorer self-regulation, more hypotonia, and more lethargy than infants whose mothers were not depressed. Interestingly, poor prenatal material diet has also been identified as a child mental health risk factor (Jacka et al., 2013; Steenweg-de Graaff et al., 2014). More specifically, low maternal vitamin D has been linked with more mental health problems in later life (Lisi et al., 2020).

This sets the stage for exploring the potentially protective role of breastfeeding in relation to later emotional problems. Breastfeeding for 6 months or more, as an early life exposure, has been

shown to buffer the risk of severe depressive symptoms in young adults; however the effect size over MDD was small (de Mola et al., 2016). This is confirmed by another retrospective analysis showing an association between not being breastfed and subsequent major depression (Peus et al., 2012) and higher childhood resilience against psychosocial stressors among those who were breastfed (Montgomery et al., 2006). Similar results have been demonstrated in a large prospective study of 4,502 adolescents showing the protective role of breastfeeding for at least 4 months in different emotional and behavioral problems later in adolescence (Hayatbakhsh et al., 2012). This link, although controversial, has been suggested to be mediated by the C/C genotype of the estrogen receptor 1 gene (Merjonen et al., 2010).

Metabolomics: A recent review of studies on metabolimcs in mood disorders provides an overview of the potential of metabolomics in examining biomarkers in mental illnesses (Padrini et al., 2019). Nuclear magnetic resonance and mass spectrometry, as valid analytical techniques, have been used in researching the metabolomics of mental illness in MDD and, in one study, it has been demonstrated that 14 and 22 differential metabolites could respectively differentiate between moderate and severe cases from healthy controls (Chen et al., 2017). Additionally, preliminary research has shown that glucose pathways can be used as diagnostic predictors in depression (Zheng et al., 2017) and another study was able to utilize metabolism profiles as predictors of specific symptoms (Setoyama et al., 2016).

1.4 Research on the External Exposome of Depression

Nutrition and gut microbiota: Although no causal links have been demonstrated (Firth et al., 2020), recent research has expanded its scope beyond the idea of healthy diets to explore the links between nutrition and psychological well-being. Nutritional psychiatry, as an evolving field based on the established connections between nutrition and mental health outcomes, has now introduced new evidence giving hope for nutrition-based therapies (Sarris et al., 2015) to be used as adjunct interventions in the management of mental health problems (Sarris et al., 2010). The substantial overlap between eating problems and depression and their comorbidity can be, at least partially, explained in terms of the common neurotransmitters that are hypothesized to

be involved in the pathways of both as serotonin (Bremner et al., 2020). Additionally, the dynamic interplay between both creates a vicious cycle that can hardly be resolved. For example, while depression is itself a risk factor for metabolic problems (Crichton et al., 2016) and GIT problems (Dinan & Quigley, 2011), the consumption of diets high in processed carbohydrates, fats, and sugars has shown to increase the risk of depression (Altun et al., 2019; Firth et al., 2020).

Given their antioxidant activity, different micronutrients are believed to impact brain health both structurally and functionally (Bourre, 2006). For example, research into vitamin B complex supplementation has shown promising potential in alleviating depressive symptoms (Lewis et al., 2013) and, besides folic acid, has shown to have the potential of decreasing the risk of onset in the first place (Reynolds, 2002). However, it has to be noted that such findings are still emerging in their very early stages, with other studies suggesting no effects of vitamin supplementation on depressive symptoms (Long & Benton, 2013). More extensive research has been done on Omega-3 polyunsaturated fatty acids (PUFAs) and depression with several randomized controlled trials showing their potential in alleviating symptoms of depression (Lespérance et al. 2011; Liao et al. 2019; Luo et al. 2020; Zhang et al., 2020a, b). Unlike the public beliefs in vitamin D, its evidence-based role is still controversial with mixed findings. Some support its potential in reducing inflammatory biomarkers (Jamilian et al., 2019) demonstrating the link between vitamin D deficiency and the risk of depression (Anglin et al., 2013), and the effectiveness of vitamin D supplementation (Cheng et al, 2020). On the other hand, other studies failed to show any significant effect of vitamin D on the reducing risk of depression (Gowda et al., 2015; Okereke et al., 2020; Parker et al.., 2017).

While the effectiveness of different micronutrients in alleviating depressive symptoms is still a subject of ongoing research with mixed and contradicting results, broader dietary styles have been proposed for their mental health benefits and, particularly, the Mediterranean diet stands out. The Mediterranean diet, characterized by its high content of fibers, fish, nuts, healthy oils and low content of meats, carbohydrates, and trans fats has been nominated as the model in re-

lation to lowering risks of depression (Huang et al., 2019) for its antioxidant and anti-inflammatory effects (Milaneschi et al., 2011). Interestingly, it has not only been linked with fewer depressive symptoms (Altun et al., 2019; Parletta et al., 2019; Skarupski et al., 2013), but also lower levels of IL-6 (Milaneschi et al., 2011).

It is also crucial here to consider the role of the gut microbioata in the pathology of depression. Recent research shows that high levels of Enterobacteriaceae and Alistipes and reduced levels of Faecalibacterium are associated with MDD and Faecalibacterium is inversely correlated with symptomatic severity (Jiang et al, 2015). However, the therapeutic potential of probiotics has not been definitively established yet (Ng et al., 2018; Nguyen et al., 2021) with a few studies demonstrating contrary findings (Amirani et al., 2020). Moving to probiotics, or "psychobiotics" for their potential mental health benefits, these have been conceptualized as mediators between nutrition and mental health (Sarkar et al., 2016) through their regulation of the HPA (Sudo et al., 2004) and reduction of inflammatory responses (Desbonnet al., 2010).

Lifestyle and psychosocial stressors: Despite the phenotypic heterogeneity, one paper aimed to provide a review of different environmental models of depression in animal models. Several factors have been identified including, intergenerational and transgenerational transmission of depressive-like traits, early life stress, social transmission of stress, poor environmental enrichment, social instability and chronic social defeat stress (Gururajan et al., 2019). As a major vulnerability factor, different forms of abuse have been significantly linked with long-term negative physical and mental health outcomes including depression (Radell et al., 2021). The epigenetic molecular mechanism of action by which this happen has been proposed in an animal model showing the effects of early maltreatment on inducing methylation changes in the BDNF DNA and therefore, the gene expression (Roth et al, 2009).

In humans, another exposure-wide study of the modifiable factors related to depression has suggested sleep, media, dietary, and exercise-related domains to be prospectively associated with depression. Additionally, a subset of factors was supported by Mendelian randomization evidence, including confiding in others, television watching time, and daytime napping to be

linked with a reduced risk of depression (Choi et al., 2020). Mindfulness-based practices have also gained recognition as effective adjunctive treatments for depression given its protective benefits in relation to depression (Saeed et al., 2019). This link might be mediated by reductions in rumination and promotion of mindful acceptance (La Rocque et al., 2021).

Among different lifestyle behaviors that are shown to be risk factors for depression, many are also reinforced by depression creating a vicious cycle. In this regard and although no causal relationships have been proved, lifestyle factors can be conceptualized both as effectors and by-products of depression. For example, a sedentary lifestyle is a risk factor for depression (Huang et al., 2020), but on the other hand, individuals with depression are more likely to engage in low or no physical activity. Similar patterns can be observed in eating behaviors, social engagement, smoking, internet use and other daily life habits.

Use of technology: Technology cannot be regarded as an inherent risk factor for depression, but it can still impact the "depressed" lifestyle that is worth investigating. In the Digital Exposome project, for example, which aimed to examine the health implications of using internet and digital technology, researchers were interested in studying depression and other mental problems associated such technological advances. Findings from many studies supported the widely-acknowledged claim that the use of technology and social media may be associated with higher rates of depression, particularly among adolescents and young adults (See Lauckner, Hill & Ingram, 2020; Twenge, 2020). On the other hand, it is noteworthy that digital exposures have also been utilized in different therapeutic applications to provide computer-based therapies (Martin-Sanchez et al., 2020). Similarly, one study suggested the effectiveness of virtual reality immersion focused on mindfulness meditation in improving symptoms of stress, depression and anxiety (Hoch et al., 2012).

Physical environmental quality: In terms of physical environmental exposures, one large exploratory analysis of the American population demonstrates a 6% increase in the prevalence of MDDs in areas with the worst air quality in addition to an increase associated with population density and urbanicity (Khan et al., 2019). Environmental noise has also been

shown as risk factor for depression through inducing the release of stress hormones and inflammatory signaling molecules. Stress hormones, specifically, regulate serotonin that is directly involved in the pathology of depression, which may at least partially explain the mediation between noise and depression (Daiber et al., 2019). On the other hand, green space exposure has been shown to predict a lower risk of depression as suggested by one meta-analysis. Although such link is not fully understood yet, it could be attributed to improved air quality and the promotion of physical health (Liu et al., 2023).

Infection: Brucellosis is one example of an infective agent that is hypothesized to induce depressive symptoms as suggested by neuropsychiatric evaluation of patients with brucellosis showing an incidence of 30% regardless of the involvement of the central nervous system (Shehata et al, 2010). Other examples of viral infections includes SARS-CoV-2, BoDV-1, ZIKV, HIV, and HHV6 and this link has been explained in terms of their effects on the glial cells which are also involved in the pathology of depression (Yu et al., 2023).

1.5 Research Significance

Inspired by the EXPOsOMICs project which aims to scrutinize the external and internal exposome at critical developmental points to better understand the means by which different environmental exposures can influence a specific health outcome, we propose a pilot exposome study of MDD in a sample of Egyptian adults. As a low-income country with more than 100 millions inhabitants that is rapidly transitioning from an agricultural to a more industrial society, the Egyptian population is encountering a wide range of changing exposures on different ecological levels. This study presents a unique opportunity to evaluate the risk of depression related to environmental and socio-demographic factors and, unlike prior environmental exposure studies focusing on specific risk factors, it attempts to provide a more complex and comprehensive model of exposure through the examination of the potential mediation of inflammatory and neurotrophic factors. This is essential given the high interdependence between different exposures when it comes to mental health outcomes (Guloksuz et al., 2018).

In addition to the various challenges in mental health care in Egypt, there is a need for more well-established epidemiological studies offering national data on the current mental health status, "considering the geographical distribution of psychiatric morbidity" to facilitate effective, evidence-based planning for mental health services. Additionally, the prevalence of different psychiatric disorders has shown to have a geographic pattern across Egypt as per the latest National Survey of Mental Health (General Secretariat of Mental Health & Addiction Treatment, 2017) which may be explained in terms of differences in individual, social, cultural and environmental influences. But, instead of aiming for "accessible mental health services" as in the National Survey of Mental Health, the scope of this paper is to expand this vision to include "*personalized*, accessible mental health services". Besides the increasing global depression trends in terms of prevalence and incidence, researching depression in Egypt in 2023 is crucial for other reasons including the recent economic challenges and the COVID-19 aftermath which both might exacerbate the psychological stressors a typical Egyptian citizen is dealing with on a daily basis.

Between 2009 and 2018, it was estimated that research from the Arab region collectively contributed to only 1% of mental health research publications globally (Zeinoun et al., 2020). Similarly, another review estimated the contribution of Arab researchers to peer-reviewed literature on mental health of university students specifically, as the most studied population, to be 5.6% of the global research output. Within this percentage, only 19.7% of research was conducted on depression (Sweileh, 2021). Despite this, both bibliometric analyses noted a significant growth in the amount of publications in recent decades, surpassing growth rates in other parts of the world. However, there remains a pressing need for more serious investments in national mental health research in order to develop robust local research and clinical references for different diseases. In this regard, this study also attempts to bridge the current research gap by evaluating the risk of depression in the environmental and socio-demographic context of Egypt.

1.6 Research Aims and Hypothesis

A systems approach is needed to unravel the multiple brain-body interactions in brain diseases. To expand beyond clinical studies in diverse populations for lifestyles, socioeconomic status (SES), and gender differences, we propose an exposome wide association study (ExWAS) of MDD in Egypt. Specific aims include the following:

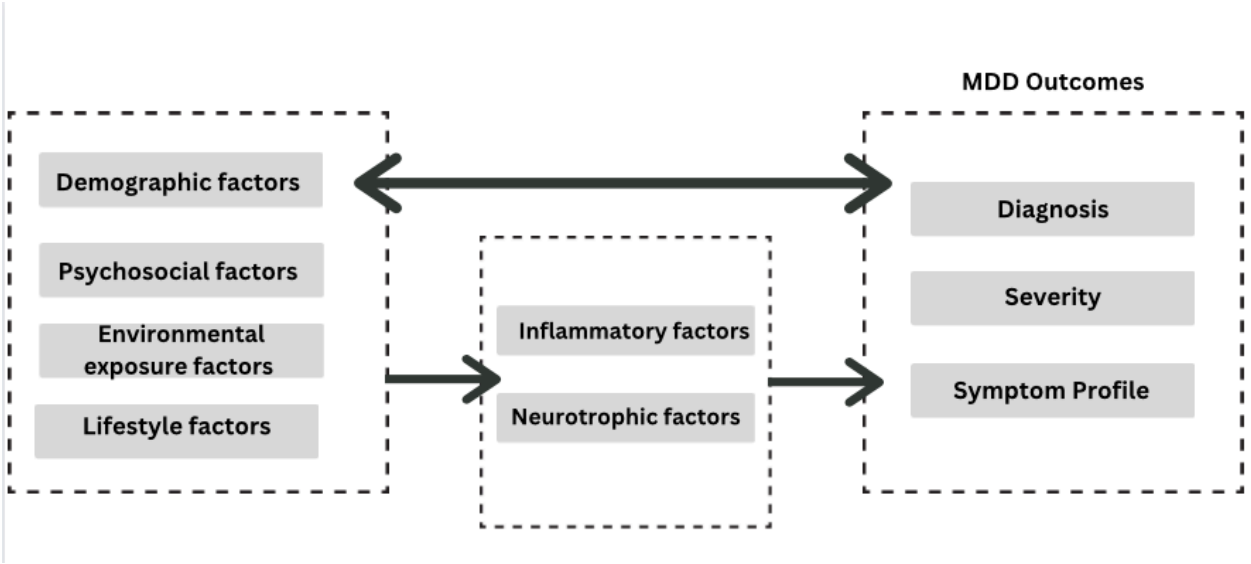
Aim 1: Identify exposomics and multi-omics datasets to enable accurate investigations of environmental contributions to MDD in Egypt.

Aim 2: Investigate the associations between individual environmental exposures and internal body responses, through the examination of appropriate biomarkers.

Aim 3: Conduct an exposome-wide association study (ExWAS) on the risks of depression by simultaneously analyzing the roles and relationships of multiple environmental exposures and lifestyle factors, and linking them with MDD outcomes (diagnosis, severity, symptom profile).

Hence, it is hypothesized that the impact of lifestyle factors on MDD outcomes may be mediated by inflammatory and/or neurotrophic biomarkers. Furthermore, the nature of this mediation may vary according to the symptom profile manifested, distinguishing between cognitive-affective and somatic symptom profiles. This shall support the assumption of symptom-specificity of the neurobiological networks association with different subtypes of MDD. The conceptual framework is illustrated in figure 1.

Figure 1: The conceptual framework illustrating key components and relationships under investigation in the current study



Chapter 2

Materials and Methods

2.1 Sampling

Initially targeting a community sample, rather than a clinical sample, of Egyptian adults between 18 and 60 years of age living in Cairo, the recruitment ads attracted participants between 18-58 years of both sexes living in Cairo who were recruited through social media platforms, word of mouth and referrals from current participants, in addition to the American University in Cairo student, faculty and staff bodies. As the capital of Egypt, Cairo was selected as the focal point for data collection due to its distinctive characteristics, notably its high levels of congestion and pollution. Participants were excluded in case of being diagnosed with comorbid psychotic and/or neurodegenerative disorder. Other exclusion criteria included having terminal illness, life-threatening medical disorders (i.e.: AIDS, cancer), or significant cognitive disability that might become evident in the mini-mental state examination (M-MSE) impairing an individual's ability to give consent and participate or interfering with their overall clinical presentation.

Targeted convenience sampling was used over a 6 month-period to recruit people diagnosed with MDD, people self-identifying as depressed and healthy controls. Although it has its own limitations increasing the risk of different types of bias, this sampling approach is appropriate given that accessibility to the population has been a priority to increase the sample size.

The following power calculation was conducted: Two independent samples, individuals with MDD and healthy controls, were used to compare between biomarker levels and exposure. A medium effect size was expected (Cohen's d = 0.5) with alpha set at 0.05 (Type 1 error), power set at 0.80 (type II error) and SD of 10 for both groups. Ideally, following the formula below, this gives an expected sample size of 62.79 participants in each group, so an approximate total of 124 participants. To facilitate the recruitment process given time and budget constraints, 124 partici-

pants were first recruited and then assessed and classified into the MDD and healthy control groups.

2.2 Measures

$$n = \left(\frac{(Z_{\alpha/2}+Z_{\beta})^2 \times (SD_1^2+SD_2^2)}{\delta^2} \right)$$

The principal investigator, as a qualified practicing psychotherapist, developed a comprehensive semi-structured questionnaire encompassing demographic, psychosocial, environmental, and lifestyle factors based on the literature review of the exposome of depression (See appendix 2). The structure of the questionnaire was designed strategically with special attention to the order of items. Sensitive items, such as exposure to abuse, income, use of drugs and sexual activity, which might have the potential of triggering distress or emotional discomfort were placed towards the end of the questionnaire. This is based on the assumption that participants would normally feel more comfortable gradually and, hence, they should be given the time they need to have a sense of ease with the interviewer without compromising their honesty in answering those questions.

Subsequently, a psychotherapist with a MSc degree in clinical psychology conducted a thorough review for editing purposes to add a layer of clinical relevance ensuring that the questions are accurately worded, appropriate, and culturally-sensitive. It was then reviewed and proofread by a psychometrics translator with a MA in Counseling Psychology. A pilot phase was done with 10 participants to assess the validity of the test, fine tune the wording of the questions, ensure clarity, and identify any technical issues including difficulty levels of the questions. It also gave an indication of the response rates and patterns to project some insights about the feasibility of the actual study and the expected level of engagement of participants. The questionnaire then underwent refinement based on the insights gained from the pilot phase and the final version included the following:

The demographic features included; sex; gender; marital status; location of residence; location of work/school; number of children; household size; educational attainment; and employment.

The health-related features included; pregnancy and delivery history; postnatal history of breastfeeding and formula feeding; weight; height; chronic diseases; communicable diseases; COVID infection; history of medical surgeries; family history of depressive disorders; family history of psychiatric disorder; current use of pharmaceuticals, antibiotics, chemotherapy, or hormonal therapy; use of supplements; tobacco smoking; hookah smooking; drug use; alcohol use; and menstrual irregularities in women.

The lifestyle and environmental features included; practice of meditation and mindful practices; religious and spiritual practices; number of close friends; number of languages spoken; receiving psychotherapy currently or in the past; use of psychopharmacological treatment currently or in the past; exposure to verbal abuse; exposure to physical abuse; exposure to sexual abuse; years lived in rural settings; years lived in urban settings; exposure to second-hand smoking at home and at work/school; presence of greenery at home and at work/school; source of cooking water; source of drinking water; average weekly consumption of fruits, vegetables, meat and poultry, fish, sugars, and fast-food; average daily consumption of caffeine; average hours of sleep; sleep quality; average hours of watching TV; average hours of work; average hours of housework; average hours of internet/smartphone use; average income; current sexual activity; low- intensity physical activity; moderate/high-intensity physical activity. Highlighting a focus on cognitive functioning, the questionnaires also included the Arabic version of the mini mental state examination (MMSE) which was administered to screen for any remarkable cognitive problems and/or poor orientation (Wrobel & Farrag, 2007).

