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DEPARTMENT OF PHYSIOLOGY

ASSOCIATION BETWEEN SLEEP QUALITY AND FUNCTIONAL CONNECTIVITY BY RESTING STATE ENCEPHALOGRAM IN PREECLAMPSIA

THIS THESIS IS SUBMITTED TO THE UNIVERSITY OF GHANA, LEGON, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF MASTER OF PHILOSOPHY IN PHYSIOLOGY

BY

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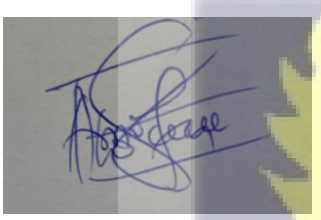
DECLARATION

I declare that this research manuscript represents the work of the principal investigator with the significant contributions, guidance and support of his supervisors. It has never been submitted to/accepted by the University of Ghana or another institution for the award of any form of a degree. The content has been solely produced under the guidance of my supervisors. The background information from respective sources has been duly referenced to reflect ownership of intellectual property.



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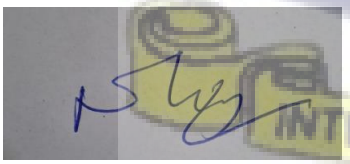

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DEDICATION

I dedicate this work to God Almighty for His mercies and grace, and to the Leadership and Staff of the Department of Physiology and the West African Genetic Medicine Centre.

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LIST OF ABBREVIATIONS

CRP- C-reactive protein

IL-6 – Interleukin-6

SDs- Sleep Disorders

PE- Preeclampsia

TNF- tumour Necrosis Factor

WHO- World Health Organization

ABSTRACT

BACKGROND: Preeclampsia (PE) is the leading cause of maternal deaths in all tertiary hospitals in Ghana. Pregnancy is accompanied by changes in maternal physiology, which result in cerebral alterations and sleep disturbance. PE may exacerbate these cerebral changes and sleep disturbance beyond the effects of normal pregnancy. It is suspected that increased inflammation underlies the cerebral changes and sleep disturbances in PE.

AIM: The study aims to investigate the resting state functional connectivity of the cerebral cortex and its association with sleep quality and markers of inflammation like IL-6 and CRP in preeclamptic and normal pregnancy.

METHODOLOGY: This case-control design compared 50 preeclamptic and 50 normotensive pregnancies. A structured questionnaire was used to collect social, demographic, pregnancy and medical history data. Sleep quality and sleepiness were assessed using the Pittsburgh Sleep Quality Index and Epworth's Sleepiness Scale. Resting-state 32-lead electroencephalography was conducted in all participants and the alpha power spectrum bands were converted to functional MRI correlates using the eLORETA software. Cerebral cortical functional connectivity was obtained from the power spectrum analysis. In addition, a 5 ml venous blood sample was collected to assay levels of highly sensitive CRP and IL-6.

RESULTS: There was no significant difference in overall sleep quality (PSQI global score p= 0.95), but sleep efficiency and sleep duration categories were significantly different (habitual sleep efficiency p= 0.024, sleep duration categorization p= 0.023). EEG results showed significant differences in β2 and β3 bands (p= 0.041 and p= 0.05, respectively), implying altered brain functional connectivity in women with PE which is supported heat and Brodmann Area mapping. Poor sleep quality significantly predicted higher IL-6, and CRP levels (p= 0.01 and p= 0.028 respectively)

CONCLUSION: Sleep disorders dysregulate maternal inflammatory response in PE, evidenced by higher serum IL-6 and C-RP levels in cases than among controls, mediating vascular endothelial and multi-organ dysfunction in PE. Functional connectivity differences between cases and controls were detected by resting-state encephalogram, particularly alterations in current densities in the β2 and β3 frequency domains originating from Brodmann areas 19 and 8- suggesting impaired functional connectivity in PE.

CHAPTER ONE
1.0 INTRODUCTION

1.1 BACKGROUND

Preeclampsia (PE) is a hypertensive disorder of pregnancy which presents as hypertension (blood pressure ≥140/90 mmHg) at or after the 20th week of gestation with associated end-organ damage, haematological involvement and or uteroplacental dysfunction (Brown, Magee et al. 2018, Sinkey, Battarbee et al. 2020). PE is diagnosed in 5-8% of pregnancies globally, (Wu, Liu et al. 2019) and claims 76,000 maternal lives annually (Vata, Chauhan et al. 2018). The prevalence of PE in Ghana is about 6.05 - 7.03% (Obed and Patience 2006, Fondjo, Boamah et al. 2019). Institution-based research reports an annual single-digit increase in the incidence of PE in Ho Regional Hospital (Adwoa, Kunfah et al. 2022) and an increasing trend at the teaching hospital- Korle Bu where hypertensive disorders account for 49.5% of the direct causes of maternal mortality (Boafor, Ntumy et al. 2021).

Sleep disorders have been proposed as the missing link that accounts for the racial disparity in cardiovascular diseases, such as hypertension (Jackson, Redline et al. 2015). African women have shorter sleep duration compared to women of other races during pregnancy, and PE is more common in women of African descent compared to other races (Johnson and Louis 2022). PE also causes severe morbidity and higher mortality among women of African descent compared to other races (Gyamfi-Bannerman, Pandita et al. 2020).

Pregnancy begins with a pro-inflammatory phase, which favours implantation, followed by a transition to an anti-inflammatory phase for the growth of the foetus, and ends as a pro-inflammatory phase that facilitates the onset of labour and parturition (Mor, Aldo et

al. 2017) (Beroukhim, Esencan et al. 2022). Sleep regulates inflammatory responses, and chronic sleep deprivation induces the transcription and translation of pro-inflammatory genes (da Costa Souza and Ribeiro 2015). Serum pro-inflammatory cytokines like interleukin (IL)-1, IL-6, IL-17, NF- κB, TNF α, and C-reactive protein (CRP) are elevated by chronic sleep deprivation (SD) to the degree of the severity and duration of sleep deprivation (Atrooz and Salim 2020). Sleep deprivation contributes to the pathogenesis of PE through immune dysregulation, a key feature of PE (Niazi, Moradi et al. 2022). IL-6 induces the transcription of C-reactive protein genes in hepatocytes, and so both are used as markers for early detection of the endothelial dysfunction resulting from PE – induced inflammation (Sproston and Ashworth 2018). Serum levels of CRP are observed to be elevated as early as the first trimester in women who later develop PE (Lagana, Favilli et al. 2016).

Resting state electroencephalogram can assess the effect of normal pregnancy on cognitive function (Luo, Liang et al. 2020) and in pregnancies with hypertensive disorders (Bartal and Sibai 2020). By measuring the summation of oscillatory components of post-synaptic potentials of cortical pyramidal neurons, using scalp electrodes, cortical organizational and functional changes can be detected (Srinivasan, Winter et al. 2007, Babiloni, Barry et al. 2020). Pregnancy, sleep and hypertensive disorders are independent contributors to changes in the functional organization of a mother's brain. In a Dutch study, women with a history of PE had different brain functional organization as compared to women without a history of PE (Canjels, Ghossein-Doha et al. 2022). The racial predisposition of Africans to hypertension, sleep disorders and hypertensive disorders of pregnancy is well-researched (Abrahamowicz et al., 2023; Ahn et al., 2021). However, limited studies have explored the contribution of

sleep disorders and hypertension to functional and cognitive changes in normotensive and preeclamptic maternal brain in the subregion and in Ghana.

1.2 PROBLEM STATEMENT

Of all global maternal mortalities, 94% occur in South Asia and Sub-Saharan Africa (World Health Organization, 2023) and PE and eclampsia account for 14% of them (Bartal and Sibai 2020). A five-year review of maternal mortalities at the Korle Bu Teaching Hospital (KBTH) revealed that hypertensive disorders accounted for 37.3% of the total maternal mortalities, translating into a maternal mortality ratio of 604 per 100,000 live births (Boafor, Ntumy et al. 2021). It has been reported that PE has an effect on the brain's organization, especially the limbic system and prefrontal cortex, and this may be responsible for the psychotic behaviour (similar to post-traumatic stress disorder) observed in some women with PE (Canjels, Ghossein-Doha et al. 2022) .

Ghanaians have a shorter sleep duration (Anujuo, Stronks et al. 2015) and severe adverse effects of SD on cardiovascular function as compared to other racial/ethnic groups (Anujuo, Agyemang et al. 2022). Sleep studies, conducted in pregnancy in the country, have established the high prevalence of PE and hypertension in pregnancies with SDs (Owusu, Anderson et al. 2013, Kugbey, Ayanore et al. 2021); however, our literature search did not identify any that focused on sleep quality domains such as sleep chronotype, sleep duration and sleep latency(Facanha et al., 2022). There is therefore a need to establish the relationship between sleep disorders and PE, since some domains of sleep, such as sleep chronotype, is modifiable (Knutson and Von Schantz 2018)

SDs cause an elevation in blood pressure, which is higher in females compared to males (Carter, Fonkoue et al. 2019). Pregnancy subjects women to nine months of SD, which predisposes them to chronic inflammation, vascular endothelial dysfunction,

hypertension, and therefore PE. Several studies have established the bi-directional relationship between SD, hypertension, and PE (DelRosso, Mogavero et al. 2020, Jung, Romero et al. 2022). Our literature search did not identify any study done in Ghana that assesses the effect of SD on IL-6, CRP levels, and functional connectivity of cerebral cortex in PE.