To assess the severity of depressive symptoms and generate a symptom profile (cognitive-affective and somatic symptoms), the standardized Arabic version of the Beck Depression Inventory (BDI-II) was used. BDI-II is a 21-items self-reported test to assess depressive symptoms on a 4-point scale from 0 (symptom absent) to 3 (severe symptoms) with a recall period of 2 weeks. The highest score possible is 63. A total score of 0-10 is considered “normal ups and downs”, 11-16 “mild mood disturbance”, 17-20 “borderline clinical depression”, 21-30 “moderate depression”, 31-40 “severe depression”, and 40 or more “extreme depression”. One comprehensive review of

118 studies examining the psychometric properties of the BDI-II in non-clinical, psychiatric and medical samples suggested high internal consistency, 0.9, and high retest reliability, between 0.73 and 0.96 (Wang & Gorenstein, 2013). And although it had high sensitivity and specificity for depression, the cutoff point to discriminate between depressed and non-depressed was not demonstrated. Hence, for the purpose of this study, BDI-II is only used for the symptomatic profiling and the rating of depression, rather than diagnosis. Additionally, factor analysis recommended the use of two constructs; cognitive-affective and somatic-vegetative (Wang & Gorenstein, 2013). The classification into the cognitive-affective and somatic sub-scales was based on Wedding and colleagues (2007) taking into consideration item differences in the translated Arabic version. The cognitive-affective sub-scale consisted of a total of 13 items; including sadness, pessimism, sense of failure, dissatisfaction/loss of pleasure, guilt, expectation of punishment, dislike of self, self-accusation/self-blame, suicidal ideation, episodes of crying, social withdrawal/loss of interest, self-worth, and indecisiveness. The somatic sub-scale consisted of a total of 8 items; retardation, sleep problems, anger, fatigue, loss of appetite, attention problems, loss of energy, and loss of libido.

Diagnostically, the Arabic version of the MINI International Neuropsychiatric Interview, M.I.N.I. 7.0.2 (Karnouk et al., 2021) was used to assess symptoms as per the criteria of the 5th version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the (International Classification of Diseases (ICD) in a structured psychiatric interview form. The original version of the MINI covering 17 psychiatric disorders, has been validated showing high validity and reliability properties similar to other diagnostic tools based on the DSM-5, in addition to having the benefit of being administered in significantly less time compared to the other diagnostic interviews (Sheehan et al., 1997; Sheehan et al., 1998). Two modules were chosen for the purpose of this study: the Major Depressive Episode module and the Suicidality module. As per the translators of the Arabic version, only the depression module (Module A) has been validated (Karnouk et al., 2021).

In terms of biomarkers and in addition to a complete blood count (CBC), the following were selected for blood analysis based on the literature review: IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10 and IL-17, VEGFC, VEGFD, IFNγ, EGF, IGF 1, FGF-2, FGF-9, FGF-21, FGF-22, and TNF-α. A more comprehensive list of biomarkers was contemplated in the initial research proposal, including biomarkers for heavy metals exposure; however, due to fiscal constraints, the scope of biomarkers to be analyzed was reduced.

The initial study proposal also involved the use of isotopically-labelled wristbands as an innovative tool for the passive assessment of chemical exposures including pollutants and other chemicals that a participant wearing the wristband is exposed to. Although it carried the benefit of personalized live data collection in a non-invasive manner, several challenges were encountered in the pilot and initial phases of the study. Some of the logistical concerns were the inconvenience associated with the return of participants for wristband collection, low participant compliance, the difficulty of ensuring that all participants adhered to the same duration of wearing the wristbands, and ensuring that the wristbands were not misplaced or used as toys by minors prior to their return to the principal investigator. Another concern raised was the assumption that some of the participants' reluctance to use the wristbands might come from their belief in, and fear from, "amal" (i.e.: a traditional term referring to magic-like tools used to induce harm in others). Put together, the use of wristbands was excluded from the procedure in order to maintain the integrity of the data collected without compromising the accuracy of other measures.

2.3 Procedure

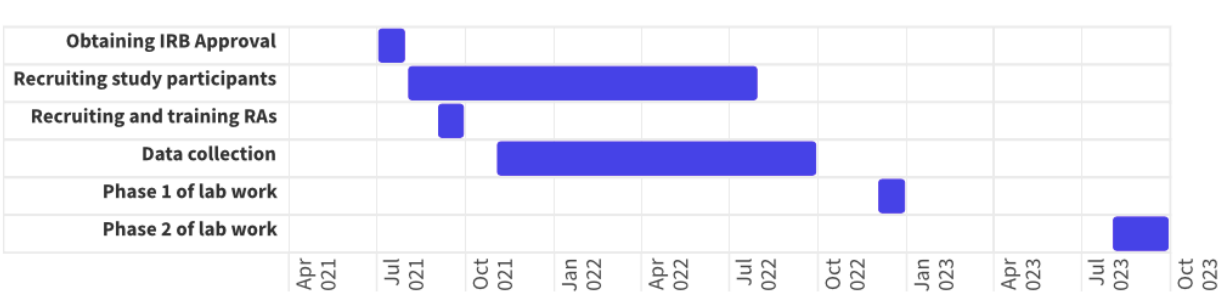
The interviewers, including 3 research assistants in addition to the principal investigator, all holding master's degrees in clinical or counseling psychology and recognized as qualified psychotherapists, underwent a training session specifically oriented towards the appropriate administration of the MINI. This main training was conducted in Arabic by Dr. Carine Karnouk, the developer of the Arabic version of the MINI, ensuring a standardized and comprehensive understanding of the assessment protocol and, hence, the consistency and validity of the data

collected. The principal investigator, through direct supervision, ensured that all interviewers followed the same procedure.

Recruited participants were assigned unique identification numbers to facilitate labeling, which were subsequently given to both the questionnaires and blood samples for anonymous tracking and organization. Participants were invited for an in-take interview that usually took 60-90 minutes either in an outpatient clinic in Mokattam or in the New Cairo AUC campus. In both settings, participants engaged in one-on-one interviews conducted in a private room to guarantee their privacy and to foster a safe atmosphere for opening up. They were briefed about the study protocol and the informed consent was discussed and signed before the beginning of the interview. Following the interview, blood samples were collected by professional nurses from the AUC clinic or Dar El Mokattam Mental Health Hospital, and transferred in iceboxes with frozen ice packs to the AUC School of Science and Engineering labs for analysis.

All data, including questionnaires and blood tests results, were kept anonymously and confidentially and are still available for reference. A summary of the study procedure timeline is illustrated in figure 2.

Figure 2: A timeline summary of key procedure and milestones in the current study starting in July 2021 and ending in September 2023 (Developed by Flourish.studio)



In terms of handling blood samples, complete blood count was first conducted using Sysmex XP-300 automated hematology analyzer, known for its precision and accuracy for its reliance on direct current detection method and coincidence correction. Samples were then centrifuged,

plasma and serum were harvested separately and were stored at -80 °C until immunoassays were performed. ELISA kits sourced from Elabscience® in Wuhan, China, were utilized for analysis. In the process of executing the laboratory work, some biomarkers were not assessed across the entire cohort of 107 participants. This primarily stemmed from the inadequacy of blood sample volumes provided by some participants, which precluded testing for all biomarkers. The manufacturer's protocol was as follows:

Reagent preparation

1. Bringing all reagents to room temperature (18-25 °C) before use. Following the Microplate reader manual for set-up and preheating it for 15 minutes before OD measurement.

2. Wash Buffer: Diluting 30 mL of Concentrated Wash Buffer with 720 mL of deionized or distilled water to prepare 750 mL of Wash Buffer Note: if crystals have formed in the concentrate, warming it in a 40 °C water bath and mixing it gently until the crystals have completely dissolved.

3. Standard working solution: Centrifuging the standard at 10,000xg for 1 minute. Adding 1.0mL of Reference Standard & Sample Diluent, letting it standing for 10 minutes and inverting it gently several times. After it dissolves fully, mixing it thoroughly with a pipette. This reconstitution produces a working solution of 100 ng/mL. Then making serial dilutions as needed. The recommended dilution gradient is as follow: 100, 50, 25, 12.5, 6.25, 3.13, 1.56, 0 ng/mL.

Dilution method: Taking 7 EP tubes, adding 500 μL of Reference Standard & Sample Dilution Diluent to each tube. Pipetting 500 μl of the 100 ng/mL working solution to the first tube and mixing up to produce a 50 ng/mL working solution. Pipetting 500 μL of the solution from the former tube into the latter one according to these steps.

4. Biotinylated Detection Ab working solution: Calculating the required amount before the experiment (100 µL/well). In preparation, slightly more than calculated should be prepared. Centrifuging the stock tube before use, diluting the 100x Concentrated Biotinylated Detection Ab to 1x working solution with Biotinylated Detection Ab Diluent.

5. Concentrated HRP Conjugate working solution: Calculating the required amount before the experiment (100 µL/well). In preparation, slightly more than calculated should be prepared. Diluting the 100x Concentrated HRP Conjugate to 1x working solution with Concentrated HRP Conjugate Diluent.

Assay procedure

1. Adding the standard working solution to the first two columns: Each concentration of the solution is added in duplicate, to one well each, side by side (100 µl for each well). Adding the samples to the other wells (100 µl for each well). Covering the plate with the sealer provided in the kit. Incubating for 90 minutes at 37 °C . Note: Solutions should be added to the bottom of the micro ELISA plate well, avoiding touching the inside wall and causing foaming as much as possible.

2. Removing the liquid out of each well without washing. Immediately adding 100 µl of Biotinylated Detection Ab working solution to each well. Covering with the plate sealer and gently mixing up. Incubating for 1 hour at 37 °C.

3. Aspirating or decanting the solution from each well and adding 350 µl of wash buffer to each well. Soaking for 1-2 minutes and spiraling or decanting the solution from each well and patting it dry against clean absorbent paper. Repeating this wash step 3 times in total. Note: A microplate washer can be used in this step and other was steps.

4. Adding 100 µl of HRP Conjugate working solution to each well. Covering with the plate sealer. Incubating for 30 minutes at 37 °C.

5. Aspirating or decanting the solution from each well, repeating the wash process for five times as conducted in step 3.

6. Adding 90 µl of Substrate Reagent to each well. Covering with a new plate sealer. Incubating for about 15 minutes at 37 °C. Protecting the plate from light. Note: The reaction time can be shortened or extended according to the actual color change, but no more than 30 minutes.

7. Adding 50 µl of Stop Solution to each well. Note: Adding the stop solution should be done in the same order as the substrate solution.

8. Determining the optical density (OD value) of each well at one, using a micro-plate reader (Optima Microplate Reader, FluoStar, BMG Labtech) set to 450 nm.

Calculation of results

1. Averaging the duplicate readings for each of the seven standard and the samples, then subtracting the average zero standard optical density.

2. Plotting a four parameter logistic curve on log-log graph paper, with standard concentration on the x-axis and OD values on the y-axis.

3. If the samples have been diluted, the concentration calculated from the standard curve must be multiplied by the dilution factor. If the OD of the sample surpasses the upper limit of the standard curve, retesting it with an appropriate diction. The actual concentration is the calculated concentration multiplied by the dilution factor.

2.4 Ethical Considerations

The study was applied in accordance with the American Psychological Association (APA, 2002) code of ethics in terms of the general ethical principles and the Research and Publication codes. An institutional review board (IRB; Approval Case # 2020-2021-134) approval was obtained prior to data collection and the principal investigator completed the Collaborative Institutional Training Initiative (CITI) program, Basic/Refresher, Biomedical Research, in bioethics (Record ID 38438943) under the requirements set by the American University in Cairo. Participants were requested to provide written informed consent upon receiving a complete explanation of the nature of the study protocol prior to their inclusion in the study, were informed about the voluntary nature of participation and that they could withdraw anytime during the research period without any consequences. They were also educated about the potential emotional distress they might experience in response to some of the study questions and were give the choice to skip questions where they did not feel comfortable. Upon signing the informed consent, they were requested to keep a soft-copy of the consent form and all participants had direct contact with the principal investigator via email and phone. Study data were entered and digitized anonymously on a secure cloud with exclusive access to the principal investigator as the authorized researcher. A numerical coding system was used to replace participants' names in all documents and electronic files. Upon completion of the interview, all participant received the results of their psychiatric assessment from the principal investigator and were offered a free self-help tool to help with depressive symptoms in addition to a list of recommended mental health care providers in public and private facilities in Cairo to guarantee access to interventions if needed. At-risk participants, identified based on the suicide module of MINI, were directly referred to the appropriate psychiatric service providers and one participant identified at high current risk of suicide was provided direct financial support to receive treatment in two private psychiatric clinic for following up with a psychiatrist and a psychotherapist during the emergency phase.

No follow-up was provided given the nature of the study design. Debriefing for all participants will take place towards the end of the study to inform them of the main findings.

Chapter 3

Results

3.1 Statistical Analysis

The initial screening of data resulted in the deletion of the data of 17 participants (An original total sample size of 124) who were unable to provide blood samples, whose blood samples were not enough for the lab work, or in cases of sample premature coagulation before arrival at the lab. No statistical outliers have been identified and no published clinical references were available from Egyptian clinical or non-clinical samples to identify clinical outliers. Data were statistically described in terms of mean, ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test. Comparison of numerical variables between the study groups was done using Kruskal Wallis test. For comparing categorical data, on the other hand, Chi-square (χ^2) test was performed. Exact test was used instead when the total expected frequency was less than 5. Correlation between various variables was done using Spearman rank correlation equation. Multivariate linear regression analysis models were used to test for the preferential significant predictors on total BDI scores, total cognitive-affective scores and total somatic scores. Two-sided p values of less than 0.05 was considered statistically significant and less than 0.01 was considered highly statistically significant. IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows was used for all statistical analyses.

3.2 Descriptive Statistics

Descriptive statistics of the demographic variables of the study participants are presented in Table 1, descriptive statistics for the examined health-related variables and life-style variables are presented in Table 2 and 3 respectively.

Table 1: Descriptive statistics of the demographic characteristics of the study sample

		n	%	
Gender	Males	24	22.4	
	Females	83	77.6	
Marital Status	Single	73	68.2	
	Engaged	4	3.7	
	Married	23	21.5	
	Divorced	6	5.6	
	Widowed	1	0.9	
Education	High School	23	21.5	
	High Diploma	4	3.7	
	University	57	53.3	
	Graduate degree	23	21.5	
Employment	Unemployed	32	29.9	
	Freelancer	8	7.5	
	Part-Time	14	13.1	
	Full-Time	53	49.5	
Income	None	14	13.1	
	Up to 5k	41	38.3	
	6-10k	30	28	
	11-15k	9	8.4	
	16-20k	4	3.7	
	21-50k	7	6.5	
	More than 50k	2	1.9	
	Mean	**SD**	**Minimum**	**Maximum**
Age	29.02	7.661	18	58
Number of Children	0.44	0.963	0	6

Household Size	3.98	1.754	0	8

The gender distribution of the sample reflects a significant disparity between males and females, with females accounting for 77.6% and males 22.4% of the total sample size. Although this may seem like a drawback, this is actually somehow reflective of the global trends of the prevalence and incidence of MDD in the general population where it is more common in females than in males. Females are almost twice as likely as males to be diagnosed as suggested by epidemiological studies (Bromet et al., 2011; Li et al., 2023; Picco et al., 2017). Similar trends have been observed in Egyptian samples (Eshak & Abd-El Rahman, 2022; Shamms-Eldin et al., 2019), and therefore, the current gender distribution of the sample in this study is assumed to be representative.

Table 2: Descriptive statistics of the health-related variables of the study sample

		n	%	
Birth	Term	89	83.2	
	Preterm	8	7.5	
	Unknown	10	9.3	
Delivery	Natural	69	64.5	
	Cesarian section	32	29.9	
	Unknown	6	5.6	
Postnatal Postnatal feeding	Natural	66	61.7	
	Formula	7	6.5	
	Mixed	23	21.5	
	Unknown	11	10.3	
Chronic diseases	No	71	66.4	
	Yes	36	33.6	
History of surgeries	No	45	42.1	

	Yes	62	57.9	
Family history of depression	Negative	52	48.6	
	Positive based on appearance	37	34.6	
	Positive based on diagnosis	18	16.8	
Family history of psychiatric disorders other than depression	Negative	62	57.9	
	Positive based on appearance	19	17.8	
	Positive based on diagnosis	26	24.3	
Chronic use of medications	No	82	76.6	
	Yes	25	23.4	
Hormonal treatment	No	101	94.4	
	Yes	6	5.6	
Menstrual irregularities	No	57	68.7	
	Yes	26	31.3	
Currently receiving psychotherapy	No	86	80.4	
	Yes	21	19.6	
Receiving psychotherapy in the past	No	56	52.3	
	Yes	51	47.7	
Currently taking psychiatric medications	No	92	86	
	Yes	15	14	
Taking psychiatric medications in the past	No	70	65.4	
	Yes	37	34.6	
Using supplements	No	44	41.1	
	Yes	63	58.9	

Vitamin D supplementation	No	84	78.5	
	Yes	23	21.5	
Omega-3 supplementation	No	90	84.1	
	Yes	17	15.9	
Tobacco use	Non-smoker	84	78.5	
	Past smoker	7	6.5	
	Current-smoker	16	15	
Hookah use	Non-smoker	88	82.2	
	Past smoker	11	10.3	
	Current smoker	8	7.5	
Alcohol use	Non-user	92	86	
	Past user	6	5.6	
	Current user	9	8.4	
Drug use	Non-user	101	94.4	
	Past user	6	5.6	
	Current user	0	0	
	Mean	**SD**	**Minimum**	**Maximum**
Body Mass Index (BMI)	26.756	5.8316	17.4	50.3

Table 3: Descriptive statistics of the lifestyle and environmental variables of the study sample

		n	%	
Meditation and mindful practices	No	66	61.7	
	Yes	41	38.3	
Religious practices	No	19	17.8	
	Yes	88	82.2	
History of exposure to verbal abuse	No	24	22.4	
	Yes	83	77.6	
History of exposure to physical abuse	No	61	57	
	Yes	46	43	
History of exposure to sexual abuse	No	66	61.7	
	Yes	41	38.3	
Second-hand smoking at home	No	75	70.1	
	Yes	32	29.9	
Second-hand smoking at work/school	No	70	65.4	
	Yes	32	29.9	
Household greenery	No	41	38.3	
	Yes	66	61.7	
Work/school greenery	No	35	32.7	
	Yes	65	60.7	
Cooking water	Bottled water	4	3.7	
	Filtered water	59	55.1	
	Tap water	44	41.1	
Drinking water	Bottled water	40	37.4	
	Filtered water	46	43	
	Tap water	21	19.6	
Quality of sleep	Excellent	13	12.1	
	Good	63	58.9	
	Bad	31	29	

Current sexual activity	No	82	76.6	
	Yes	25	23.4	
Practice of moderate/high intensity sports	Never	60	56.1	
	Monthly	3	2.8	
	Weekly	27	25.2	
	Daily	17	15.9	
	Mean	**SD**	**Minimum**	**Maximum**
Number of languages spoken	2.25	0.688	1	5
Number of close friends	3.07	1.815	0	8
Years spent in rural settings	2.14	6.208	0	34
Years spent in urban settings	26.87	9.656	0	58
Consumption of fruits (days/week)	3.26	2.341	0	7
Consumption of vegetables (days/week)	4.26	2.466	0	7
Consumption of meat and poultry (days/week)	5.15	2.055	0	7
Consumption of fish (days/week)	0.62	0.773	0	3
Consumption of sugars (days/week)	3.72	2.798	0	7
Consumption of junk food (days/week)	1.6	1.806	0	7

Consumption of caffeine (cups/day)	2.02	2.009	0	13
Hours of sleep per day	6.97	1.767	2	16
Hours of watching TV per day	1.01	1.342	0	6
Hours of working per day	6.08	3.812	0	20
Hours of housework per day	1.34	1.962	0	12
Hours of internet use per day	5.01	3.043	1	15
Low-intensity physical activity (days/week)	4.22	2.672	0	7

Descriptive data for the BDI-II variables and other MDD variables based on the MINI are presented in table 4.