RELEVANCE OF THE STUDY

Though the cause of PE has been elusive, SD and systemic inflammation have both been established as independent risk factors for the development of hypertension; the common pathway being vascular endothelial dysfunction and increased sympathetic tone (Venkataraman, Vungarala et al. 2020). Studies assessing their bidirectional relationship and concerted effect on pregnancy and maternal cognitive function in PE and normal pregnancy have not been done in the country. Sleep has also been reported to be of a shorter duration (Anujuo, Stronks et al. 2015) and more adversely impactful on the cardiovascular system in Ghanaians as compared to other racial/ethnic groups (Anujuo, Agyemang et al. 2022). PE is currently the leading cause of maternal mortality in nearly all tertiary hospitals in the country(2022). The study was designed to generate evidence that can potentially be used to assess the effect of sleep disorders on maternal brain functional connectivity and the role of IL-6 and CRP for in the pathogenesis (Mora-Palazuelos, Bermúdez et al. 2022). Analysis of the resting state encephalogram would facilitate the mapping of maternal cortical areas which are susceptible to the effects of PE

1.3 AIM

The study aims to investigate the resting state functional connectivity of the cerebral cortex and its association with sleep quality and markers of inflammation like IL-6 and CRP in preeclamptic and normal pregnancy.

1.4 OBJECTIVES

1. To compare the sleep chronotype and quality between pregnant women with and without PE.
2. To compare the power spectrum of brain waves and functional connectivity analysis from resting state EEG recordings in women with and without PE.
3. To find out the association between inflammatory markers such as interleukin-6 and C-reactive protein, sleep quality, and functional connectivity in pregnant women with and without PE.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 DEFINITION AND EPIDEMIOLOGY OF PREECLAMPSIA

Hypertension is the most common medical disease in pregnancy, and the burden of the disease is increasing rapidly worldwide (Khedagi & Bello, 2021). Hypertensive disorders in pregnancy (HDP) include gestational hypertension, chronic hypertension, preeclampsia, chronic hypertension with new onset PE, and eclampsia (Gemechu et al., 2020). HDP may also present during the puerperium as post-partum preeclampsia or eclampsia (Berhan & Endeshaw, 2015; Hauspurg & Jeyabalan, 2022). PE is characterized by hypertension with evidence of malfunctioning maternal end-organ(s) or placenta at or after 20 weeks of pregnancy (Ives et al., 2020a). PE may also be a progression from any of the other hypertensive disorders of pregnancy (Magley & Hinson, 2024). Globally, 2-8% of pregnancies are affected by PE, with an annual loss of lives of 2 million newborns and 76,000 mothers (Kinshella et al., 2023; Poon et al., 2019). The incidence of PE and its related mortalities are higher in low and middle-income countries in Sub-Saharan Africa and South East Asia (Gemechu et al., 2020). The prevalence in Sub-Saharan Africa is about 13% and West Africa has the second-highest prevalence of HDP globally (Jikamo et al., 2023)

In Ghana, the prevalence of PE is between 6.05 to 7.03% (Fondjo et al., 2019; Obed & Patience, 2006). Over the past five years, it has continued to be the leading direct cause of maternal mortality in many tertiary hospitals in Ghana (Awuah et al., 2020; Boafor et al., 2021). The trajectory is expected to continue in an ascending order due to a sustained increase in the incidence of hypertension in Sub-Saharan Africa and globally. The World

Health Organization estimates that 46% of adults aged 25 years or in SSA are hypertensive, and a large proportion are unaware of the condition (Ferdinand, 2020; Nguyen & Chow, 2021). PE also significantly affects health expenditures with a budgetary allocation of 2.18 billion dollars incurred by the United States health system in 2012 (Li et al., 2017)

2.2 CLASSIFICATIONS OF PREECLAMPSIA

The definition of preeclampsia continues to evolve as knowledge of the condition increases. A systolic blood pressure of 140mmHg or more and/or a diastolic blood pressure of 90mmHg or more in a previously normotensive pregnancy at or after 20 weeks is diagnostic criteria if there is also maternal organ dysfunction. Organ dysfunction may present as reduced blood flow in placental arteries, elevation of maternal liver enzymes, maternal proteinuria, pulmonary oedema, and cardiovascular disorders (Beckett et al., 2023). The progression of chronic hypertension to preeclampsia is termed superimposition of PE. Eclampsia is a severe form of the disease, it causes new onset of tonic-clonic seizures, without a prior history of seizures or any other attributable cause (Laskowska, 2023).

PE has been classified according to the severity of the symptoms into PE with severe features and PE with no severe features (M. A. Brown et al., 2018). Severe features include low platelet count, two-fold elevation of liver transaminase enzymes, pulmonary oedema, visual disturbances, severe hypertension of 160/110mmHg, intractable headaches and the onset of seizures (Kongwattanakul et al., 2018). The fetal-placental unit may also present with abruption of the placenta, severe retardation of growth or intrauterine fetal demise (Kupferminc et al., 2024). The severity of symptoms is used as a basis to determine the management of a mother and the delivery modality of each pregnancy(Cordero et al., 2021). This is because expulsion of the placenta is the most

effective treatment for PE and it is often expedited to preserve maternal organs (Chen et al., 2023). A classification based on gestational age class PE as preterm and term. PE is preterm if it occurs before 37 gestational weeks and term PE if it occurs after the 37th gestational week (Robillard et al., 2023). PE is also categorized into early-onset PE (occurs before 34 gestational weeks) and late-onset PE (occurs at or after the 34th gestational week). Both late onset and term PE are associated with better maternal and neonatal outcomes (Robillard et al., 2023; ROCHA, 2023; Rolnik et al., 2017)

2.3 RISK FACTORS OF PREECLAMPSIA

Several factors have been correlated in the theories on the pathogenesis of preeclampsia. These are multifactorial with a strong interaction between maternal medical history, genetic and environmental factors. Advanced maternal age, primiparity, primipaternity, obesity, sedentary lifestyle, assisted reproduction, inter-pregnancy interval exceeding 10 years and a family history of PE pose a high risk. History of chronic kidney disease, hypertension, diabetes mellitus, polycystic ovarian syndrome, and sickle cell disease are also strongly associated with preeclampsia (Dai et al., 2023; Jung et al., 2022; Prophet et al., 2018; Weinberg et al., 2017).

Environmental factors such as altitude, seasons of the year, rainfall patterns, tropical infections such as malaria, high ambient temperature and exposure to noise and air pollutants also increase the odds of new onset or recurrence of preeclampsia (Nwokocha et al., 2020a)(Parinaz et al., 2015; Unger et al., 2023a). A strong association between sleep disorders and preeclampsia has also been established. These include eveningness sleep chronotype, sleep-disordered breathing, obstructive apnoea in sleep and insomnia. Sleep disorders may also be imposed by high temperatures, noise pollution and obesity, showing an interaction between environmental factors and biophysical profile (Dominguez et al., 2018a, 2018b; Querejeta Roca et al., 2020)

PE incidence is higher for a male foetus, in immunization of a mother with foetal cells termed chimerism, multiple gestation and in the presence of a large placenta as in hydatiform molar pregnancy (and in multiple gestation) (Broere-Brown et al., 2020; Hahn et al., 2019; J. M. Roberts & Escudero, 2012).

Polygenic defects interacting with lifestyle and environmental factors contribute to the onset and progression of the syndrome. Defects of maternal, paternal and placental genes contribute to PE. This makes the condition heritable by non-Mendelian inheritance (Parada-Niño et al., 2022). Key gene candidates regulating blood pressure, oxidative stress, renal and endothelial function, thrombosis and formation and growth of the placenta have been identified and their defects or polymorphism contribute to the development of the syndrome (Christians et al., 2017; Parada-Niño et al., 2022; Sari et al., 2017). About 9 gene loci associated with hypertensive disorders (NPPA, NPR3, PLCE1, TNS2, FURIN, RGL3, and PREX1), placental development (PGR, TRPC6, ACTN4, and PZP), remodelling of uterine spiral arteries (NPPA, NPPB, NPR3, and ACTN4), and renal function (PLCE1, TNS2, ACTN4, and TRPC6) have been identified (Tyrmi et al., 2023).

2.4 THE TWO-STAGE HYPOTHESIS

Several theories have been proposed to explain the syndrome of PE, and the body of knowledge keeps growing. The theories have also been presented as a two-stage model that explains how the disease develops. In the first stage, there is malperfusion of the placenta due to impaired invasion of the decidualized endometrium and remodelling of maternal spiral arterioles by trophoblastic tissue. In the second stage, there is an exaggerated inflammatory response, which results in systemic, generalized endothelial dysfunction which affects all organ systems(Ives et al., 2020b). The blood flow to the placenta, under high pressure, induces oxidative stress with a resultant shedding of

placental factors which triggers an immune response. These have been identified as placental villous fragments, tumour necrosis factor, placental-derived growth factor, soluble fms-like tyrosine kinase, soluble endoglins and several cytokines (Rana et al., 2022). This emphasizes the fact that placental dysfunction is central in the physiopathology of preeclampsia since PE can occur in abdominal pregnancy, without the involvement of the uterus, and in molar pregnancy, even when a foetus is absent (Camacho-Montaño & Niño-Alba, 2020; Hailu et al., 2017; Redman, 2014; Yagel et al., 2022). Priming of the maternal immune system, by placental elements, leads to immune deregulation and endothelial dysfunction. This is a link between the first and the second stage of the disease (Zanini et al., 2020).