Table 4: Descriptive statistics of depression and suicidality variables as per the BDI-II and MINI

	Mean	**SD**	**Minimum**	**Maximum**
BDI total score	19.05	11.001	1	47
BDI cognitive-affective score	11.75	7.904	1	31
BDI somatic-vegetative score	7.30	4.498	0	19
		n	%	

BDI severity	Normal	30	28	
	Mild	21	19.6	
	Borderline	12	11.2	
	Moderate	22	20.6	
	Severe	19	17.8	
	Extreme	3	2.8	
History of past depressive episodes	No	48	44.9	
	Yes	59	55.1	
Diagnosis	Healthy control	39	36.4	
	Past	22	20.6	
	Current	11	10.3	
	Recurrent	35	32.7	
Currently in a depressive episode	No	81	75.7	
	Yes	26	24.3	
Suicidal history	Negative	103	96.3	
	Positive	4	3.7	
Current suicidal risk	None	57	53.3	
	Weak	33	30.8	
	Moderate	3	2.8	
	High	14	13.1	
	Mean	**SD**	**Minimum**	**Maximum**
Total depressive episodes	1.66	2.695	0	20
Total suicidal attempts	0.24	0.834	0	5

Total suicidality score	7.47	19.030	0	110

Figure 3 illustrates frequency of professional help-seeking behaviors among the 26 participants who were identified as meeting the full diagnostic criteria for a current MDD episode as per the MINI. These are categorized in terms of currently being in psychotherapy and current utilization of psychiatric medications.

Figure 3: Frequency of professional help-seeking behaviors among 26 participants meeting full diagnostic criteria for a current MDD episode (Developed by Flourish.studio)

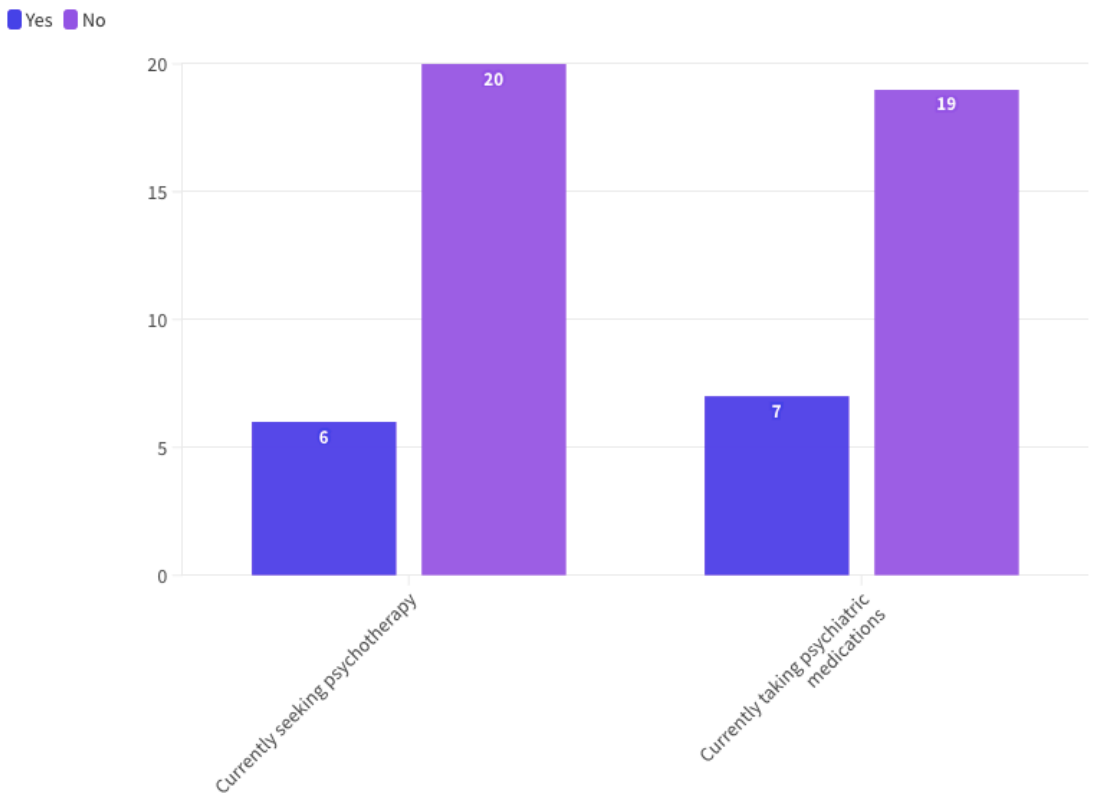


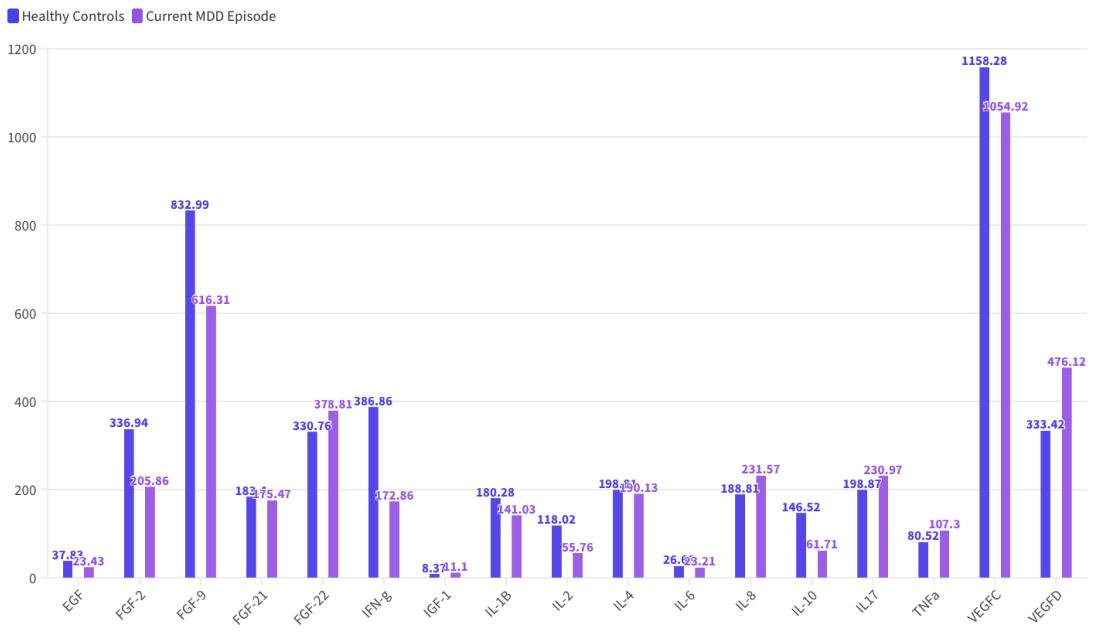
Table 5: Descriptive statistics of all inflammatory and neurotrophic biomarkers in addition to complete blood parameters

	Mean	**SD**	**Minimum**	**Maximum**
EGF (pg/ml)	34.56	80.206	0	687
FGF-2 (pg/ml)	306.49	628.725	7	4,187
FGF-21 (pg/ml)	181.44	146.630	2	698
FGF-22 (pg/ml)	342.64	314.770	1	1,155
FGF-9 (pg/ml)	779.84	1,715.747	0	15,331
IFN-γ (pg/ml)	331.70	771.968	12	6,228
IGF-1 (ng/ml)	8.94	7.683	0	37
IL-1β (pg/ml)	171.19	261.372	0	1,074
IL10 (pg/ml)	126.02	299.236	0	1,907
IL17 (pg/ml)	206.11	284.537	3	2,013
IL2 (pg/ml)	103.19	264.483	1	2,092
IL4 (pg/ml)	196.71	206.694	2	1,128
IL6 (pg/ml)	25.86	38.110	0	205
IL8 (pg/ml)	199.20	418.419	6	2,910
TNF-α (pg/ml)	87.21	91.188	1	704
VEGFC (pg/ml)	1,133.16	1,925.521	22	10,096
VEGFD (pg/ml)	365.60	365.631	5	2,046
WBC (10^3/uL)	6.501	1.8968	1.3	12.8
RBC (10^3/uL)	4.915	0.5232	4.0	6.6
HGB (g/dL)	12.449	1.7185	3.6	17.4
HCT (%)	40.376	3.9366	30.1	53.2
MCV (fL)	82.450	6.1672	62.1	103.9

MCH (pg)	25.410	3.1381	8.9	32.4
MCHC (g/dL)	30.774	2.5413	10.1	33.8
PLT (10^3/uL)	284.08	83.020	121	671
LYM (%)	36.826	9.1179	12.3	64.5
MXD (%)	9.054	4.7869	1.6	28.9
NEUT (%)	54.041	10.8050	22.3	81.2
LYM# (10^3/uL)	2.297	0.5775	0.4	3.7
MXD# (10^3/uL)	0.584	0.3369	0.1	1.8
NEUT# (10^3/uL)	3.599	1.6096	0.8	10.4

Mean levels of inflammatory and neurotrophic factors in healthy controls and participants with current MDD episodes are illustrated in figure 4.

Figure 4: Mean biomarker concentrations in healthy controls and participants with a current MDD episode (Developed by Flourish.studio). No statistically significant differences were found between both groups.



3.3 Correlational Statistics

BDI-II items were then tested for correlation with the corresponding MINI items to check for convergent validity between both tools. Strong correlations indicate high convergent validity suggesting that items on both scales are designed to measure the same construct. Results are presented in tables 6 and 7.

Table 6: The correlations between MINI diagnostic items and the items corresponding to the same MDD symptoms on the BDI-11. * *p* value significant at the 0.05 level, ** *p* value significant at the 0.01 level.

		A1b	**A2b**	**A3a**	**A3b**	**A3c**	**A3d**	**A3e**	**A3e Delusion**	**A3f**	**A3g**
BDI Sadness	r	.517**									
	p value	0.000									
BDI Pessimism	r	.351**									
	p value	0.000									
BDI Pleasureloss	r		.411**								
	p value		0.000								
BDI Guilt	r							.328**			
	p value							0.001			

BDI Punishment	r								.280**		
	p value								0.004		
BDI Selfdislike	r								.273**		
	p value								0.004		
BDI Suicidal	r										.494**
	p value										0.000
BDI Lossofinterest	r		.398**								
	p value		0.000								
BDI Indecisiveness	r									.410**	
	p value									0.000	
BDI Selfworth	r							.459**			
	p value							0.000			
BDI Irritability	r					.239*					
	p value					0.013					
BDI energy	r						.571**				

	p value						0.000				
BDI sleep	r				.409**						
	p value				0.000						
BDI anger	r					.332**					
	p value					0.000					
BDI appetite	r			.431**							
	p value			0.000							
BDI attention	r									.498**	
	p value									0.000	
BDI exhaustion	r						.493**				
	p value						0.000				

Table 7: The correlations between the diagnostic status and the identification of a current MDD episode as per the mini, and the BDI-II total score and overall severity. * *p* value significant at the 0.05 level, ** *p* value significant at the 0.01 level.

		Diagnosis as per MINI	Current Episode as per MINI
BDI Total Score	df	3	3
	p value	<0.001**	<0.001**

BDI Severity	df	3	3
	p value	<0.001**	<0.001**

The chord diagram below (Figure 5) illustrates the significant correlations between all inflammatory and complete blood biomarkers covered in this study.

Figure 5: A chord diagram illustrating the significant correlations between all blood biomarkers (Developed by Flourish.studio). The thickness of the chords reflects the weight of the correlation with thicker chords showing stronger correlations whether positive or negative. As illustrated, some biomarkers are placed as central points (i.e.: FGF-21, IFN-γ and VEGFC) given their numerous significant correlations with other biomarkers of interest. This reflects the interconnectedness of biomarkers and the significant role of specific ones.

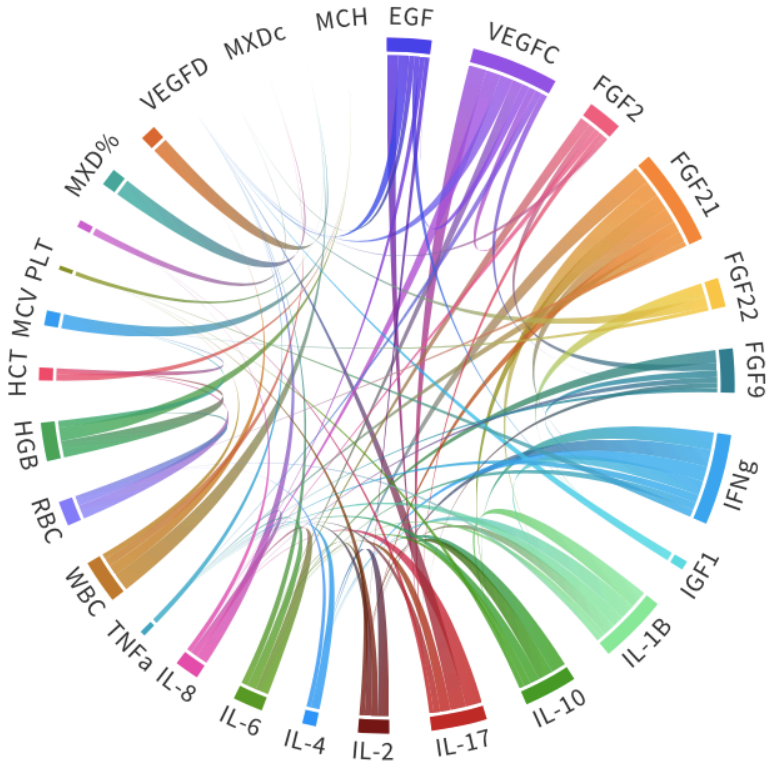


Table 8: The correlations between demographic and lifestyle/environmental variables and BDI total score, BDI Cognitive-Affective total score, BDI Somatic total score, and current diagnosis of MDD. * *p* value significant at the 0.05 level, ** *p* value significant at the 0.01 level.

		BDI Total	**BDI Cognitive-Affective Totle**	**BDI Somatic Total**	**Current diagnosis of MDD**
Sex	r	-0.038	-0.011	-0.077	-0.113
	p value	0.694	0.911	0.428	0.245
Age	r	0.090	0.018	0.165	0.018
	p value	0.356	0.854	0.089	0.857
Number of children	r	-0.156	-0.185	-0.074	-0.053
	p value	0.108	0.854	0.450	0.585
Household size	r	-0.012	0.038	-0.097	0.039
	p value	0.901	0.694	0.322	0.693
Education	r	0.006	-0.024	0.046	-0.184
	p value	0.951	0.803	0.638	0.058
Employment	r	-0.222	0.105	0.077	-0.164
	p value	**0.022***	0.280	0.431	0.091
Birth	r	0.088	-0.072	-0.115	-0.167
	p value	0.393	0.481	0.260	0.102
Delivery	r	-0.080	0.105	0.054	-0.045
	p value	0.424	0.298	0.593	0.652
Postnatal feeding	r	0.224	0.204	0.076	0.081
	p value	**0.029***	**0.046***	0.463	0.434
BMI	r	0.270	0.259	0.214	0.168
	p value	**0.005****	**0.007****	**0.027***	0.085
Chronic diseases	r	0.125	0.067	0.159	0.058
	p value	0.201	0.493	0.101	0.555
Surgeries	r	0.031	0.045	-0.028	0.085
	p value	0.754	0.649	0.772	0.382

Family history of depression	r	0.039	0.050	-0.009	0.104
	p value	0.693	0.607	0.927	0.288
Family history of psychiatric disorders	r	-0.029	0.004	-0.055	-0.018
	p value	0.770	0.964	0.576	0.855
Chronic use of medications	r	0.138	0.138	0.112	0.215
	p value	0.157	0.158	0.252	**0.027***
Hormonal treatment	r	0.006	-0.027	0.075	-0.136
	p value	0.951	0.786	0.445	0.164
Menstrual irregularities	r	0.205	0.156	0.200	-0.040
	p value	0.063	0.161	0.072	0.718
Currently receiving therapy	r	0.014	0.019	-0.005	0.049
	p value	0.888	0.845	0.960	0.615
Receiving therapy in the past	r	-0.136	-0.140	-0.118	-0.061
	p value	0.162	0.152	0.225	0.534
Currently taking psychiatric medications	r	0.133	0.064	0.194	0.211
	p value	0.172	0.514	**0.045***	**0.029***
Taking psychiatric medications in the past	r	0.219	0.159	0.247	0.181
	p value	**0.024***	0.104	**0.011***	0.064
Religious practices	r	-0.224	-0.170	-0.236	-0.107
	p value	**0.022***	0.083	**0.015***	0.276
History of exposure to verbal abuse	r	0.316	0.355	0.197	0.148
	p value	**0.001****	**0.000****	**0.042***	0.128
History of expo-	r	0.149	0.146	0.125	0.036

sure to physical abuse	*p* value	0.127	0.134	0.201	0.711
History of exposure to sexual abuse	r	0.104	0.042	0.158	0.136
	p value	0.288	0.669	0.104	0.162
Number of languages spoken	r	-0.009	0.010	-0.006	0.059
	p value	0.930	0.920	0.948	0.548
Meditation or breathing	r	-0.168	-0.160	-0.101	-0.133
	p value	0.083	0.100	0.299	0.173
Number of close friends	r	-0.098	-0.142	-0.139	-0.148
	p value	0.319	0.147	0.155	0.132
Years spent in rural settings	r	-0.041	0.064	0.164	0.015
	p value	0.678	0.512	0.091	0.877
Years spent in urban settings	r	0.124	0.064	0.164	0.024
	p value	0.204	0.512	0.091	0.809
Second-hand smoking at home	r	0.178	0.196	0.115	0.153
	p value	0.067	**0.043***	0.237	0.115
Second-hand smoking at work	r	0.104	0.148	0.006	0.056
	p value	0.299	0.137	0.948	0.573
Household greenery	r	-0.312	-0.297	-0.292	-0.209
	p value	**0.001****	**0.002****	**0.002****	**0.031***
Workplace greenery	r	-0.047	-0.100	0.103	0.152
	p value	0.643	0.324	0.307	0.131
Cooking water	r	0.024	-0.062	0.061	0.095
	p value	0.810	0.528	0.535	0.329
Drinking water	r	0.092	-0.083	-0.049	0.130
	p value	0.344	0.394	0.617	0.182
Consumption of	r	0.049	0.045	0.057	0.033

fruits (days/ week)	*p* value	0.618	0.394	0.561	0.737
Consumption of vegetables (days/ week)	r	-0.043	-0.006	0.109	0.045
	p value	0.663	0.952	0.263	0.642
Consumption of meat and poultry (days/week)	r	-0.015	0.030	-0.085	0.005
	p value	0.881	0.761	0.383	0.961
Consumption of fish (days/week)	r	0.041	0.029	0.058	-0.041
	p value	0.679	0.771	0.556	0.676
Consumption of sugars (days/ week)	r	0.063	0.106	-0.040	0.057
	p value	0.520	0.276	0.679	0.557
Daily consump-tion of caffeine (cups/day)	r	0.260	0.200	0.294	0.110
	p value	**0.007***	**0.039***	**0.002***	0.260
Consumption of Junk food (days/ week)	r	0.119	0.136	0.072	0.063
	p value	0.221	0.164	0.463	0.518
Supplements	r	0.002	-0.049	0.098	0.075
	p value	0.980	0.619	0.315	0.443
Vitamin D	r	-0.070	-0.099	0.000	-0.084
	p value	0.474	0.311	1.000	0.388
Hours of sleep per day	r	-0.125	-0.133	-0.099	-0.173
	p value	0.198	0.172	0.311	0.075
Quality of Sleep	r	-0.353	-0.226	-0.477	-0.166
	p value	**0.000****	**0.019***	**<0.001****	0.087
Hours of watch-	r	-0.030	-0.010	-0.057	0.059

ing TV per day	*p* value	0.762	0.918	0.560	0.546
Hours of working per day	r	0.048	0.030	0.089	-0.203
	p value	0.620	0.758	0.360	**0.036***
Hours of housework per day	r	0.102	0.108	0.105	0.045
	p value	0.295	0.268	0.281	0.646
Hours of internet use per day	r	0.283	0.313	0.161	0.209
	p value	**0.003***	**0.001****	0.099	**0.031***
Income	r	-0.093	-0.098	-0.052	-0.314
	p value	0.339	0.314	0.594	**0.001****
Tobacco use	r	0.076	0.015	0.141	0.076
	p value	0.438	0.879	0.148	0.437
Hookah use	r	0.101	0.093	0.068	0.081
	p value	0.301	0.340	0.487	0.409
Alcohol use	r	-0.069	-0.087	-0.022	0.019
	p value	0.483	0.371	0.824	0.848
Drugs use	r	0.070	0.056	0.050	0.145
	p value	0.475	0.567	0.608	0.138
Current sexual activity	r	-0.088	-0.133	0.019	-0.004
	p value	0.365	0.173	0.846	0.969
Physical activity Days	r	-0.093	-0.090	-0.062	0.007
	p value	0.340	0.354	0.525	0.943
Practice of moderate/high intensity sports	r	-0.210	-0.194	-0.200	-0.155
	p value	**0.030***	**0.045***	**0.038***	0.110