The immune dysfunction involves activation of an innate immune response, complement activation, elaboration of cytokines and culminates in an adaptive immune response. In PE, pro-inflammatory macrophage subtypes exceed the anti-inflammatory subtype, which leads to the elaboration of pro-inflammatory cytokines such as interleukin 6 (IL-6), tumour necrosis factor and interleukin-1beta. Natural Killer cells also secrete pro-inflammatory cytokines such as tumour necrosis factor alpha which has been implicated in the pathogenesis of hypertension in pre-eclampsia. TNF- alpha has receptor types 1 and 2 (TNFR1, TNFR2). TNFR2 is implicated in mediating inflammatory and renal dysfunction. (Mehaffey & Majid, 2017). Through oxidative stress in placental mitochondrial cells, TNFR2 increases the levels of vasoconstrictive placental factors such as soluble endogelin, endothelin-1 and autoantibodies for angiotensin II type 1 receptor. Even though TNF-alpha is produced by other tissues such as renal tubules, and epithelial cells among others, their levels are elevated up to three folds in preeclampsia compared to normal pregnancy (Cunningham et al., 2020; Vaka et al., 2019). Elevated angiotensin II and oxidative stress further increase the levels of TNF-alpha by a positive feedback

mechanism. TNF-alpha also causes volume retention, dysfunction of renal arteries, endothelial dysfunction and infiltration of renal tubules by monocytes.

Following an increased inflammation, there is generalized vascular endothelial dysfunction which culminates in the clinical manifestations of organ system dysfunction. Aside from the role of pro-inflammatory factors and the immune system, soluble fms-like tyrosine kinase 1 inhibits angiogenic factors such as placental growth factor (PlGF) and vascular endothelial growth factor(VEGF). Vasodilators such as nitric oxide and prostacyclins are also depleted while there is an increase in the levels of vasoconstrictors such as Angiotensin II and endothelin-1 (Opichka et al., 2021a; Tomimatsu et al., 2019). The vascular endothelium also becomes damaged and increasingly adhesive both attracting and activating platelets. Platelet aggregation leads to microclot formation, depleting circulating platelets, plugging blood vessels and leading to haemolysis (Opichka et al., 2021b)

Cytokines are a family of proteins that drive inflammation, including attraction and activation of leukocytes, and increasing vascular permeability. The families of cytokines include interleukins 1 and 6 (IL-1, IL-6) tumour necrosis factor, interferons and transforming growth factor. The interleukin 6 family of cytokines include IL-6, neuropoietin, and ciliary inhibitory factors among others (Aneman et al., 2020). IL-6 is a cardinal pro-inflammatory cytokine which has been strongly associated with the progression of PE from the first to the second stage. IL-6 is produced by T, and B lymphocytes, mesangial cells, endothelial cells and fibroblasts. High serum titres of IL-6 are associated with preterm pregnancy loses and chronic inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis which are both risk factors for PE (Bermas & Sammaritano, 2015; Dong et al., 2020; Zhang et al., 2022). IL-6 is considered to be a serum biomarker of impaired vascular endothelial function and is used in

predicting preeclampsia (Marczynski et al., 2021). Highly sensitive C-reactive protein, also a marker of dysfunction of liver cells is used together with IL-6 as biomarkers for assessing the presence and severity of inflammation including PE. Hepatocytes produce it in response to signalling by IL-6 in acute inflammatory states such as PE (Agrawal & Wu, 2024)(Del Giudice & Gangestad, 2018)(Kara et al., 2019).

Considering that inflammation leads to the progression of PE, other infections have also been linked to a higher likelihood of PE. These include placental malaria, chronic inflammation of the decidua, and urinary tract infection among others (Nwokocha et al., 2020b; Unger et al., 2023b; Yan et al., 2018). This may account for the high prevalence of PE in developing countries where infectious diseases are endemic and outbreaks are frequent (Nourollahpour Shiadeh et al., 2017; Weekly Bulletin on Outbreaks and Other Emergencies, 2024)

2.5 PREGNANCY AND SLEEP DISORDERS

Sleep is essential for coordinating circadian rhythms including hormone release, regulation of inflammation, and tissue repair. Quality sleep increases the chances of success of fertilization and implantation, and facilitates immune tolerance between a mother's immune system and the foetus so that pregnancies are not aborted. Sleep disorders have been identified to result in non-communicable diseases including Alzheimer's and Parkinson's disease, psychosis, depression, bipolar disease, polycystic ovarian syndrome, diabetes, and arterial hypertension. (Ibrahim et al., 2023; Monzon et al., 2022; Perry et al., 2024; Reschini et al., 2022).

Pregnancy is often associated with de novo sleep disorders and worsening of existing sleep disorders. Sleep-disordered breathing, long sleep latency, restless leg syndrome,

insomnia, wakefulness after sleep onset and other forms of sleep disorders are commonly reported in pregnancy (Facco et al., 2022; Miller et al., 2020). Sleep-disordered breathing is defined as sleep-related upper airway collapse. This results in episodic disruption of the respiratory cycle, resulting in oxygen deprivation and carbon dioxide retention in blood and oxidative stress. Sleep-disordered breathing presents with snoring at night, sleep fragmentation and frequent waking from sleep (Pamidi & Kimoff, 2018). Sleep latency is the period between when a person attempts to sleep and the onset of sleep. Sleep latency is long if it exceeds 30 minutes (Albqoor & Shaheen, 2021b). In insomnia, there is difficulty in initiating and maintaining sleep, and waking too early in the morning, with difficulty returning to sleep (Patel et al., 2018). WASO is a feature of insomnia and is described as how long a person stays awake following the disruption of an initial sleep. Restless leg syndrome is also a sleep-related disorder presenting as a compulsive urge to move the legs during sleep. The urge is circadian, higher during inactivity and during sleep. There is a strong correlation between restless leg syndrome and pregnancy because iron deficiency anaemia is common to both. In pregnancy, there is rapid depletion of iron stores, while low iron levels in the brain lead to restless leg syndrome (Allen, 2015).

All persons have sleep-wake preferences called sleep chronotypes. Sleep chronotypes refer to a spectrum of sleep propensities described as morningness chronotype, eveningness chronotype and neither-type. A person has a morningness chronotype if they go to bed early at night and rise early in the morning. The eveningness chronotype is characterized by optimal performance peaking late at night, sleeping late at night and rising late during the day. The Neither-type does not identify with either of the afore (Correa et al., 2020; Montaruli et al., 2021). Sleep chronotypes are predispositions to sleep disorders and diseases (Bishehsari et al., 2020; Yang et al., 2023). The eveningness chronotype is associated with cardiovascular, metabolic, inflammatory and

neurodegenerative diseases including hypertension, diabetes, inflammatory bowel disease, Parkinson's disease and preeclampsia (Chrobak et al., 2018; Knutson & von Schantz, 2018; Kobayashi Frisk et al., 2022; Mortaş et al., 2023).

The suprachiasmatic nucleus of the hypothalamus is the central biological clock that regulates peripheral clocks. Sleep, inflammation, reproduction and stress responses are a few of several life processes, coordinated by the suprachiasmatic nucleus in concert with peripheral receptors in organs, tissues, and at the level of genes (Rosenwasser & Turek, 2015; Van Erum et al., 2018). Sleep disorders evoke an inflammatory response through the activation of the hypothalamic-pituitary-adrenal axis. This leads to the upregulation of systemic inflammatory markers such as IL-6, C-reactive protein and tumour necrosis factor. There is also increased expression of inflammatory genes and as sleep disorders persist, the cycle is perpetuated by a seeming positive feedback mechanism. Therefore chronic sleep disorders lead to vascular endothelial dysfunction and are implicated in several diseases including PE (Irwin, 2019; Irwin et al., 2016).

2.6 PHYSIOLOGICAL CHANGES IN PREGNANCY AND SLEEP DISORDERS

Pregnancy is associated with anatomical and physiological changes which impact sleep quality and vice versa. High levels of estrogen in pregnancy cause oedema of the nasopharyngeal mucosa increasing airway resistance. Mucosal changes in the pharynx also increase its tendency to collapse during sleep resulting in obstructive sleep apnoea an oxidative stress from hypoxia. Increased blood volume, glomerular filtration rate and nocturnal sodium excretion lead to frequent urination at night which fragments sleep (Gangakhedkar, 2022; Gjørup et al., 2008; Kazma et al., 2020a).

In the latter part of pregnancy, the enlarged uterus affects maternal sleep posture and has been associated with sleep disorders. A supine posture leads to the compression of abdominal blood vessels by the gravid uterus, depression of respiration and oxygen

desaturation. Supine sleep position also worsens obstructive sleep apnoea and is associated with adverse maternal and neonatal outcomes such as preeclampsia. (Dunietz et al., 2020; Humphries et al., 2019; Robertson et al., 2019).The common pathway for all sleep disorders is to evoke an inflammatory response to the activation of pro-inflammatory genes, oxidative damage of cells and endothelial function.

2.7 SLEEP DISORDERS AND ORGAN DYSFUNCTION

Sleep disorders are independently associated with altering organ structure and function which may be amplified during pregnancy. Supine sleep posture is associated with inferior vena caval obstruction impairing sufficient blood flow through the uteroplacental unit (Deer et al., 2023; Humphries et al., 2017). A hypoxic placental environment is associated with common features of preeclampsia such as intrauterine fetal growth restriction and stillbirth (Deer et al., 2023). Obstructive sleep apnoea (OSA) is also associated with maternal cardiovascular changes including arrhythmias, vascular atherosclerosis, and hypertension (Korostovtseva et al., 2021). OSA stimulates the sympathetic nervous system during and after sleep. This increases heart rate and blood pressure. There is therefore a positive correlation between OSA and cardiovascular diseases such as hypertension, resistant hypertension, heart failure and arrhythmias. Persistent hypertension results in the remodelling of the heart and these structural changes predispose to disorders of electrical conduction (arrhythmias) and heart failure if untreated (J. Brown et al., 2022; Carnethon & Johnson, 2019).