Table 9: The correlations between exposure to verbal, physical and sexual abuse and drug use. * *p* value significant at the 0.05 level, ** *p* value significant at the 0.01 level

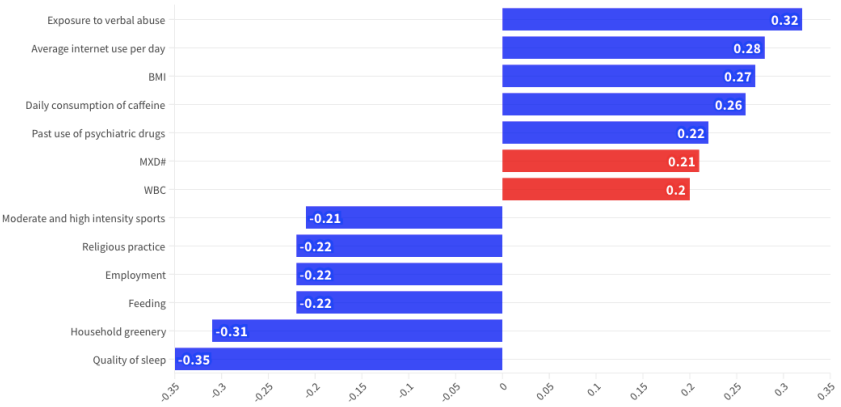
		Drug use
Exposure to verbal abuse	r	0.121
	p value	0.728
Exposure to physical abuse	r	4.221
	p value	**0.040***
Exposure to sexual abuse	r	0.067
	p value	0.796

Table 10: The correlations between biomarkers and BDI total score, BDI Cognitive-Affective total score, BDI Somatic total score, and current diagnosis of MDD. * *p* value significant at the 0.05 level, ** *p* value significant at the 0.01 level

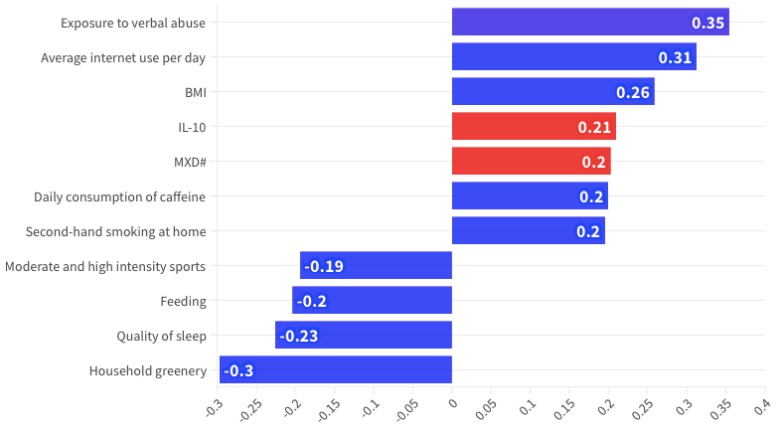
		BDI Total Score	**BDI Cognitive-Affective Total Score**	**BDI Somatic Total Score**	**Current diagnosis of MDD**	Total number of MDD episodes
EGF	r	-0.139	-0.141	-0.082	0.001	0.059
	p value	0.196	0.191	0.447	0.992	0.587
FGF-2	r	-0.053	-0.031	-0.062	-0.026	-0.129
	p value	0.603	0.762	0.544	0.799	0.202
FGF-21	r	-0.005	-0.005	-0.009	0.032	-0.056
	p value	0.959	0.962	0.932	0.763	0.602
FGF-22	r	-0.129	-0.121	-0.122	0.039	0.021
	p value	0.230	0.257	0.256	0.720	0.842
FGF-9	r	0.095	0.101	0.115	0.022	-0.118
	p value	0.330	0.301	0.242	0.821	0.229
IFN-γ	r	0.070	0.108	-0.006	-0.035	-0.095
	p value	0.498	0.290	0.955	0.731	0.354

IGF-1	r	0.066	0.079	0.023	0.141	-0.032
	p value	0.533	0.453	0.825	0.181	0.759
IL-1β	r	0.179	0.197	0.116	0.080	0.098
	p value	0.082	0.055	0.265	0.440	0.347
IL10	r	0.174	.210	0.057	0.102	-0.091
	p value	0.099	**0.046***	0.591	0.335	0.389
IL17	r	0.123	0.127	0.085	0.046	-0.007
	p value	0.218	0.202	0.394	0.647	0.940
IL2	r	0.009	0.033	-0.013	-0.030	-0.080
	p value	0.931	0.741	0.891	0.759	0.415
IL4	r	0.048	0.065	-0.006	0.062	-0.044
	p value	0.653	0.538	0.951	0.562	0.682
IL6	r	0.148	0.159	0.114	0.084	-0.151
	p value	0.132	0.106	0.245	0.394	0.124
IL8	r	0.021	0.042	0.006	-0.095	-0.069
	p value	0.827	0.667	0.955	0.329	0.478
TNF-α	r	0.037	0.079	-0.037	0.024	-0.083
	p value	0.719	0.442	0.719	0.814	0.420
VEG-FC	r	-0.019	-0.008	-0.009	-0.080	-0.061
	p value	0.846	0.937	0.929	0.410	0.534
VEGFD	r	0.078	0.071	0.064	0.107	-0.014
	p value	0.435	0.481	0.523	0.284	0.888
WBC	r	0.203	0.175	.204	0.135	0.043
	p value	**0.036***	0.072	**0.035***	0.165	0.662
RBC	r	0.159	0.172	0.096	-0.025	-0.120
	p value	0.101	0.077	0.328	0.798	0.220
HGB	r	0.112	0.104	0.100	0.074	0.011
	p value	0.249	0.285	0.306	0.446	0.911
HCT	r	0.141	0.148	0.090	0.069	0.109
	p value	0.149	0.127	0.355	0.481	0.265
MCV	r	-0.017	-0.022	-0.006	0.067	0.322

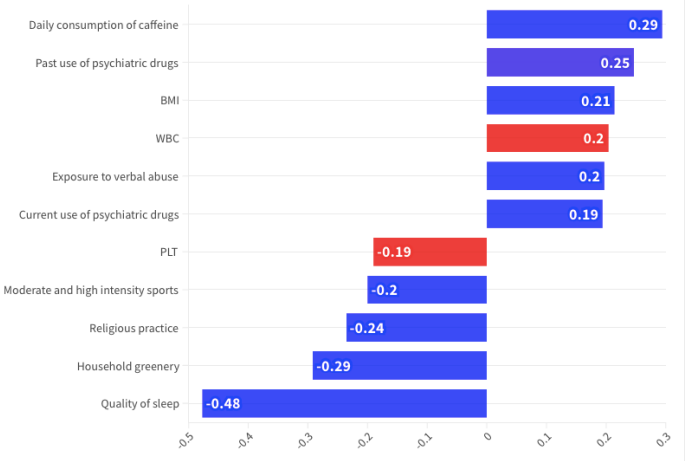
BDI Total



BDI Cognitive-Affective



BDI Somatic



	p value	0.858	0.818	0.949	0.493	**0.001****
MCH	r	-0.051	-0.061	-0.009	0.029	0.121
	p value	0.599	0.534	0.928	0.770	0.214
MCH C	r	-0.060	-0.073	-0.007	0.005	-0.075
	p value	0.541	0.455	0.942	0.957	0.443
PLT	r	-0.156	-0.114	-.192	-0.181	0.023
	p value	0.109	0.244	**0.047***	0.062	0.812
LYM%	r	-0.118	-0.070	-0.135	-0.113	0.103
	p value	0.227	0.474	0.166	0.245	0.291
MXD %	r	0.080	0.097	0.026	0.198	0.303
	p value	0.444	0.348	0.803	0.054	**0.003****
NEUT %	r	0.034	-0.010	0.083	0.026	-0.221
	p value	0.740	0.925	0.423	0.802	**0.031***
LYM#	r	0.104	0.110	0.095	0.026	0.175
	p value	0.286	0.258	0.329	0.792	0.072
MXD#	r	0.215	.203	0.187	0.223	0.260
	p value	**0.037***	**0.048***	0.069	**0.030***	0.011*
NEUT #	r	0.158	0.109	0.194	0.097	-0.066
	p value	0.123	0.290	0.058	0.348	0.525

Significant correlations between environmental and life-style factors and biomarkers on one hand and BDI total score, BDI cognitive-affective score and BDI somatic score on the other hand are summarized in figure 6.

Figure 6: A summary of all significant correlations for BDI total score, BDI cognitive-affective score and BDI somatic scores, including environmental and life-style factors and inflammatory biomarkers (Developed by Flourish.studio)

Based on the findings from Table 10, another correlational analysis was conducted between biomarkers and specific symptoms of depression based on the BDI-II. Statistically significant results are presented in Table 11.

Table 11: The correlations between biomarkers and individual BDI items. * *p* value significant at the 0.05 level, ** *p* value significant at the 0.01 level

		Sadness	**Pessimism**	**Failure**	**Dissatisfaction**	**Guilt**	**Suicidal ideation**	**Crying**	**Loss of interest**	**Indecisiveness**	**Self-worth**	**Retardation**	**Loss of energy**	**Anger**	**Loss of appetite**	**Loss of libido**
EGF	r	-0.016	-0.080	-0.144	0.016	-0.098	-0.093	0.124	0.065	0.076	-0.165	.225*	-0.088	0.022	-0.153	-0.043
	p value	0.883	0.458	0.181	0.879	0.366	0.388	0.250	0.547	0.481	0.124	**0.035**	0.418	0.835	0.154	0.690
FGF-2	r	-0.060	-0.052	-0.031	0.006	0.120	.213*	-0.078	0.126	-0.043	0.089	-0.033	0.091	0.014	0.007	-0.095

	p value	0.558	0.610	0.760	0.955	0.236	**0.034**	0.440	0.214	0.669	0.379	0.743	0.369	0.894	0.947	0.351
FGF-21	r	0.140	0.109	0.031	-0.032	-.215*	0.108	0.123	0.128	-0.126	-0.099	0.009	0.053	-0.037	0.081	-0.136
	p value	0.191	0.308	0.773	0.763	**0.043**	0.316	0.251	0.230	0.241	0.358	0.930	0.625	0.730	0.451	0.205
FGF-9	r	-0.111	-0.013	0.046	0.033	0.063	0.120	-0.086	.236*	-0.031	0.027	0.017	0.110	0.026	0.187	.219*
	p value	0.258	0.896	0.642	0.738	0.522	0.222	0.381	**0.015***	0.751	0.786	0.864	0.264	0.795	0.056	**0.024***
IGF-1	r	0.167	-0.002	0.024	-0.033	0.029	0.004	0.126	-0.031	0.089	-0.080	.261*	0.057	0.042	-0.066	-0.191
	p value	0.112	0.987	0.824	0.751	0.782	0.969	0.230	0.766	0.398	0.446	**0.012***	0.589	0.690	0.530	0.068
IL-1β	r	0.075	0.044	0.004	0.015	-0.178	0.122	-0.025	.204*	-0.034	0.053	0.029	0.087	-0.019	0.127	-0.048
	p value	0.472	0.675	0.971	0.884	0.084	0.238	0.812	**0.048***	0.741	0.613	0.777	0.403	0.855	0.219	0.645

IL-17	r	0.072	0.058	0.147	0.146	0.022	0.061	0.184	0.183	0.162	0.109	.233*	0.052	0.053	-0.042	.220*
	p value	0.472	0.561	0.139	0.144	0.824	0.542	0.064	0.066	0.104	0.278	**0.019***	0.606	0.599	0.677	**0.026***
IL-6	r	-0.061	0.039	0.088	-0.005	0.105	.281**	-0.020	0.173	0.073	0.163	0.004	0.097	0.061	0.096	0.115
	p value	0.535	0.695	0.374	0.960	0.287	**0.004****	0.841	0.078	0.462	0.097	0.970	0.323	0.538	0.329	0.241
TNF-α	r	0.075	.243*	0.126	-0.041	0.029	0.180	-0.043	.221*	0.155	0.179	0.019	0.102	0.032	0.098	0.062
	p value	0.470	**0.017***	0.222	0.690	0.779	0.080	0.678	**0.031***	0.131	0.082	0.851	0.324	0.759	0.340	0.546
VEGFD	r	0.108	0.078	.216*	0.099	0.135	0.131	0.193	0.139	0.172	0.055	.270**	0.051	0.144	-0.112	0.083
	p value	0.281	0.438	**0.029***	0.320	0.176	0.189	0.052	0.163	0.084	0.583	**0.006****	0.610	0.148	0.260	0.408
WBC	r	0.010	0.047	0.120	0.144	0.029	0.096	.211*	0.176	0.159	0.165	0.091	.193*	0.161	.245*	0.073
	p value	0.920	0.632	0.218	0.139	0.767	0.328	**0.029***	0.070	0.102	0.089	0.354	**0.047***	0.098	**0.011***	0.456

RBC	r	0.019	0.067	0.070	.210*	0.058	0.156	0.063	0.166	0.143	.199*	0.066	0.045	0.037	.207*	0.054
	p value	0.845	0.490	0.476	**0.030***	0.552	0.109	0.522	0.087	0.143	**0.039***	0.501	0.648	0.705	**0.033***	0.580
MCH	r	.194*	0.127	-0.052	-0.058	0.050	0.024	0.022	-0.042	0.084	-0.046	0.014	0.162	-0.068	-0.048	-0.120
	p value	**0.045***	0.194	0.595	0.552	0.611	0.807	0.821	0.670	0.388	0.637	0.890	0.095	0.485	0.623	0.219
PLT	r	-0.097	-0.044	0.037	-0.190	-.232*	-0.167	0.027	-0.159	-0.117	-0.007	-0.049	-0.187	-0.119	-0.068	-0.113
	p value	0.320	0.655	0.704	0.050	**0.016***	0.086	0.785	0.101	0.231	0.944	0.619	0.054	0.222	0.484	0.246
LMP%	r	0.061	-0.023	-0.011	-0.026	-0.011	-0.062	-0.017	-0.085	-0.069	-0.055	0.054	-.193*	-0.085	-0.111	-0.034
	p value	0.533	0.816	0.907	0.793	0.913	0.525	0.859	0.385	0.479	0.573	0.580	**0.046***	0.382	0.253	0.731
MXD%	r	0.118	0.111	0.180	0.044	-0.037	0.112	0.071	0.025	-0.037	0.040	-0.183	0.041	0.109	-0.036	.215*

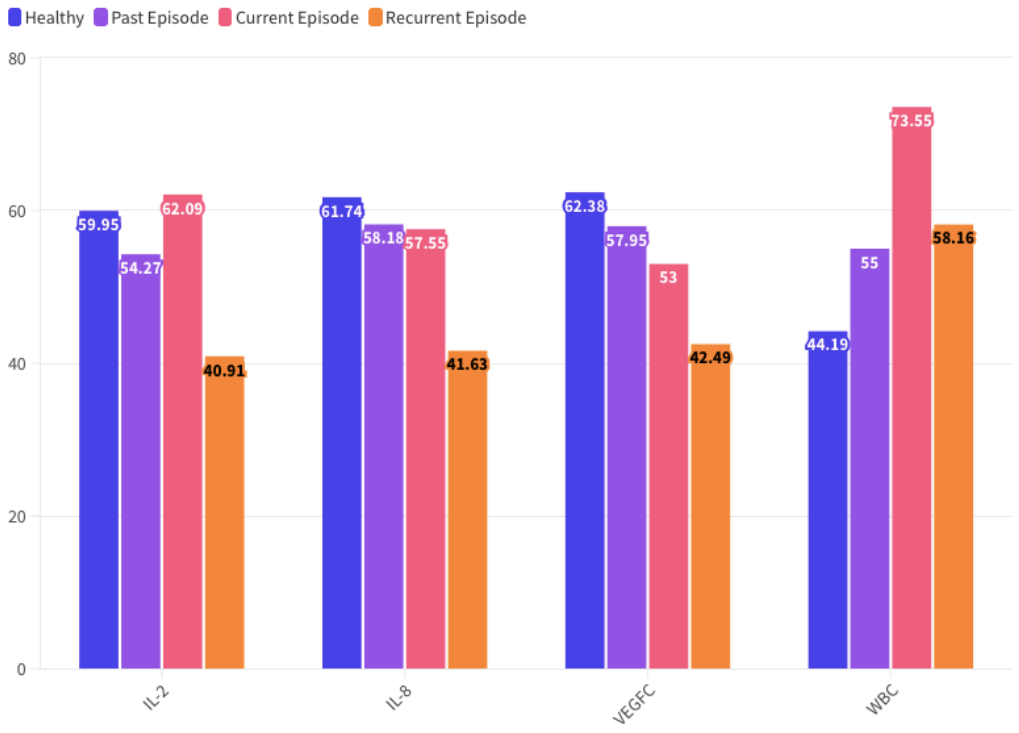
	p value	0.254	0.284	0.081	0.670	0.722	0.281	0.494	0.809	0.721	0.703	0.076	0.692	0.295	0.728	**0.036***
LYM #	r	0.061	0.070	0.159	0.154	0.069	0.091	.211*	0.094	0.084	0.157	0.067	0.029	0.111	0.124	0.065
	p value	0.531	0.473	0.102	0.114	0.482	0.354	**0.029***	0.335	0.391	0.105	0.491	0.765	0.255	0.204	0.505
MXD #	r	0.112	0.153	.223*	0.138	-0.027	0.192	0.177	0.099	0.078	0.121	-0.105	0.137	.216*	0.058	.233*
	p value	0.278	0.138	**0.030**	0.182	0.798	0.062	0.087	0.342	0.455	0.242	0.310	0.185	**0.035**	0.576	**0.023**
NEUT #	r	-0.062	-0.028	0.017	0.095	-0.003	0.032	0.117	0.135	.212*	0.058	0.105	0.099	0.143	.203*	0.015
	p value	0.545	0.785	0.866	0.355	0.978	0.754	0.257	0.189	**0.038**	0.574	0.307	0.052	0.163	**0.047**	0.884

Additionally, some biomarkers have shown to be able to discriminate between diagnostic status as per the MINI; healthy controls, past episode, current episode, and recurrent episode. These are presented in table 12. A summary of mean biomarker concentration in each of the four diagnostic statuses is presented in figure 7.

Table 12: Significant results of Kruskal-Wallis analysis of the association between different biomarkers and the diagnostic status as per the MINI. * *p* value significant at the 0.05 level, ** *p* value significant at the 0.01 level

	Chi-Square	***df***	***p* value**
IL-2	8.250	3	**0.041***
IL-8	8.534	3	**0.036***
VEGFC	8.034	3	**0.045***
WBC	8.917	3	**0.03***

Figure 7: Median biomarker concentration in each of the four diagnostic statuses. Only biomarkers that have shown to have a significant association are shown in this figure. (Developed by Flourish.studio)



Additionally, several biomarkers that were able to significantly differentiate participants with recurrent MDD, as the highest-risk group, from the rest of the sample. These included FGF-2 (p=

0.0492*, mean in recurrent group = 177.14, mean in the rest of the sample = 365.46), IL-2 (p= 0.0060**, mean in recurrent group = 30.95, mean in the rest of the sample = 136.31), IL-6 (p= 0.0247*, mean in recurrent group = 15.93, mean in the rest of the sample = 30.41) and IL-8 (p= 0.0219*, mean in recurrent group = 95.53, mean in the rest of the sample = 249.59). On the other hand, FGF-2 was able to discriminate between healthy controls and the rest of the sample (p= 0.0150*, mean in the healthy controls group = 503.90, mean in the rest of the sample = 188.68), as well as WBC (p-value= 0.0163*, mean in the healthy controls group = 5.92, men in the rest of the sample = 6.83) and NEUT# (p-value= 0.0199*, mean in the healthy controls group= 3.10, mean in the rest of the sample, 3.89).

3.4 Multivariate Linear Regression Model

Three multivariate linear regression models were then used to identify preferential significant predictors of total BDI score, total cognitive-affective score and total somatic score. After conducting multicollinearity diagnostics using Variance Inflation Factor (VIF), no substantial evidence among independent variables was found. Factors that were initially significantly correlated with the outcome variable were included in the preliminary regression models which were then refined by removing insignificant variables and developing the most predictive model. Results are presented below in table 13 for total BDI score, table 14 for cognitive-affective score and table 15 for somatic score.

Table 13: Comparative analysis of the initial and most predictive multivariate linear regression models highlighting key significant predictors of total BDI score

	Preliminary Regression Model	***p* value**	**Most Predictive Regression Model**	***p* value**
Verbal abuse	0.263	0.001	0.275	0.001

Average internet use per day	0.316	0.001	0.349	0.000
BMI	0.336	0.000	0.309	0.000
Daily consumption of caffeine	0.282	0.007	0.439	0.000
Quality of sleep	-0.200	0.062	0.247	0.003
Feeding	0.119	0.296		
Past Psychiatric drugs	0.201	0.030		
MXD#	0.141	0.148		
WBC	-0.160	0.111		
Moderate/high intensity sports	-0.052	0.549		
Religious practices	-0.079	0.368		
Employment	0.017	0.870		
Household greenery	-0.200	0.032		
R-squared	0.598		0.520	
Adjusted R square	0.522		0.489	

Table 14: Comparative analysis of the initial and most predictive multivariate linear regression models highlighting key significant predictors of BDI cognitive-affective score

	Regression 1	***p* value**	**Regression 2**	***p* value**
Verbal abuse	0.373	0.000	0.386	0.000
Average internet use per day	0.226	0.028	0.293	0.003
BMI	0.266	0.011	0.297	0.003
Daily consumption of caffeine	0.308	0.007	0.419	0.000

Feeding	0.093	0.403		
MXD#	0.082	0.440		
IL-10	-0.151	0.127		
Moderate/high intensity sports	-0.116	0.285		
Second-hand smoking at home	-0.038	0.708		
Household greenery	-0.131	0.223		
Quality of sleep	0.114	0.275		
R-squared	0.493		0.411	
Adjusted R square	0.397		0.374	

Table 15: Comparative analysis of the initial and most predictive multivariate linear regression models highlighting key significant predictors of BDI somatic score

	Regression 1	***p* value**	**Regression 2**	***p* value**
Verbal abuse	0.191	0.018	0.184	0.024
Daily consumption of caffeine	0.139	0.124	0.254	0.002
WBC	0.147	0.095	0.172	0.033
Current psychiatric drugs	0.143	0.086	0.169	0.035
Quality of sleep	0.367	0.000	0.445	0.000
Past psychiatric drugs	0.125	0.158		
BMI	0.089	0.293		
PLT	-0.120	0.159		

Moderate/high intensity sports	-0.028	0.727		
Religious practices	-0.121	0.145		
Household greenery	-0.156	0.069		
R-squared	0.463		0.391	
Adjusted R square	0.399		0.360	

As shown above, the three most predictive models exhibit moderate explanatory strength with approximately 48.7%, 37.4% and 36% of the variability by the predictors in total BDI score, cognitive affective score and somatic scores respectively.

3.5 Mediational Analysis

Given the large number of variables in this study, artificial intelligence was used to determine candidate mediators between different risk factors, and MDD-related outcomes. The following were preliminarily recommended for further mediational analyses:

a. *MXD#* as a mediator between *average internet use* and *BDI total* (Table 16)

b. *MXD#* as a mediator between the *being breastfed* and *BDI total* (Table 17)

c. *PLT* as a mediator between *quality of sleep* and *BDI somatic* (Table 18)

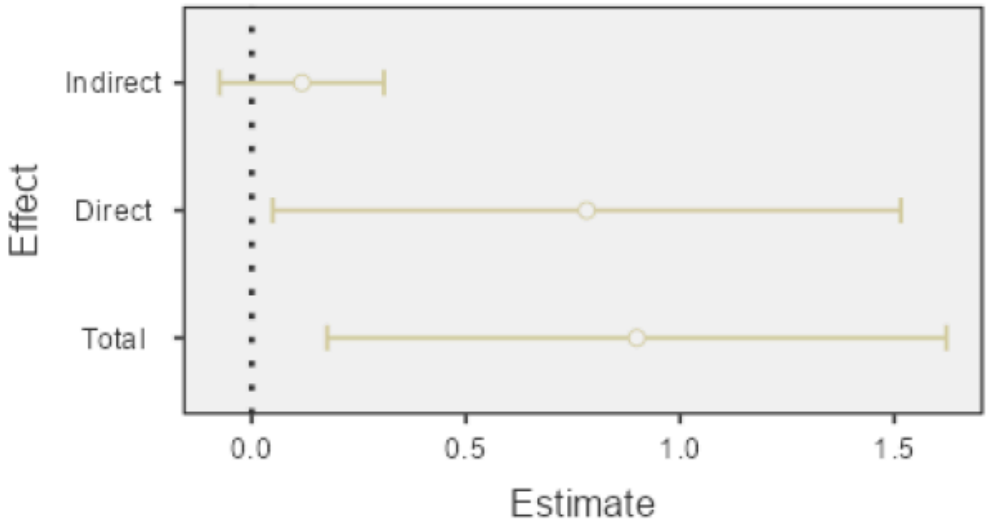
Two levels of statistical analysis were computed including direct and indirect effects. Direct effect refers to the effect of the independent variable on the dependent variable, whereas the indirect effect refers to the effect of the mediation.

Table 16: Results of meditational analysis of the effect of MXD# between average internet use and BDI total

Effect	**Estimate**	**SE**	***p***	**% Mediation**
Indirect	0.117	0.0979	0.233	13.0

Direct	0.782	0.2740	0.037	87.0
Total	0.899	0.3688	0.015	100.0

Figure 8: Estimate plot for the meditational effect of MXD# between average internet use and BDI total



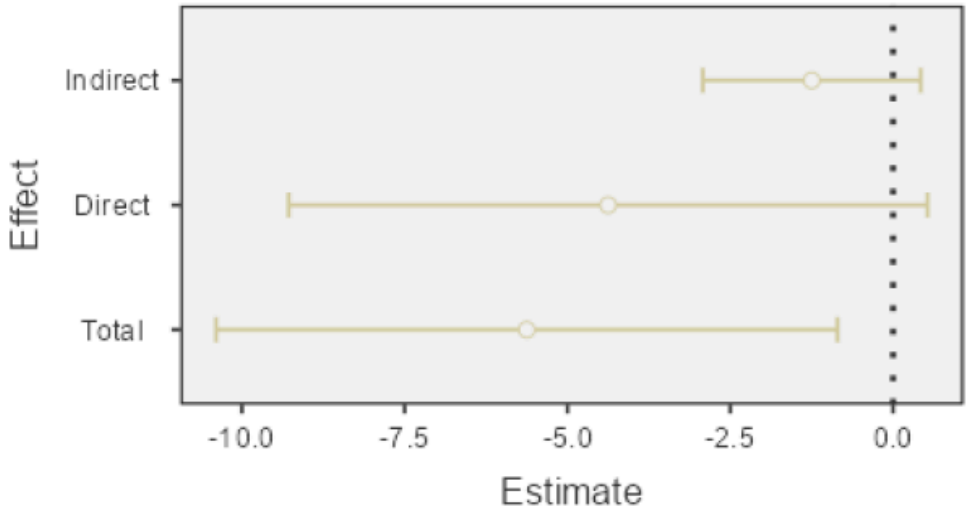
The low indirect effect means that the pure effect of MXD# on BDI is not significant, accounting only for 13% in the variation in BDI total. The direct effect, on the other hand, is significant suggesting average internet use as the main effector on the BDI total. However, given that the total effect is moderately increased by the MXD#, his suggests that MXD# is a weak-medium mediator with an additive effect on the direct effect.

Table 17: Results of meditational analysis of the effect of MXD# between being breastfed and BDI total

Effect	**Estimate**	**SE**	***p***	**% Mediation**
Indirect	-1.25	0.853	-0.143	22.2

Direct	-4.38	2.502	0.080	77.8
Total	-5.62	2.434	0.021	100.0

Figure 9: Estimate plot for the meditational effect of MXD# between being breastfed and BDI total



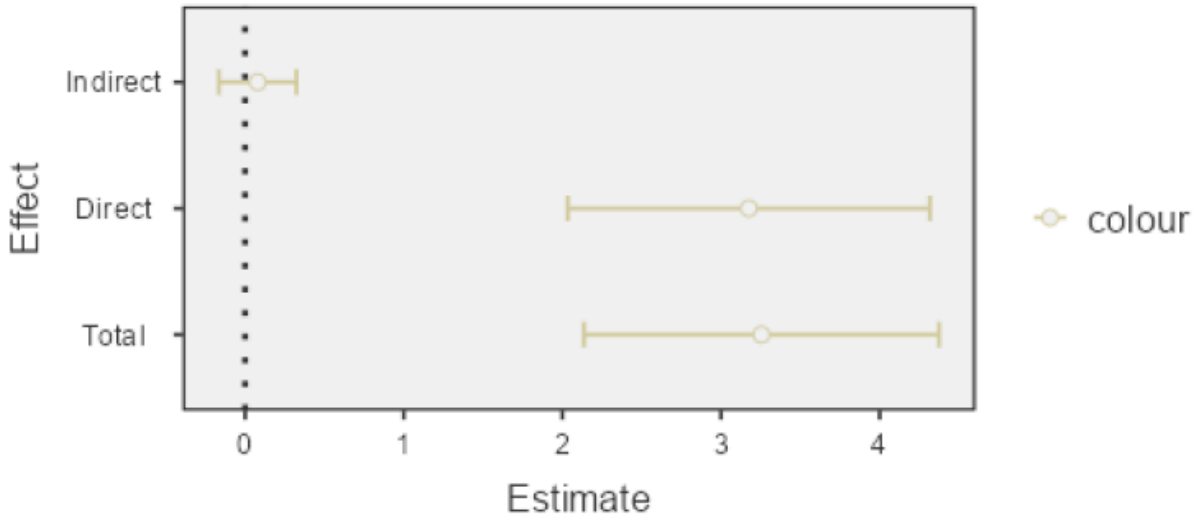
Both the direct and indirect effects are insignificant. However, the total effect is significant. This means that being breastfed is a significant predictor of BDI total, only when combined with the effect of MXD#. This suggests that the mediation is a significant mediation given the additive effect, despite the insignificance of the indirect effect.

Table 18: Results of meditational analysis of the effect of PLT between sleep quality and BDI somatic

Effect	**Estimate**	**SE**	***p***	**% Mediation**

Indirect	0.0797	0.125	0.523	2.45
Direct	3.1755	0.582	<0.001	97.55
Total	3.2552	0.571	<0.001	100.0

Figure 10: Estimate plot for the meditational effect of PLT between sleep quality and BDI somatic



The insignificant indirect effect of PLT between sleep quality and BDI somatic suggests that it only accounts for 2.45% of the variation in BDI somatic. The direct effect, on the other hand, is highly significant. The total effect is not increased significantly by the additive value of PLT. This means that the mediation is insignificant suggesting sleep quality as the main effector on BDI somatic without mediation.

Chapter 4

Discussion

This chapter shall present a detailed analysis of the findings of this study highlighting significant implications pertaining to precision mental health, in addition to discussion of the main limitations of the study providing a critical evaluation of such limitations and offering suggestions for future research. This study has explored the relationship between MDD and various biomarkers, particularly inflammatory markers and their correlation with MDD severity and

symptomatology. The findings shall contribute to a growing body of evidence that underscores the significance of systemic inflammation in the pathology of MDD, representing a step forward towards a better understanding of the environmental and biological underpinnings of MDD. Ideally, this should pave the way for more advancements in the research, treatment and prevention of MDD, ultimately contributing to better and more personalized patient outcomes.

4.1. MDD Outcomes

First of all, the strong positive correlations between diagnostic items on the MINI and the corresponding items of BDI-II indicates high convergent validity supporting the use of both in the assessment of MDD as a clinical construct. This is further supported by the strong positive association between the BDI total score and severity on one hand, and the diagnostic status as per the MINI on the other hand. The sub-scaling of the BDI-II offered an additional benefit facilitating the differentiation of subtypes of depression. This is crucial for several reasons including improving diagnostic accuracy and understanding the etiology of depression more thoroughly. For the purpose of this study, cognitive-affective symptoms of depression have been differentiated from somatic symptoms of depression. Although both are prevalent, somatic symptoms are of great importance given their significant impact on the disease disability burden (Morin et al., 2019). Additionally, somatic symptoms might be more prevalent in cultures, such as Egypt, where stigma and other sociocultural factors, may favor somatization over the open expression of emotions (Bagayogo et al., 2013). Besides social acceptance of somatic symptoms rather than emotional symptoms, in such cultures psychological distress might be culturally indicative of personal weakness or lack of faith which are both frowned upon (Okasha, 2019). In this regard, and in addition to categorical diagnosis and total depression scores, a symptom-based approach has been adopted to understand the link between different exposures and/or biomarkers, and specific symptoms of MDD.

Rates of help-seeking behaviors among those in a current MDD episode are alarming given the low proportion of people seeking psychotherapy (23.1%) and taking psychiatric medications (27%). Reasons for not seeking psychotherapy were not examined in the questionnaire; however,

during the interviews some participants casually referred to the high cost of psychiatric care and the prevailing economic challenges which necessitated prioritizing other needs over mental health. Others were concerned about the reputation of mental health professionals and the bad experience encountered by others seeking treatment. Literature from Egypt suggests several other reasons of similar patterns in the larger population. Some reasons include the dichotomous view of mental health assuming that people are either mentally ill or healthy and, in this sense, someone with depressive symptoms would not be culturally perceived as "mentally ill" if more serious considered are taken into consideration (i.e.: psychosis). The stigma, poor treatment capacity and disappointment with the status of the mental health care system are other reasons (Kamel et al., 2021), seeking help from traditional and faith healers (Rakhawy & Hamdi, 2010). Other studies have proposed the preference to solve one's own problems (Baklola et al., 2023).

4.2 Psychosocial and Environmental/Lifestyle Factors

In terms of psychosocial factors, our findings confirm findings showing a link between religious practices and lower severity of depressive symptoms and somatic symptoms of depression suggesting religiosity as a protective factor in depression (Braam et al., 1997; Braam & Koenig, 2019; Hahn et al., 2004; Ronneberg et al., 2016). More specifically, this is in line with findings by McCullough & Larson (1999) showing a negative correlation between involvement in formal religious and somatic-retarded depressive symptoms among Christians at 7-year follow up and other findings suggesting a link between spirituality and increased tolerance of pain (Rush et al., 2020). In other words, people who are spiritually and tend to practice religious rituals may be more able to attribute meaning to their painful experiences, including physical experiences. A more detailed study suggested that spirituality may be associated with less somatic symptoms of depression through the moderation of positive emotions, but only in some cultures and not in others (Maulina, Yogo, & Ohira, 2022). Ironically, some of the factors initially hypothesized to have a protective role in relation to depressive risk is meditation and mindful practices (Reangsing et al., 2020) to the point that research has examined the neurophysiological mechanisms by

which this relation can be explained (Kasala et al., 2014). However, none of this has been established by our findings. Several reasons behind this might include, the variation in the type of practice (i.e.: yoga, meditation, mindfulness, … etc), the consistency and duration of practice, the quality of the practice, the individual's expectations, in addition to other methodological concerns discussed later in the study limitations. However, put together with the significant findings from religious practices, this might highlight the cultural element involved here given the Egyptian context where the popularity and belief in religious practices might outweigh other spiritual and mindful practices. In this regard, it has to be noted that most literature originates from non-Arab and non-Islamic communities, so the comparison of findings without adequately accounting for cultural variations might not yield accurate results given the high interplay between culture and psychosocial factors.

As another significant lifestyle factor, moderate/high intensity sports, rather than low-intensity physical activity, has been shown to reduce risk of depression severity, in addition to severity of cognitive-affective symptoms and somatic symptoms. Psychosocially, this relationship can be mediated by improved self-esteem and social support received from sports groups (Babiss & Gangwisch, 2009). Biologically, physical activity can improve neuroplasticity, and attenuate inflammation and oxidative stress (Kandola et al., 2019). More specifically, physical exercise has been shown to up regulate the expression of the PGC1α gene which is involved in reducing pro-inflammatory cytokines and promoting anti-inflammatory cytokines. Therefore, it is also hypothesized to induce changes in the monoaminergic neurotransmission and reduce glutamateregic neurotoxicity (Ignácio et al., 2019). Physical exercise has also been shown to increase IGF-1 and increase the expression of BDNF which interfere with the expression of depressive-like symptoms (De Sousa et al., 2021). In one interesting study, physical activity has also been correlated with hippocampal volume and hippocampal volume has been negatively correlated with depressive symptoms in boys (Gorham et al., 2019).

Transitioning from physical activity to sleep, sleep problems have been shown to be a core symptom in depression in addition to a prospective risk factor for non-depressed individuals

(Nutt et al., 2022). Findings shows the poor sleep quality, rather than number of hours of sleep, and number of hours using internet as two risk factors for high severity of depressive symptoms, somatic symptoms and cognitive-affective symptoms, and severity of depressive symptoms and cognitive-affective symptoms respectively. This is well-documented in research highlighting the effects of problematic smartphone use on both sleep quality and depression (Jiaxin et al., 2020). Problematic internet use can be also linked with emotional problems through the mediation of experiential avoidance of reality and desire thinking as two problematic cognitive processes (Faghani et al., 2020).

Another major psychosocial factor that has been conceptualized in research as a risk factor for mental health problems is exposure to different types of abuse (Radell et al., 2021). Before discussing the correlations demonstrated by the current study, it has to be noted that the lifetime prevalence of verbal abuse (83%), physical abuse (46%) and sexual abuse (41%) in the sample is alarming given its long-term impacts on individuals' wellbeing. Such exposures are not only linked with depression, but can also significantly increase an individual's risk of various other problems including anxiety and post-traumatic stress disorder which were not assessed in this study. In the current study exposure to verbal abuse has been linked with both depression severity and more specifically, the severity of the cognitive-affective symptoms of depression. This can be explained in terms of the mediating role of self-criticism in individuals exposed to verbal abuse (Sachs-Ericsson et al., 2006) as they internalize what they have been exposed to and start incorporating it into their own self-narratives. The lack of significant association between exposure to physical abuse and any MDD outcome can be explained, instead, in terms of the positive association between physical abuse and drug use which has been documented in this study and other studies (Lansford et al., 2002; Malinosky-Rummell & Hansen, 1993; Strathearn et al., 2020). That is to say, individuals subjected to physical abuse did not develop typical depressive symptoms that would typically qualify them for an MDD diagnosis. Instead, they were at significantly higher risk of engaging in self-medication using drugs compared to those who were exposed to verbal and sexual abuse. This does not necessarily mean that exposure to physical abuse does

not increase the risk of MDD, but rather that it could increase the risk of a masked depression profile.

Looking at other lifestyle factors, the negative association between employment status and severity of depressive symptoms can be interpreted in terms of the disability burden of depression leaving patients unable to be functional on one hand (Campbell et al., 2022) or the protective role of employment in relation to depression and other mental health outcomes on the other hand (van Der Noordt et al., 2014). Similarly, the link between BMI and severity of depressive symptoms can be interpreted from two directions, or put together, as a vicious cycle. First, the metabolic consequences of high BMI increase the biological risk factors for depression (Tyrrell et al., 2019) including neuroinflammation (Fulton et al., 2021). Alternatively, depression can increase the risk of emotional eating problems which therefore increase one's risk of obesity (Konttinen, 2020).