The respiratory system is also susceptible to sleep disorders. Obstructive sleep apnoea (OSA) causes periodic abrupt changes in intra-thoracic pressure which causes tractional injury, hypoxia, oxidative stress and lung injury. Successful treatment of OSA is associated with improvement in oxygen saturation, resolution of increased pulmonary arterial pressure and hypertension (Adir et al., 2021; Locke et al., 2022). The prevalence

of OSA increases with increasing gestational age from about 10% in first trimester of pregnancy to about 27% at term (R. Gupta & Rawat, 2020)

2.8 SLEEP DISORDERS, INFLAMMATION AND BRAIN FUNCTION

Sleep disorders impair cognitive functioning and manifests as an impairment of alertness, executive functions, and memory (Fjell et al., 2023). In wakeful states, memories are encoded to the point of saturation. During sleep both declarative and procedural memories are processed and consolidated (Klinzing et al., 2019). The hippocampus Chronic sleep disorders are also associated with grossly lower brain volumes (Bubu et al., 2020). Specific brain areas may be more vulnerable to sleep deprivation evidenced by reduced activation of these areas following sleep deprivation. These include the frontal lobe, thalamus, supplementary motor cortex and other brain areas(Wang et al., 2023).

Sleep deprivation leads to elevated serum concentrations of inflammatory cytokines particularly IL-6 and C-reactive protein through pro-inflammatory gene expression (Sang et al., 2023). C-reactive protein and IL-6 are both markers of peripheral and systemic inflammation. They are both predictors of cardiovascular diseases, hypertension, diabetes mellitus and their elevated levels in serum result in disruption of the blood-brain barrier, neuroinflammation and axonal death (Palta et al., 2015; Pastorello et al., 2023). These deleterious changes affect neurotransmission and processing of stimuli and translate into early onset atrophy of gray matter of the brain. Several studies have also proven the hippocampus (central to the processing of memory) as vulnerable to vascular endothelial dysfunction from systemic inflammation. These underlie the long-term memory deficits commonly reported in preeclampsia survivors. Intrauterine exposure to preeclampsia is also associated with neurocognitive and neuropsychiatric diseases. Children have larger brain volumes, decreased intelligence quotients, and lesser scores for arithmetic and

cognitive tests compared to controls (Ra tsep et al., 2016; Tuovinen et al., 2014). Autistic disorders, brain palsy, epilepsy and other neurocognitive diseases have a higher prevalence, following prenatal PE exposure compared to controls (Dachew et al., 2018; Gumusoglu et al., 2020; Sun et al., 2020).

2.9 PREECLAMPSIA, ENCEPHALOGRAPHY AND NEUROIMAGING

Imaging is essential in assessing the impact of PE on the fetus as well as major maternal organs such as the heart, placenta, and brain. Imaging options such as magnetic resonance imaging, ultrasound and resting-state electroencephalography are useful tools in establishing diagnosing, assessment of severity and prognostication in preeclampsia (Joubert et al., 2022; Mai et al., 2021a, 2021b).

Magnetic resonance imaging (MRI) is used in high-income countries in assessing the effect of preeclampsia on the brain. It is able to detect gross white matter defects as hyperintensities (Griffanti et al., 2016). Diffusion tensor imaging technology, an advanced form of MRI, detect early, subtle changes which affect the microstructural integrity of the brain (Okudzhava et al., 2022). It assesses the diffusion of water molecules aiding the generation of visuals depicting neural circuits and functional connectivity of the brain (’Razenberger et al., 2024). Quantitative measures from these imaging technologies are used to assess changes in attenuation, volume, and activation of brain regions of interest (Leiby et al., 2024).

Electroencephalography offers a non-invasive, readily available alternative, in low resource settings, for evaluating functional connectivity of the brain. The functional connectivity signals are used to generate spatial maps for assessing the functional organization or neural networks and to assess the differences between normal and diseased brain (N. Xu et al., 2022). It can also be used to assess the interconnection and overlap between spatially distinct brain regions (Du et al., 2018; J. Yuan et al., 2018).

Resting state encephalogram assesses spontaneous brain electrical activity when participants are not engaged in any specific task. Participants are asked to relax during the procedure. After scalp preparation, electrodes are placed according to international systems such as the 10-20 international system of scalp electrode placement (Acharya & Acharya, 2019). Transcranial recordings are taken with their eyes closed or open. The baseline neural activity and functional connectivity is then recorded.

Functional connectivity is often assessed by examining the correlation of EEG recordings between different brain regions. High correlation indicates strong connectivity, suggesting that these regions are functionally linked. The brain is organized into networks that are active even at rest. These include the default mode network (DMN), which is involved in self-referential thinking and mind-wandering, and other networks related to sensory, motor, and cognitive functions. While EEG gives an overview of generalized brain activity, it can be used to localize the source of stimuli as in seizures and to ascertain the brain hemisphere involved.