Although none of the dietary or supplementary factors have shown to influence MDD outcomes, caffeine did. As having psychostimulant effects and modulatory effects on the dopaminergic pathways, caffeine is hypothesized and proven to have protective effects against depression (Alasmari, 2020; Ferré et al., 2008). This may explain findings showing reduced risk of depression associated with higher caffeine intake (Lucas et al., 2014). However, the current findings shows the opposite which might be attributed to the unhealthy lifestyle factors that are usually associated with high caffeine intake including poor sleep (ref), high anxiety (Botella & Parra, 2003) which both increase the risk and severity of depression.

Moving from lifestyle factors towards the foundational influences occurring in early life, the very intriguing link between being breastfed and a lower risk of depressive symptoms is supported by research body highlighting the protective effects of breastmilk on brain health. For example, one study showed lower neuroticism, as a personality trait, among individuals who were breastfed supporting the assumption that breastfeeding can have long-term psychological benefits (Sutin et al., 2016). Breastfeeding has also been linked with better cognitive functioning in adolescents (Beaver et al., 2010) and less psychological distress in adults (Cable et al., 2012) in

adults. Although the mechanism of action by which this relationship exists is not fully understood, it can be at least partially explained in terms of the immunological components of breast milk (Hosea Blewett et al., 2008) which is aligned with the inflammatory theory of depression. Finally, in terms of exposures and looking at the broader environmental context, in a city that is heavily populated and largely urbanized with very little greenery such as Cairo, our study supports other findings showing a negative correlation between exposure to greenery and depressive symptoms (Zhang et al., 2023), lower risk of depression (Perrino et al., 2019), better quality of life (Carver et al., 2018) and lower suicide mortality (Helbich et al., 2020). This does not only shed light on the interaction between environment and mental health outcomes, but also on the importance of thought-out urban planning that takes into consideration different biopsychosocial factors on the inhabitants and the environment in which they live.

4.3 Inflammatory and Neurotrophic Factors

In terms of biomarkers, despite the study's inability to demonstrate statistically significant differences in levels of inflammatory and neurotrophic factors between healthy controls and individuals with current MDD episodes, a notable merit is its contribution with a reference for different biomarkers derived from an Egyptian sample, which is particularly valuable given the lack of such clinical benchmarks from local research. A list of international studies examining the same biomarkers in patients with MDD with the estimated mean peripheral concentration is summarized in table 19. For the sake of having a fair comparison, studies using samples with comorbid medical conditions and specific clinical groups were excluded (i.e.: cancer, cardiovascular disease, pregnancy, ..etc). It is notable that the ranges in different studies for the same biomarker are wide, and in this regard no specific standard can be set. Apart from clinical conditions which might directly impact the expression of different inflammatory and neurotrophic factors, such substantial differences can be attributed genetic variations in genes **coding** for such factors (Biong et al., 2010; Song et al., 2012) and lifestyle factors such as smoking (Haddy et al.,

2004), all of which can vary from one population to the other. This underscores the empirical importance of investigating the expression of such factors independently in different populations instead of using external reference standards as normal.

Table 19: A summary of international studies examining the same biomarkers in patients with MDD with the estimated mean peripheral concentration

Biomarker	**Reference**	**Population**	**Citation**
EGF	524.70 ± 27.25 pg/ml in MDD patients and 672.52 ± 49.64 pg/ml in healthy controls	Patients with MDD and healthy controls in Bangladesh	(Sohan et al., 2023)
EGF	9.2 µg/dL (2.6–26.3) in MDD patients and 9.7 µg/dL (3.9–39.7) in healthy controls	Elderly patients with MDD, with the majority receiving treatment and healthy controls	(Wu et al., 2019)
FGF-2	3.51 pg/ml ±4.62 in MDD patients and 3.19 pg/ml ±3.28 in healthy controls	Patients with MDD and healthy controls in Japan	(Takebayashi et al., 2010)

FGF-2	Baseline level of 200.49 pg/ml ±134.48 And after-treatment level of 188.12 pg/ml ±128.18	Patients with MDD in China	(He et al., 2014)
FGF-2	27.8 μg/dL (1.8–92. 9) in MDD patients and 35.7 μg/dL (4.4–117.7) in healthy controls	Elderly patients with MDD, with the majority receiving treatment and healthy controls	(Wu et al., 2019)
FGF-21	7.3 pg/mL1.3± in MDD patients and 6.3 pg/mL1.5± in healthy controls	Patients with MDD and healthy controls in the US	(Mason et al., 2022)

IGF-1	23.4 ng/mL ± 6.8 in MDD patients and 16.4 ng/mL ± 4.1 in healthy controls	Patients with MDD and healthy controls in China	(Li & Guo, 2017)
IGF-1	128.1 pg/mL ± 48.3 in MDD patients and 121.2 pg/mL ± 51.6 in healthy controls	Patients with MDD and healthy controls in Italy	(Rosso et al., 2016)
IL-17	10.03 pg/mL ± 0.6 in MDD patients and 7.6 pg/mL ±0.6 in healthy controls	Patients with MDD and healthy controls in Iran	(Davami et al., 2016)
IL-17	60.80 pg/mL in late-life depression and 61.32 pg/mL in healthy controls	PAtients with late-life depression and healthy controls in Brazil	(Saraykar et al., 2017)

VEGFC	2.45 pg/mL ± 0.29 before treatment and 2.28 pg/mL ± 0.48 after treatment	Patients with treatment-resistant depression in UK	(Pisoni et al., 2018)
VEGFD	2.77 pg/mL ± 0.20 before treatment and 2.79 pg/mL ± 0.19 after treatment	Patients with treatment-resistant depression in UK	(Pisoni et al., 2018)
IL-**1**β	0.48 pg/mL ± 0.17 in healthy controls 1.16 pg/mL ± 0.23 in mild depression 1.71 pg/mL ± 0.21 in moderate depression 2.66 pg/mL ± 0.33 in severe depression	Patients with depression versus healthy controls in Poland	(Oglodek, 2022)

Il-2	118.04 pg/mL ± 166.55 before treatment and 102.93 pg/mL ± 211.28 after treatment	Patients with MDD in Korea	(Kim et al., 2007)
Il-2	29.79 pg/mL 6.18 ± in MDD patients and 12.77 pg/mL 4.84 ± in healthy controls	In Bangladesh	(Suhee et al., 2023)
IL-2	33.10 pg/mL ± 28.8; in faster onset and 64.06 pg/mL ± 141.7 in slower onset	Patiets with MDD in Berlin	(Buspavanich et al., 2021)
IL-4	20.90 pg/mL ± 4.6 in faster onset and 28.29 pg/mL ± 28.8 in slower onset	Patiets with MDD in Berlin	(Buspavanich et al., 2021)

Il-4	9.71 pg/mL ± 0.5 in healthy controls 11.65 pg/mL ± 0.95 in mild depression 14.99 pg/mL ± 0.38 in moderate depression 16.85 pg/mL ± 0.38 in severe depression	Patients with depression versus healthy controls in Poland	(Oglodek, 2022)
Il-4	10.92 ± 1.04 pg/ml in MDD and 21.67 ± 20.73 pg/ml in healthy controls	Patients with MDD and healthy controls in Korea	(Myint et al., 2005)
Il-4	76.96 pg/ml ± 60.48 before treatment and 77.21 pg/ml ± 65.70 after treatment	Patients with MDD in Korea	(Kim et al., 2007)

IL-6	15.6 pg/ml ± 28.4 in MDD patients and 9.6 pg/ml ± 11.3 in healthy controls	Patients with MDD and healthy controls in Bulgaria	(Mikova et al., 2001)
IL-6	30.57 pg/ml ± 14.9 in faster onset and 67.64 pg/ml ± 134.4 in slower onset	Patiets with MDD in Berlin	(Buspavanich et al., 2021)
IL-6	442.90 pg/mL ±124.71 before treatment and 408.31 pg/mL ± 136.26 after treatment	Patients with MDD in Korea	(Kim et al., 2007)
IL-8	77.70 pg/mL ± 146.4 in faster onset and 82.33 pg/mL ± 69.2 in slower onset	Patiets with MDD in Berlin	(Buspavanich et al., 2021)

IL-8	0.54 pg/mL ± 0.2 in healthy controls 0.70 pg/mL ± 0.16 in mild depression 1.45 pg/mL ± 0.15 in moderate depression 1.56 pg/mL ± 0.27 in severe depression	Patients with depression versus healthy controls in Poland	(Oglodek, 2022)
IL-8	231.19 pg/mL ± 754.78 in MDD patients and 1.09 pg/mL ± 3.5 in healthy controls	Patients with MDD and healthy controls in the US	(Simon et al., 2008)
IL-10	59.55 pg/mL ± 24.9; in faster onset and 122.67 pg/mL ± 214.3 in slower onset	Patiets with MDD in Berlin	(Buspavanich et al., 2021)

IL-10	44.44 pg/mL ± 1.93 in healthy controls 40.57 pg/mL ± 1.47 in mild depression 37.51 pg/mL ± 2.15 in moderate depression 30.31 pg/mL ± 1.76 in severe depression	Patients with depression versus healthy controls in Poland	(Oglodek, 2022)
IFN-γ	23.57 pg/ml ± 8.2 in faster onset and 31.49 pg/ml ± 18.2 in slower onset	Patiets with MDD in Berlin	(Buspavanich et al., 2021)
IFN-γ	41.28 pg/ml ± 20.2 in MDD patients and 82.1 pg/ml ± 124.39 in healthy controls	Patients with MDD and healthy controls in Korea	(Myint et al., 2005)

IFN-γ	444.13 pg/ml ± 323.63 before treatment and 352.51 pg/ml ± 300.37 after treatment	Patients with MDD in Korea	(Kim et al., 2007)
TNF-α	Before agomelatine treatment 512.5 pg/ml ±86.2 After agomelatine treatment 391.64 pg/ml ±104.8 After fluoxetine treatment 554.14 pg/mL ±46.8 After fluoxetine treatment 484.15 pg/mL ±49.9	Indian patients with MDD with severe symptoms	(Gupta et al., 2017)

TNF-α	751.66 pg/mL ± 312.31 before treatment and 731.31 pg/mL ± 269.20 after treatment	Patients with MDD in Korea	(Kim et al., 2007)
TNF-α	47 pg/mL ± 6.6 in MDD patients and 28.06 pg/mL ±1.07 in healthy controls	Bangladeshi	Nayem et al, 2023
TNF-α	24.20 pg/mL ± 5.9 in faster on-set and 30.31 pg/mL in slower onset	Patiets with MDD in Berlin	(Buspavanich et al., 2021)
TNF-α	77.68 pg/mL ± 16.21 in MDD patients and 36.04 pg/mL ± 12.63 in healthy control	Patients with MDD in Turkey	(Sutcigil et al., 2007)

TNF-α	19.64 pg/mL ± 2.445 in MDD patients and 10.88 pg/mL ± 1.314 in healthy controls	Patients with MDD in Ireland and healthy controls	(O'Brien et al., 2007)

The significant correlations identified between different inflammatory factors, growth factors and whole blood parameters may indicate a complex network of communication between them in the pathology of MDD and other health outcomes. This relationship has been well-documented in relevant scientific literature. For example, some growth factors are able to functionally act as leukocyte chemoattractants, whereas some inflammatory molecules have the ability to induce the transcription of different growth hormone genes. Adding another layer to this complexity, T-lymphocytes are able to secrete growth factors in response to interaction with antigens which, consequently, leads to the regulation of the production of other growth factors by monocytes (Wahl et al., 1989). Research also suggests that different inflammatory molecules can trigger the dysregulation, whether up regulation or down regulation, of growth factors which mediates to the pathogenesis of depressive disorders. According to the synaptic plasticity theory of MDD, levels of growth factors can differentiate between individuals with MDD and healthy controls. One example to explain such mechanisms of action involves the neurotoxic effects of TNF-α, as an inflammatory biomarker, that trigger the down-regulation of brain-derived neurotrophic factor (BDNF) leading to neuronal death as in the pathophysiological model of MDD (Hoshikawa et al., 2022).

Similarly, WBC count has shown to be positively correlated with both depression severity and somatic symptoms severity. Platelets, on the other hand, was negatively correlated with somatic

symptoms severity. As an less examined inflammatory biomarker in depression, the link between white blood cells and severity of depressive symptoms confirms similar findings by other studies (Beydoun et al., 2016; Shafiee et al., 2017) and other findings suggesting a positive correlation between WBC and somatic symptoms of depression specifically (Gialluisi et al., 2020). The correlation between other complete blood count parameters and different outcomes demonstrated in this study is supported by similar findings showing a positive correlation between MCH and MCHC and the severity of depressive symptoms among older adults (Jong Oh et al., 2020), and other findings demonstrating higher WBC count, neutrophil percentage, platelet count in adolescent patients with MDD compared to healthy controls. Interestingly, in this particular study, the link between such biomarkers was even more significant in relation to suicidality severity than to depression severity (Puangsri & Ninla-aesong, 2021). Such findings were also established among more specific clinical populations (i.e.: coronary artery disease) promoting hematological inflammatory biomarkers as good parameters for depression risk (Demircan et al., 2016). In terms of response to treatment, research shows that a higher baseline platelet count could predict non-response to treatment among patients and that, following response to treatment, RBC count, hematocrit, RDW and lymphocyte percentage all increase compared to neutrophil and monocyte percentages (Puangsri et al., 2023). Put together along with findings from other biomarkers, this supports the hypothesis of systemic inflammation in the pathology of MDD.

IL-10 has been shown to be positively correlated with the overall severity of cognitive-affective symptoms of depression. Similarly, four biomarkers, IL-2, IL-8, VEGFC and WBC, have shown to be able to discriminate between healthy controls, individuals with history of episode of MDD, individuals with current episodes or MDD and individuals with recurrent MDD. No specific explanation is available from literature; however, such findings still support the growing body of research indicating the role of inflammatory and neurotrophic factors in neural and behavioral processes evident in MDD. Findings from mediation analysis may also support the hy-

pothesis of systemic inflammation in the pathology of MDD by highlighting the role of inflammatory mediators, rather than effectors, between some risk factors and the MDD outcomes. Out of all biomarkers which were linked to individual symptoms of depression in this study, the positive link between IL-6 and suicidality is the most intriguing. This has been documented in other studies examining the role of different inflammatory cytokines in the pathophysiology of suicidality and demonstrating consistently increased levels of IL-6 among suicide attempters (Amitai et al., 2020; Black & Miller, 2015; Gananca et al., 2016; Lindqvist et al., 2009; Mina et al., 2015; Serafini et al., 2013). This can be, at least, partially explained in terms of abnormal metabolism of dopamine and serotonin due to the inflammatory effect of IL-6 (Lindqvist et al., 2009).

4.4 Limitations

While this study has provided some insights into the exposome of MDD in a pilot Egyptian sample, it is important to acknowledge several limitations that may impact the robustness of its findings. First, in terms of sampling, the relatively small sample size limits the power of the study. Some subpopulations might have been unintentionally underrepresented including males, people with lower levels of education, ….etc. The use of non-random sampling increases the likelihood of bias and may, therefore, limit the generalizability of the findings. Methodological limitations pertaining to data collection include the absence of biomarkers of central inflammation such as biomarkers in cerebrospinal fluid and the complete reliance on peripheral biomarkers. Single-time blood analysis may be unable to show the dynamic nature and the complexity of biomarker fluctuations under different conditions. So, the cross-sectional study design has its own limitations not allowing the inference of temporal links between exposure and outcomes. Furthermore, no medical reference from the Egyptian population is available to determine clinical outliers of different biomarkers.

When it comes to the questionnaire, data collection relied mainly on self-reports leaving room for respondent's bias (i.e.: recall bias, social desirability bias, …etc). It would have also been prudent to investigate other culturally relevant variables hypothesized to pose potential risks to men-

tal health. These include the absence of one or both parents at a young age, exposure to female genital mutilation, and access to perinatal care. Potentially influential physiological variables such as menstruation during the time of the blood sample collection should have also been added. Moving to diagnosis and although current psychotic episodes were excluded based on the Mini mental-state examination, other potential psychiatric comorbidity was not screened, particularly for disorders that commonly co-occur with MDD such as anxiety disorders. This could have been performed using the M.I.N.I. Screen which is able to indicate whether it is likely that the patient has a major psychiatric disorder and, if yes, to provide additional questions to aid in diagnosis. However, this oversight occurred because of the researcher's unfamiliarity with such a tool.

Finally, the large number of variables and the possible interactions between them makes the interpretation of results challenging, possibly requiring more sophisticated statistical methods. This is particularly relevant when it comes to discussing the inflammatory processes and the involvement of different peripheral cytokines that are known to be constantly influenced by a wide range of factors. Therefore, tying inflammation to single predictors can be significantly problematic given that ruling out all other confounders is technically impossible.

Chapter 5

Conclusion and Recommendations

This study highlights the complex nature of MDD and its association with various biomarkers, particularly those related to inflammation and neurotrophic factors. Such findings do not only have the potential to enhance our understanding of the biological underpinnings of depression, but, if developed further, they may also pave the way for more personalized and effective treatment strategies. The study also acknowledges the well-established role of different lifestyle factors as risk factors for MDD and poor mental health outcomes in general.

Admitting the limitations of this study as discussed earlier opens a new opportunity for other researchers to dig deeper into our findings with more integrative approaches and methodologies. First, given that inflammation is a long-term process, involving short- and long-term effects, it is recommended to carry out longitudinal and follow-up studies to better understand the relationships between different biomarkers and depression. The temporal factor should also be taken into consideration in order to track the inflammatory progression over time. Another area of research that might be very promising with a great applied value, in light of the findings of this study, is investigating the effectiveness of anti-inflammatory

treatments in MDD, especially among patients with clinically high levels of inflammatory biomarkers. Such insights might help identify both at-risk individuals and those who might benefit therapeutically from specific targeted treatments.

On a broader scale, the Egyptian healthcare system may benefit from integrating biomarkers data and relevant clinical data from actual patients, and assessing their psychiatric profiles to add to the national research database related to this topic. This shall facilitate the adoption of a more holistic approach in treating MDD and in inspiring the development of personalized treatment for mental health problems. Research institutes should also invest in more advanced molecular and neuroimagining methodologies with larger samples to discover the mechanisms by which different biomarkers influence brain health and, more specifically, depression. With big advances in precision medicine software market (i.e.: 2bPrecise, PierianDx) and artificial intelligence modeling, research should invest in its findings using such modern technologies in order to facilitate data management and move faster towards personalized management of mental health issues (Deif & Salama, 2021).

This study highlights the effect of different lifestyle factors on MDD outcomes, such as physical exercise. In terms of implications, this underscores the importance of non-medication adjunctive treatment in the comprehensive management of MDD for several reasons. Rather than merely dealing with depression from a neurobiological perspective, it is important to tackle its psychosocial root causes to at least reduce risk of relapse. Lifestyle changes are affordable and have no side effects. They also reinforce a sense of empowerment and agency in patients who are able to practice the management of their own mental health. In this regard, further research investigation is warranted to examine the efficacy of lifestyle-based adjunctive treatments in the treatment of MDD.

In terms of raising awareness, the biological basis of depression concluded from this study and similar studies should be highlighted in order to reduce the stigma of psychiatric disorders and to promote effective early interventions. Such attempts should also aim to educate the public about modifiable life-style factors (i.e.: exercise, diet) that might influence depres-

sion outcomes directly, or indirectly through influencing such biomarkers.

In conclusion, these recommendations aim to bridge the research gap between current findings and actual psychiatric practice through a personalized approach to mental health taking into consideration both psychosocial and biological/environmental factors. The current study was able to unravel some of the link between different risk factors and MDD outcomes, but many questions regarding the biological mechanisms underpinning them remain unanswered.

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Appendix 1: Informed Consent Form

الجـامـعـة الأمـريكيـة بالقـاهـرة

استمارة موافقة مسبقة للمشاركة في دراسة بحثية

عنوان البحث : التعرضات المتعلقة بالاضطرابات الاكتئابية في السكان المصريين

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انت مدعو للمشاركة فى دراسة بحثية عن التعرضات المختلفة المتعلقة بالاضطرابات الاكتئابية.

هدف الدراسة هو فهم ورصد كل التعرضات الداخلية والخارجية (البيئية) التى تزيد من احتمالية حدوث الاضطرابات الاكتئابية.

نتائج البحث ستنشر فى دورية متخصصة أو مؤتمر علمي أو ربما كليهما.

المدة المتوقعة للمشاركة فى هذا البحث هي ساعة.

اجراءات الدراسة تشتمل على الإجابة على استبيان في صورة مقابلة إكلينيكية وجمع عينة دم للتحليل وارتداء إسورة مصنوعة من مادة السيليكون لرصد التعرض للمواد الكيميائية.

المخاطر المتوقعة من المشاركة فى هذه الدراسة: قد تشعر ببعض من الحزن أو التوتر عند الإجابة عن بعض الأسئلة ذات الطابع الخاص. ولكن يقوم بالمقابلة متخصّصون في المجال النفسي متدربون على عمإ المقابلة بأقل ضغط على المشارك.

الاستفادة المتوقعة من المشاركة في البحث: الاستفادة من معرفة نتائج اختبارات الحالة النفسية وتحاليل الدم الخاصة بك.

السرية واحترام الخصوصية: المعلومات التى ستدلى بها فى هذا البحث سوف تكون سرية.

- اذا زادت المخاطر المتوقعة نتيجة هذا البحث عن الحد الادنى المقبول سوف يتم تحويل المشارك لتلقي الخدمة الطبية المطلوبة مجاناً. لمزيد من المعلومات، يمكنك التواصل مع الباحث الرئيسي.

أي أسئلة متعلقة بهذه الدراسة أو حقوق المشاركين فيها أوعند حدوث أى اصابات ناتجة عن هذه المشاركة يجب ان توجه الى ريم ضيف على ٠١٠٠٢٤٠٢٣٩٥ بصفتها الباحث الرئيسي.

ان المشاركة فى هذه الدراسة ماهى الا عمل تطوعى, حيث أن الامتناع عن المشاركة لايتضمن أى عقوبات أو فقدان أى مزايا تحق لك. ويمكنك أيضا التوقف عن المشاركة فى أى وقت من دون عقوبة أو فقدان لهذه المزايا.

الامضاء: .....

اسم المشارك : .....

التاريخ : ...../...../.....

Appendix 2: Questionnaire

I. Basic Personal Data البيانات الشخصية الأساسية

1. Gender الجنس:
    - Female أنثى
    - Male ذكر
2. Age in years العمر بالسنوات: – – – – – – – – –
3. Martial Status الحالة الاجتماعية: – – – – – – – – –
    - Single أعزب
    - Engaged خاطب
    - Married متزوج
    - Widowed أرمل
    - Divorced مطلق
4. Number of Children عدد الأطفال: – – – – – – – – –
5. Household size عدد أفراد الأسرة في المسكن: – – – – – – – – –
6. Educational attainment المستوي الدراسي:
    - Illiterate أمي
    - Primary School ابتدائي

- Middle School إعدادي
- High School (ثانوي – دبلوم) مؤهل متوسط
- مؤهل أعلي من المتوسط)معهد سنتين(
- University level مؤهل عالي
- دبلومة عليا
- ماجيستير - دكتوراه

7. Employability status الحالة الوظيفية:
    - Full-time employed موظف بدوام كامل
    - Part-time employed موظف بدوام جزئي
    - Unemployed عاطل
    - Freelancer حر
8. Job الوظيفة :

II. Prenatal and Neonatal Data بيانات ما قبل الولادة وما بعد الولادة

1. Birth الولادة:
    - Preterm قبل الميعاد
    - Term في الميعاد
    - Unknown غير معلوم
2. Deliveryعملية الولادة:
    - Natural طبيعية
    - C-section قيصرية
    - Unknown غير معلوم
3. Postnatal feeding الرضاعة:
    - BreastPostnatal feeding رضاعة طبيعية
    - Formula Postnatal feeding رضاعة لبن صناعي
    - A mixture of both مزيج من الطبيعي والصناعي
    - Unknown غير معلوم

III. Physical Data بيانات جسدية

- Weight الوزن: – – – – – – – – – –
- Height الطول: – – – – – – – – – –
- Body mass index (to be calculated) مؤشر كتلة الجسم: – – – – – – – – – –

V. Medical History Data

1. Comorbid chronic diseases هل تعاني من أي أمراض مزمنة :
    - Yes, (If yes, please specify) نعم (قم بتحديدها) – – – – – – – – – –
    - No لا
2. Comorbid communicable diseasesهل تعاني من أي أمراض معدية :
    - Yes, (If yes, please specify) نعم) (قم بتحديدها – – – – – – – – – –
    - No لا

3. COVID Infection
    - Yes, (If yes, please specify date) (نعم (قم بتحديد التوقيت ـ ـ ـ ـ ـ ـ ـ ـ ـ ـ
    - No لا
4. History of medical surgeries
    - Yes, (If yes, please specify) (نعم (قم بتحديدها ـ ـ ـ ـ ـ ـ ـ ـ ـ ـ
    - No لا
5. Family history of depressive disorders التاريخ العائلي لاضطرابات الاكتئاب:
    - Positive based on clinical diagnosis إيجابي بناء على تشخيص إكلينيكي …. Degree of kinship درجة القرابة
    - Positive based on appearance and affect إيجابي بناء على تقييم المظهر والمزاج …. Degree of kinship درجة القرابة
    - Negative سلبي
    - Specify:
4. Family history of psychiatric disorders other than depression التاريخ العائلي للاضطرابات النفسية في ما عدا اضطرابات الاكتئاب
    - Positive based on clinical diagnosis إيجابي بناء على تشخيص إكلينيكي …. Specify diagnosis: Degree of kinship درجة القرابة
    - Positive based on appearance and affect إيجابي بناء على تقييم المظهر والمزاج ….Specify diagnosis: Degree of kinship درجة القرابة
    - Negative
    - Specify:
5. Current chronic use of pharmaceuticals تعاطي حالي ومزمن للأدوية
    - Yes (Please specify) نعم (قم بتحديدها)
    - No لا
6. Current of chronic use of chemotherapy تلقي للعلاج الكيماوي حاليًا
    - Yes (Please specify) نعم (قم بتحديدها)
    - No لا
7. Current of chronic use of antibiotics استخدام مزمن للمضادات الحيوية
    - Yes (Please specify) نعم (قم بتحديدها)
    - No لا
8. Current of chronic use of hormonal therapy استخدام مزمن للعلاج الهورموني
    - Yes (Please specify) نعم (قم بتحديدها)
    - No لا
9. Menstrual irregularities in women عدم انتظام الدورة الشهرية لدى السيدات
    - Yes نعم
    - No لا

VI. Psychosocial Data

1. Exposure to abuse التعرض للإيذاء:

- Physical الجسدي, (If yes, please specify time and duration) (في حالة نعم، قم بتحديد الوقت والمدة)
- Verbal اللفظي, (If yes, please specify time and duration) (في حالة نعم، قم بتحديد الوقت والمدة)
- Sexual الجنسي, (If yes, please specify time and duration) (في حالة نعم، قم بتحديد الوقت والمدة)
- None لا

2. Number of close friends in whom you can confide عدد الأصدقاء الذين يُمكن الوثوق بهم: _ _ _ _ _ _ _ _ _ _
3. Practice of meditation ممارسة التأمل:
   - Yes نعم, (If yes, please specify average number of times per week) (في حالة نعم، قم بتحديد متوسط عدد المرات في الأسبوع)
   - No لا
4. Seeking psychotherapy or counseling تلقى العلاج النفسي عن طريق جلسات العلاج النفسي المتخصصة أو الإرشاد النفسي:
   - Yes نعم (If yes, please specify time and duration) (في حالة نعم، قم بتحديد الوقت والمدة)
   - No لا
5. Taking pharmacological drugs استخدام العقاقير أو الأدوية النفسي
   - Yes نعم (If yes, please specify time and duration) (في حالة نعم، قم بتحديد الوقت والمدة)
   - No لا
6. Religious and spiritual practice الممارسات الدينية والروحانية:
   - Yes نعم (Please specify, regular/irregular) (من فضلك حدد بصورة مستمرة أو بصورة غير مستمرة)
   - No لا
6. Number of languages spoken عدد اللغات التي تتحدثها: _ _ _ _ _ _ _ _ _ _

VII. Environmental Data البيانات البيئية

1. Location of residence مكان السكن: Neighborhood المنطقة _ _ _ _ _ _ _ _ _ _ Governorate المحافظة _ _ _ _ _ _ _ _ _ _
2. Location of workplace مكان العمل: Neighborhood المنطقة _ _ _ _ _ _ _ _ _ _ Governorate المحافظة _ _ _ _ _ _ _ _ _ _
3. Exposure to second-hand smoking in the household التعرض للتدخين السلبي في مكان السكن:
   - Yes نعم
   - No لا
4. Exposure to second-hand smoking in the workplace التعرض للتدخين السلبي في مكان العمل:
   - Yes نعم
   - No لا

5. Presence of greenery around the household وجود خضرة حول مكان السكن:
    - Yes نعم
    - No لا
6. Presence of greenery around the workplace وجود خضرة حول مكان العمل:
    - Yes نعم
    - No لا
7. In your lifetime, for how many years have you lived in the countryside? ــــــــــــ
8. In your lifetime, for how many years have you lived in the city? ــــــــــــ
9. From which source do you primarily get your water for cooking?
    - Tape الحنفية
    - Filter الفلتر
    - Bottled water المياة المعبأة
10. From which source do you primarily get your drinking water?
    - Tape الحنفية
    - Filter الفلتر
    - Bottled water المياة المعبأة

VIII. Lifestyle Data بيانات نمط الحياة

1. On average, on how many days per week do you consume fruits? ما هو متوسط عدد أيام الأسبوع التي تأكل فيها الفاكهة؟ ــــــــــــ
2. On average, on how many days per week do you consume vegetables? ما هو متوسط عدد أيام الأسبوع التي تأكل فيها الخضروات؟ ــــــــــــ
3. On average, on how many days per week do you consume poultry or meat? ما هو متوسط عدد أيام الأسبوع التي تأكل فيها الدجاج أو اللحوم؟ ــــــــــــ
4. On average, on how many days per week do you consume fish? ما هو متوسط عدد أيام الأسبوع التي تأكل فيها الأسماك؟ ــــــــــــ
5. On average, on how many days per week do you consume sugars and desserts? ما هو متوسط عدد أيام الأسبوع التي تأكل فيها السكريات والحلويات ــــــــــــ
6. On average, on how many days per week do you consume fast food? ما هو متوسط عدد أيام الأسبوع التي تأكل فيها الوجبات السريعة؟ ــــــــــــ
7. On average, how many cups of caffeine do yo consume per day? ما هو متوسط عدد أكواب الكافيين التي تشربها يومياً؟ ــــــــــــ
8. Do you take any nutritional supplements or vitamins?
    - Yes نعم , please specify من فضلك قم بتحديدها
    - No لا
9. Average hours of sleep per day متوسط عدد ساعات النوم في اليوم: ــــــــــــ
10. Quality of sleep:
    - Excellent
    - Good

- Bad

4. Average hours of watching TV per day متوسط عدد ساعات مشاهدة التلفزيون في اليوم: ــ ــ ــ ــ ــ ــ ــ ــ ــ ــ
5. Average hours of using internet and smart phones per day متوسط عدد ساعات استخدام الإنترنت والهواتف الذكية: ــ ــ ــ ــ ــ ــ ــ ــ ــ
6. Average number of hours spent at work متوسط عدد ساعات العمل: ــ ــ ــ ــ ــ ــ ــ ــ ــ
7. Average number of hours spent at housework متوسط عدد ساعات الأعمال المنزلية: ــ ــ ــ ــ ــ ــ ــ ــ
8. Average income per month متوسط الدخل الشهري: ــ ــ ــ ــ ــ ــ ــ ــ ــ
9. Tobacco smoking status التدخين:
    - Current smoker مدخن حالي, average number of cigarettes per day متوسط عدد السجائر في اليوم) ــ ــ ــ ــ ــ ــ ــ ــ ــ)
    - Past smoker مدخن سابق, average number of cigarettes per day متوسط عدد السجائر في اليوم) ــ ــ ــ ــ ــ ــ ــ ــ ــ)
    - Non-smoker غير مدخن
10. Hookah smoking status الشيشة:
    - Current smoker مدخن حالي, average number of cigarettes per day متوسط عدد السجائر في اليوم) ــ ــ ــ ــ ــ ــ ــ ــ ــ)
    - Past smoker مدخن سابق, average number of cigarettes per day متوسط عدد السجائر في اليوم) ــ ــ ــ ــ ــ ــ ــ ــ ــ)
    - Non-smoker غير مدخن
11. Alcohol consumption تعاطي الكحوليات
    - Current user مُتعاطي حالي, type النوع ــ ــ ــ ــ ــ ــ ــ ــ ــ and average number of cups per day متوسط عدد الكاسات في اليوم ــ ــ ــ ــ ــ ــ ــ ــ ــ
    - Past user مُتعاطي سابق, type النوع ــ ــ ــ ــ ــ ــ ــ ــ ــ and average number of cups per day متوسط عدد الكاسات في اليوم ــ ــ ــ ــ ــ ــ ــ ــ ــ
    - Non-user غير مُتعاطي
12. Current sexual activity النشاط الجنسي الحالي:
    - Yes نعم
    - No لا
13. Over the past week, on how many days did you at least walk for 10 minutes? خلال الأيام السبعة الماضية، كم يوماً مارست فيه المشي لمدة ١٠ دقائق على الأقل؟ ــ ــ ــ ــ ــ ــ ــ
14. How often do you practice moderate/high intensity sports? إلى أي مدى تمارس الرياضات متوسطة وعالية الشدة؟
    - Never لا أمارسها مطلقًا
    - Once or twice per year مرة أو مرتين في السنة
    - Monthly شهريًا
    - Weekly أسبوعيًا
    - Everyday يوميًا

IX. Mini-Mental State Examination (MMSE) اختبار الحالة العقلية المصغر

1. احنا في سنة كام
2. في أي فصل من فصول السنة
3. طيب احنا في شهر ايه
4. تاريخ انهاردة ايه
5. احنا فين دلوقتي
6. احنا في الدور الكام
7. احنا في اي حي
8. ايه اسم المحافظة اللي احنا فيها
9. احنا في جمهورية ايه
10. خلي بالي.. هقولك ٣ كلمات عايزك تقولهم ورايا وحفظهم عشان هرجع أسألك فيهم بعد شوية .. كورة، شجرة، كرسي
11. تقدم الكلمات بفارق ثانية واحدة بينهم. كرر تقديم الثلاث كلمات حتى يستطيع إعادتهم جميعًا
12. عايزك تطرح ٧ من ١٠٠
13. كمل وانت نازل اطرح ٧ من ٣٣ وتوقف بعد خمس عمليات للطرح
14. إذا كان المريض غير متعلم، عايزك تعيدلي أيام الأسبوع بالعكس
15. فاكر الكلمات اللي حفظناها من شوية، عايزك تعيدهم لي.
16. يشار إلي بعض الأشياء ويطلب من المريض أن يسميها: يشار إلي الساعة
17. يشار إلي القلم
18. اطلب من المريض أن يكرر جملة: ولا كاني ولا ماني ولا حاجة عجباني
19. اطلب من المريض أن ينفذ أمر من ثلاث أجزاء: خذ الورقة بيدك اليمنى، اثني الورقة إلي نصفين، وضع الورقة على الأرض
20. اقرأ المكتوب على الورقة ونفذه: غمض عينيك
21. أعطي المريض ورقة وقلم واطلب منه أن يكتب جملة مفيدة بها فاعل ومفعول
22. ارسم هذا الشكل

Appendix 3: Arabic BDI-II

		البنـد			البنـد
الحزن (1)	0	لا أشعر بالحزن.	التشاؤم (12)	0	لم تفتر همتي فيما يتعلق بمستقبلي.
	1	أشعر بالحزن اغلب الوقت.		1	أشعر بفتور الهمة فيما يتعلق بمستقبلي بطريقة اكبر مما اعتدت
	2	أنا حزين طول الوقت.		2	لا أتوقع أن تسير الأمور بشكل جيد بالنسبة لي.
	3	أنا حزين أو غير سعيد لدرجة لا استطيع تحملها.		3	أشعر بأن لي في المستقبل وأنه سوف يزداد سوءاً.
الفشل (2)	0	لا أشعر بأنني شخص فاشل.	فقدان الاستمتاع (13)	0	أستمتع بالأشياء بنفس قدر استمتاعي بها من قبل.
	1	لقد فشلت أكثر مما ينبغي.		1	لا أستمتع بأشياء بنفس القدر الذي اعتدت عليه.
	2	كلما نظرت إلى الوراء أرى الكثير من الفشل.		2	أحصل على قدر قليل جداً من الاستمتاع بالأشياء التي اعتدت أن استمتع بها.
	3	أشعر بأنني شخص فاشل تماماً.		3	لا أستطيع الحصول على أي استمتاع من الأشياء التي أعتدت الاستمتاع بها.
	0	لا أشعر بالإثم (تأنيب الضمير).	مشاعر	0	لا أشعر بأنه يقع على عقاب.

مشاعر الإثم (3)	1	أشعر بالإثم(تأنيب الضمير)عن العديد من الأشياء التي قمت بها أو أشياء كان يجب أن أقوم بها.	العقاب (14)	1	اشعر بأنه ربما يقع على عقاب.
	2	أشعر بالإثم (تأنيب الضمير) أغلب الوقت.		2	أتوقع أن يقع علي عقاب.
	3	أشعر بالإثم (تأنيب الضمير) طول الوقت.		3	اشعر بأنه يقع عليا عقاب.
عدم حب الذات (4)	0	شعوري نحو نفسي كما هو.	نقد الذات (15)	0	لا أنقد أو ألوم نفسي أكثر من المعتاد.
	1	فقدت الثقة في نفسي.		1	أنقد نفسي أكثر مما اعتدت.
	2	خاب رجائي في نفسي.		2	أنقد نفسي على كل أخطائي.
	3	لا أحب نفسي.		3	ألوم نفسي على كل ما يحدث من أشياء سيئة.
الأفكار والرغبات الانتحارية (5)	0	ليس لدي أي أفكار انتحارية.	البكاء (16)	0	لا أبكي أكثر مما اعتدت.
	1	لدي أفكار للانتحار ولكن لا يمكنني تنفيذها.		1	أبكي أكثر مما اعتدت.
	2	أريد أن انتحر.		2	أبكي كثيراً من أي شيء بسيط.
	3	قد انتحر لو سنحت لي الفرصة.		3	أشعر بالرغبة في البكاء ولكني لا استطيع.
		البنـد			**البنـد**
التهيج أو الاستثارة (6)	0	لست أكثر تهيجاً أو استثارة عن المعتاد.	فقدان الاهتمام (17)	0	لم أفقد الاهتمام بالآخرين أو بالأنشطة.
	1	أشعر بالتهيج أو الاستثارة أكثر من المعتاد.		1	أهتم بالآخرين أو بالأمور أقل من قبل.
	2	اهتاج أو استثار لدرجة انه من الصعب عليا البقاء بدون حركة.		2	فقدت أغلب اهتمامي بالآخرين والأمور الأخرى.
	3	اهتاج أو استثار لدرجة تدفعني للحركة أو فعل شيء ما.		3	من الصعب أن اهتم بأي شيء.
التردد (7)	0	أتخذ القرارات بنفس كفاءتي المعتادة.	انعدام القيمة (18)	0	لا أشعر بأنني عديم القيمة.
	1	أجد صعوبة أكثر من المعتاد في اتخاذ القرارات.		1	لا أعتبر نفسي ذو قيمة وذو نفع كما اعتدت أن أكون.
	2	لدي صعوبة أكثر بكثير مما اعتدت في اتخاذ القرارات.		2	أشعر بأنني عديم القيمة بالمقارنة بالآخرين.
	3	لدي مشكلة اتخاذ أي قرارات.		3	أشعر بأنني عديم القيمة تماماً.
فقدان	0	لدي نفس القدر من الطاقة كالمعتاد.	زيادة أو قلة	0	لم يحدث لي أي تغير في نمط (نظام) نومي.
	1	لدي قدر من الطاقة أقل مما اعتدت.		1	ا. أنام أكثر من المعتاد إلى حد ما. ب. أنام اقل من المعتاد إلى حد ما.

الطاقة (8)	2	ليس لدي طاقة كافية لعمل الكثير من الأشياء.	النوم (19)	2	ا. أنام أكثر من المعتاد بشكل كبير. ب. أنام اقل من المعتاد بشكل كبير.
	3	ليس لدي طاقة كافية لعمل أي شيء.		3	ا. أنام اغلب اليوم. ب. استيقظ من نومي مبكرا ساعة أو ساعتان ولا استطيع أن أعود للنوم مرة أخرى.
القابلية للغضب أو الانزعاج (9)	0	قابليتي للغضب أو الانزعاج لم تتغير عن المعتاد.	ضعف أو زيادة الشهية (20)	0	لم يحدث أي تغير في شهيتي.
	1	قابليتي للغضب أو الانزعاج أكبر من المعتاد.		1	ا. شهيتي أقل من المعتاد إلى حد ما. ب. شهيتي أكبر من المعتاد إلى حد ما.
	2	قابليتي للغضب أو الانزعاج اكبر بكثير من المعتاد.		2	ا. شهيتي اقل كثيرا من المعتاد. ب. شهيتي اكبر كثيرا من المعتاد.
	3	قابليتي للغضب أو الانزعاج طول الوقت.		3	ا. ليست لي شهية على الإطلاق. ب. لدي رغبة قوية للطعام طول الوقت.
صعوبة التركيز (10)	0	أستطيع التركيز بكفاءتي المعتادة.	الإرهاق أو الإجهاد (21)	0	لست أكثر إرهاقا أو إجهاداً من المعتاد.
	1	لا أستطيع التركيز بنفس الكفاءة المعتادة.		1	أصاب بالإرهاق أو الإجهاد بسهولة أكثر من المعتاد.
	2	من الصعب عليا أن أركز عقلي أي شيء مدة طويلة.		2	يعوقني الإرهاق أو الإجهاد عن عمل الكثير من الأشياء التي اعتدت عملها.
	3	أجد نفسي غير قادر على التركيز على أي شيء.		3	أنا مرهق أو مجهد جداً لعمل اغلب الأشياء التي اعتدت عليها.
فقدان الاهتمام بالجنس (11)	0	لم ألاحظ أي تغير في اهتمامي بالجنس حديثاً			
	1	أنا أقل اهتمام بالجنس مما اعتدت.			
	2	أقل اهتماماً بالجنس الآن بدرجة كبيرة.			
	3	فقدت الاهتمام بالجنس تماماً.			

Appendix 4: Arabic MINI 7.0.2

نوبة اكتئاب كبرى A.
MAJOR DEPRESSIVE EPISODE

هذا السهم ← يعني انتقل إلى مربع التشخيص النهائي الخاص بالوحدة واختر (لا) في مربع التشخيص.
انتقل بعدها إلى الوحدة التالية.

A1.a	هل سبق لك وأن شعرت بالاكتئاب أو الإحباط، أو هل شعرت بالحزن، أو شعرت بالفراغ أو اليأس، معظم اليوم، كل يوم تقريباً، لمدة أسبوعين؟	نعم	لا
	إذا كانت الإجابة "لا"، فقم بتسجيل إجابة البند A1.b "لا": **إذا كانت الإجابة "نعم" اسأل التالي:**		
b	خلال الأسبوعين الماضيين، هل كنت مكتئبًا أو محبطا، أو هل شعرت بالحزن، أو الفراغ أو اليأس، معظم اليوم، تقريبًا كل يوم؟	نعم	لا

A2.a	هل سبق لك وكنت أقل اهتماما بمعظم الأشياء أو أقل قدرة على الاستمتاع بالأشياء التي اعتدت على الاستمتاع بها معظم الوقت، لمدة أسبوعين؟	نعم	لا
	إذا كانت الإجابة "لا"، فقم بتسجيل إجابة البند A2.b "لا": **إذا كانت الإجابة "نعم" اسأل التالي:**		
b	خلال الأسبوعين الماضيين، هل كنت أقل اهتماما بمعظم الأشياء أو أقل قدرة على الاستمتاع بالأشياء التي اعتدت على الاستمتاع بها معظم الوقت؟	نعم	لا

هل أجبت بـ "نعم" على البند A1.a أو البند A2.a؟	نعم	لا ←

A3	**إذا كانت الإجابة على البند A1.b أو البند A2.b "نعم"، استعلم عن النوبة الحالية والنوبة ذات الأعراض الأكثر شدة في الماضي، وإلا ..** **إذا كانت إجابة كلاً من البند A1.b و البند A2.b "لا" استعلم فقط عن النوبة ذات الأعراض الأكثر شدة في الماضي.**				
	خلال فترة الأسبوعين، عندما شعرت بالاكتئاب أو بعدم الاهتمام:	**الأسبوعين الماضيين**		**النوبة الماضية**	
a	هل انخفضت أو ازدادت شهيتك كل يوم تقريباً؟ هل انخفض أو ازداد وزنك دون قصدٍ منك (على سبيل المثال، ±5% من وزن الجسم، أو ما يعادل 8 أرطال أو ±3,5 كجم في شهرٍ واحد لشخص يبلغ وزنه 160 رطل/ 70 كجم)؟	**نعم**	**لا**	**نعم**	**لا**
b	هل واجهتك صعوبات في النوم، كل ليلة تقريباً؟ (صعوبة في الخلود إلى النوم، أو الاستيقاظ في منتصف الليل، أو الاستيقاظ في وقت مبكر جداً، أو النوم بشكل مفرط)	**نعم**	**لا**	**نعم**	**لا**
c	هل تحدثت أو تحركت بطريقة أبطأ من المعتاد أو كنت عصبي، متململ أو تواجه صعوبة في البقاء ساكناً، كل يوم تقريباً؟ هل لاحظ أحدهم ذلك؟	**نعم**	**لا**	**نعم**	**لا**
d	هل شعرت بالتعب وبفقدان الطاقةالحيوية، كل يوم تقريباً؟	**نعم**	**لا**	**نعم**	**لا**

e	هل شعرت أنك بلا قيمة أو رافقك شعور بالذنب، كل يوم تقريباً؟	نعم	لا	نعم	لا
	إذا كانت الإجابة "نعم"، اسأل عن أمثلة. ابحث عن *ضلالات (Delusions) الفشل أو عدم الكفاءة أو الخراب أو الشعور بالذنب أو الحاجة إلى العقاب أو ضلالات المرض أو الوفاة أو الضلالات العدمية (أن الحياة بلا معنى) أو الجسدية. على الأمثلة أن تتسق مع فكرة ضلالية. *الضلالات هي معتقدات/معتقد خاطئ يؤمن به المريض على الرغم من تناقضه مع الواقع أو تناقضه مع الحجة المنطقية، وتعتبر الضلالات عادةً كأحد أعراض الاضطراب العقلي (الذهاني).	نعم	لا	نعم	لا
f	هل واجهتك صعوبات في التركيز، التفكير أو في اتخاذ القرارات، كل يوم تقريباً؟	نعم	لا	نعم	لا
g	هل فكرت بشكل متكرر في الموت (الخوف من الموت لا يُحتسب هنا)، أو كانت لديك أي أفكار بقتل نفسك، أو كانت لديك أي نية أو خطة لقتل نفسك؟ هل حاولت الانتحار؟ إذا كانت الإجابة بنعم على أياً من هذه الأسئلة، ضع علامة نعم	نعم	لا	نعم	لا
A4	هل سببت لك هذه الأعراض بمعاناة ملحوظة (كبيرة) أو سببت لك مشاكل في المنزل أو العمل أو المدرسة أو في علاقاتك الاجتماعية أو بطريقة أخرى ذات أهمية، وهل تغيّر أداؤك في أحد هذه الجوانب المذكورة عن السابق؟	نعم	لا	نعم	لا
A5	بين نوبة اكتئاب وأخرى، هل سبق لك وأمضيت مدّة لا تقل عن شهرين، لم تشعر فيها بأي اكتئاب أو فقدان اهتمام؟	نعم	لا	نعم	لا

	هل قمت بتسجيل 5 إجابات أو أكثر بـ "نعم" في أسئلة البنود (A1-A3) وهل تم تسجيل إجابة "نعم" على البند A4 في تلك الفترة الزمنية؟	نعم	لا	نعم	لا
	و هل تم تسجيل إجابة "نعم" على البند الخاص بـ "استبعاد السبب العضوي" التابع للملخص O2	نعم	لا	نعم	لا
	حدد إذا كانت النوبة حالية و(أو) ماضية. إذا كانت إجابة A5 "نعم" فقم بتسجيل "نعم" عند نوبة متكررة الحدوث " Recurrent Episode"				

نوبة اكتئاب كبرى Major Depressive Episode	
حالي	□
ماضي	□
متكررة الحدوث	□

A6	كم عدد نوبات الاكتئاب التي مررت بها في حياتك؟ يجب أن يكون هناك فاصل زمني لا يقل عن شهرين بين كل نوبة وأخرى بدون أي اكتئاب ملحوظ	_____

B. الانتحار
SUICIDALITY

				النقاط
	في الشهر الماضي:			
B1	هل تعرضت لأي حادث؟ يشمل ذلك تناولك كمية كبيرة من أدويتك دون قصد (عن طريق الخطأ)	نعم	لا	0
	إذا كانت الإجابة على البند B1 "لا", انتقل إلى البند B2 **إذا كانت الإجابة "نعم" اسأل B1.a**			
B1.a	هل خطت أو قصدت إيذاء نفسك في أي حادث إما عن طريق عدم تجنب المخاطر عند حدوثها أو عن طريق التسبب بالحادث عن قصد؟	نعم	لا	0
	إذا كانت الإجابة على البند B1.a "لا", انتقل إلى البند B2 **إذا كانت الإجابة "نعم" اسأل B1b**			
B1.b	هل تعمدت الموت كنتيجة لأي حادث؟	نعم	لا	0
B2	هل فكرت (حتى للحظات) بأنك ستكون أفضل حالاً لو مُت أو تمنيت أن تكون ميتاً أو أنك بحاجة للموت؟	نعم	لا	1
B3	هل فكرت (حتى للحظات) بإيذاء، إصابة أو جرح نفسك؟ - مع وجود (ولو بعض) التعمد أو الوعي بأنك قد تموت نتيجةً لذلك. - أو التفكير بالانتحار (أي قتل نفسك)؟	نعم	لا	6
	إذا كانت إجابة البند B3 + B2 بـ "لا"، فانتقل إلى B4 **عدا ذلك اسأل عن التالي:**			
	التكرار:		الشدة:	
	أحياناً	☐	خفيفة ☐	
	غالباً	☐	متوسطة ☐	
	كثيراً	☐	شديدة ☐	

B4	هل سمعت صوتاً أو أصواتاً تقول لك أن تقتل نفسك أو راودك حلم له علاقة بالانتحار؟	نعم	لا	4
	إذا كانت الإجابة "نعم", اختر أحد هذين الخيارين أو كليهما			
	هل كان صوتا واحداً أم عدة أصوات؟ ☐		هل كان هذا حلما؟ ☐	

B5	هل فكرت بطريقة معينة للانتحار (كيف)؟	نعم	لا	8
B6	هل فكرت بوسيلة انتحار معينة (ما هي)؟	نعم	لا	8
B7	هل فكرت بمكان معين لمحاولة الانتحار (أين)؟	نعم	لا	8
B8	هل فكرت بتاريخ أو إطار زمني معين للانتحار (متى)؟	نعم	لا	8
B9	هل فكرت في أي مهمة ترغب بالقيام بها قبل محاولتك قتل نفسك؟ (على سبيل المثال: كتابة رسالة انتحار)	نعم	لا	8
B10	هل كنت تنوي تنفيذ الأفكار المتعلقة بقتل نفسك؟	نعم	لا	8
	إذا كانت الإجابة "نعم", اختر أحد هذين الخيارين أو كليهما			
	هل كنت تنوي تنفيذ مخططاتك في ذلك الوقت؟ ☐		هل كنت تنوي تنفيذ مخططاتك في وقت ما في المستقبل؟ ☐	

B11	هل كنت تنوي الموت نتيجة لتصرف انتحاري؟	نعم	لا	8
	إذا كانت الإجابة "نعم", اختر أحد هذين الخيارين أو كليهما			
	هل كنت تنوي الموت في ذلك الوقت؟ ☐		هل كنت تنوي الموت في وقت ما في المستقبل؟ ☐	

B12	هل شعرت بحاجة أو بدافع (رغبة قوية وملحة) لقتل نفسك أو التخطيط لقتل نفسك عاجلاً دون تأجيل؟		نعم	لا	8
	إذا كانت الإجابة "نعم"، اختر أحد هذين الخيارين أو كليهما				
	هل ارتبطت هذه الرغبة/الدافع بقتلك لنفسك؟	□	هل ارتبطت هذه الرغبة/الدافع بالتخطيط لقتل نفسك؟		□
	إذا كانت الإجابة "نعم"، اختر أحد هذين الخيارين أو كليهما				
	هل كانت هذه الرغبة/الدافع بشكل عام غير ناتجة عن حافز أو سبب مباشر؟ (ليست ناتجة عن حدث أو مشاعر معيّنة)	□	هل كانت هذه الرغبة/الدافع ناتجة عن حافز أو سبب مباشر؟ (نتيجة حدث معين أو مشاعر معينة)		□

عند تقييم لكون هذا الدافع أو الرغبة الملحة غير ناتجة بشكل عام عن حافز أو سبب مباشر، اسأل: "قبل ٥ دقائق من هذا الدافع، هل كان بإمكانك التنبؤ به"؟	نعم	لا
إذا كان الإجابة على البند B12 "لا"، انتقل إلى البند B14.		

B13	هل تواجه صعوبة في مقاومة هذه الدوافع الملحة/القوية؟	نعم	لا	8
B14	هل اتخذت أي خطوات عمليَّة للتحضير لمحاولة انتحار توقعت أو قصدت فيها الموت (بما في ذلك أي فعل مقصود أو غير مقصود دفعك للقيام بمحاولة انتحار)؟ يتضمن ذلك الأوقات التي كنت ستقتل فيها نفسك، ولكن تمت مقاطعتك أو توقفت، قبل إيذاء نفسك.	نعم	لا	
B14. a	هل اتخذت خطوات عمليَّة للتحضير لقتل نفسك، لكنك لم تبدأ بمحاولة الانتحار؟	نعم	لا	9
B14. b	هل اتخذت خطوات عمليَّة للتحضير لقتل نفسك، لكنك بعدها توقفت مباشرةً قبل إلحاق الأذى بنفسك ("لم تكتمل المحاولة")	نعم	لا	10
B14. c	هل اتخذت خطوات عمليَّة للتحضير لقتل نفسك، ولكن شخصاً ما أو شيء ما أوقفك مباشرةً قبل إلحاق الأذى بنفسك ("تم مقاطعتك أثناء المحاولة")	نعم	لا	11
B15	هل جرحت/أذيت نفسك عمداً، لكن دون أن تنوي قتل نفسك؟	نعم	لا	0
B16	هل حاولت الانتحار (لقتل نفسك)؟	نعم	لا	
	إذا كانت الإجابة على البند B16 "لا"، انتقل إلى البند B17.			
B16. a	هل بدأت بمحاولة انتحار (لقتل نفسك)، ولكنك قررت التوقف ولم تُكمل المحاولة؟	نعم	لا	12
B16. b	هل بدأت بمحاولة انتحار (لقتل نفسك)، ولكن تمت مقاطعتك ولم تُكمل المحاولة؟	نعم	لا	13
B16. c	هل قمت بمحاولة انتحار (لقتل نفسك)، تماماً كما كان مخططاً لها؟ محاولة الانتحار تعني أنك قمت بفعل معين كان يمكن أن يلحق بك الأذى، مع وجود ولو نية بسيطة للموت. **إذا كانت الإجابة على البند B16c "لا"، فانتقل إلى البند B17**	نعم	لا	14
	تمنيت أن يتم إنقاذك/أن تنجو □	توقعت/تمنيت الموت		□

B17	الوقت الذي تقضيه في اليوم مع دوافع ملحة، أفكار أو أفعال انتحار:		
	الوقت المعتاد الذي تقضيه في اليوم	ساعة.	دقيقة.
	أقل قدر من الوقت الذي تقضيه في اليوم	ساعة.	دقيقة.
	أكبر قدر من الوقت الذي تقضيه في اليوم	ساعة.	دقيقة.

B18	على مدار حياتك هل سبق لك أن حاولت الانتحار (حاولت أن تقتل نفسك)؟	نعم	لا	4
	إذا كانت الإجابة "نعم"، كم مرة؟ _____			

	إذا كانت الإجابة "نعم"، متى كانت آخر محاولة انتحار؟					
	مرحلة حالية: خلال الـ ١٢ شهراً الماضية	☐	مرحلة تعافي مُبكر: ما بين الـ ١٢ والـ٢٤ شهراً الماضية	☐	مرحلة تعافي: منذ أكثر من ٢٤ شهر	☐
	"محاولة الانتحار هي أي سلوك مُضر بالنفس، مع توافر ولو شيء من التعمد البسيط (> 0) للموت كنتيجة لهذا الفعل. قد يكون الدليل على أن الفرد يعتزم قتل نفسه (بدرجة معينة على الأقل) على شكل قول صريح أو يمكن الاستدلال عليه من السلوك أو الموقف. على سبيل المثال، يعْرف الفعل على أنه محاولة انتحار إذا لم يكن حادثاً بشكل واضح أو إذا ظن الفرد أن الفعل قد يكون قاتلاً، على الرغم من إنكاره النية لذلك." (FDA Guidance for Industry Suicidal Ideation and Behavior Document 2012 and C-CASA definition). Posner K et al. Am J Psychiatry 2007; 164 (7): 1035-1043 & http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm/					
B19	ما هي احتمالية قيامك بمحاولة قتل نفسك في غضون الأشهر الثلاثة القادمة؟ 0-100% _____ إذا كان الاحتمال أكبر من الصفر، سجّل "نعم" في البند B19					13

هل قُمت بتسجيل إجابة "نعم" في واحد من البنود السابقة على الأقل؟ (باستثناء B1)	نعم	لا	
إذا كانت الإجابة "نعم"، احسب مجموع النقاط للبنود (B1-B19) التي تم الإجابة عليها بـ "نعم". حدد بناءً على عدد النقاط قلة خطر الانتحار كما هو موضح في مربع التشخيص:			
حدد ما إذا كان سلوك الانتحار حالي (حدث في الشهر الماضي) أو مزمن مدى الحياة، أو كليهما عن طريق تحديد الإجابة المناسبة في مربع التشخيص (أو ترك أحدهما أو كليهما دون علامة).			
حالي: إذا تمت الإجابة بـ "نعم" على كل البنود من (B1.a - B16.c باستثناء B15) أو في حال وجود أي وقت مستغرق في البند B17	محاولات مزمنة مدى الحياة: إذا تمت الإجابة بـ "نعم" على البند B18	احتمال وارد في المستقبل القريب: إذا تمت الإجابة بـ "نعم" على البند B19	

يمكنك كتابة أي تعليقات إضافية حول تقييمك للمريض فيما يخص سلوك الانتحار الحالي أو في المستقبل القريب في المكان/الفراغ التالي:

الانتحار SUICIDALITY			
ضعيف = 1 - 8 نقطة	☐	حالي	☐
متوسط = 9 - 16 نقطة	☐	محاولات مزمنة مدى الحياة	☐
مرتفع = فوق 17 نقطة	☐	احتمال وارد في المستقبل القريب	☐