EEG signals are categorized into different frequency bands- delta, theta, alpha, beta, gamma ('Chetan & 'Arayamparambil, 2023). Functional connectivity can be analyzed within these bands to understand how different types of brain activity are coordinated. Changes in functional connectivity patterns can be indicative of various conditions, including but not limited to preeclampsia, ageing. For example, altered connectivity in the DMN has been observed in conditions like Alzheimer's disease, depression, and schizophrenia. Functional connectivity analysis gives insight into the brain's intrinsic organization, aiding the development of biomarkers for early diagnosis and monitoring of treatment effects. EEG can clinically predict seizures (X. Xu et al., 2022) and in preeclampsia, it could be a helpful tool in predicting and preventing a progression from preeclampsia to eclampsia. The assessment of baseline activity as well as intermittent and

paroxysmal tracings, averting the deleterious effect of overt seizures on the brain (Brussé et al., 2010).

Processing of EEG data begins with the removal of contaminants or artefacts (Jatoi et al., 2014a). These artefacts are generated from ocular movements, contraction of scalp muscles, sweat, tongue movements associated with swallowing, and respiratory movements. Other non-physiological artefacts could also be from wearable electrical devices or electrical devices in the immediate environment of the patient (American Epilepsy Society, n.d.).

Artefacts can imitate neurological disorders and introduce biases into EEG data. The first step to limiting artefacts is to limit human errors during data collection, and clearly instructing the participant to restrict movements. Manual preprocessing of the data is then done as presented by the sequential steps presented in a review by Garces et al in (Garcés et al., 2022). Beyond these, several methods can be used to denoise artefacts as extensively presented in the review by Jiang et al in (Jiang et al., 2019). The decontaminated EEG data is then analyzed using MATLAB (MATrix Laboratory) and the LORETA (low-resolution electromagnetic tomography) family of algorithms including LORETA, sLORETA and eLORETA. The LORETA family of applications are for localizing the source of lesions or

LORETA was introduced to solve large localization errors. It however has fewer voxels (2,394) and 7mm spatial resolution (Dattola & La Foresta, 2020). sLORETA, for standardized LORETA, was introduced to improve the former. It has a spatial resolution of 5mm and 6239 voxels providing better source localization. eLORETA (exact LORETA) is the latest addition to the LORETA family of algorithms. It has better resolution than sLORETA and outperforms the latter in localization error and has better

acuity of source reconstructed images (Jatoi et al., 2014b). eLORETA is also able to visualize deeper brain structures and can be used to generate a 3D representation of neural activity (Michel & He, 2019).

MATLAB uses a matrix-based programming language to process data for both 2D and 3D visualization (Jatoi et al., 2014a; *MATLAB*, n.d.). The power spectral density of EEG signals can be estimated using nonparametric MATLAB functions such as Welch's periodogram. Welch's function allows the frequency content of signals to be characterized as well as their amplitude, power densities and power spectra and has been widely used to assess baseline brain activity, cognition, disorders of memory and in brain disease (Hu et al., 2020; Ponciano et al., 2020; Rihs et al., 2007).

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CHAPTER THREE

3.0 METHODOLOGY

3.1 STUDY DESIGN

The study used a case-control design, with preeclamptic singleton gestations as cases and normotensive singleton gestations as controls.d

3.1.1STUDY SITE

The research was carried out outpatient clinic and maternity ward of the Department of Obstetrics and Gynaecology, KBTH. The KBTH is the largest referral centre in Ghana. The Obstetrics and Gynaecology Department records 10,000 annual deliveries (Adu-Bonsaffoh, Gyamfi-Bannerman et al. 2019). The institutional maternal mortality ratio for 2020 was 677 per 100,000 live births. Hypertensive disorders of pregnancy accounted for 52.3% of the 5 leading causes of maternal mortality in 2020 (2022).

3.1.2 STUDY PARTICIPANTS AND SAMPLING

The study population was pregnant women receiving antenatal and emergency obstetric care at the Obstetrics and Gynaecology Department of the Korle Bu Teaching Hospital. The study sample consisted of pregnant women of gestation age ranging from twenty (20) to forty-two (42) completed weeks. The cases were consecutive consenting women with singleton gestations diagnosed with PE. The case definition was according to the protocol of the department for diagnosing preeclampsia: elevated blood pressure of $\geq$ 140/90mmHg with evidence of maternal end-organ or fetal-placental unit dysfunction after the 20th gestational week. Maternal end-organ dysfunction was evidenced by any of the following: low maternal platelet count, elevated maternal liver enzymes, high serum uric acid and significant proteinuria. The dysfunction of the fetal-placental unit was detected if there was reduced blood flow in the umbilical vessels on Doppler ultrasound or intrauterine growth retardation.

The controls were normotensive women with singleton gestations without preeclampsia. The consenting consecutive participants were invited to join the study after meeting the eligibility criteria. The cases and controls were recruited concurrently, matched for gestational age within 1 week and 2-3 years for maternal age.

3.1.3 SAMPLE SIZE CALCULATION

The sample size required was calculated using IBM SPSS version 27 based on already reported values. Since no study had reported serum levels of IL-6 and CRP levels in pregnant women with/without preeclampsia in sub-Saharan Africa, we used data from (Scholaske, Buss et al. 2018) which reports the mean levels for IL-6 levels (18-35 week of pregnancy) and (Teran, Escudero et al. 2005) for CRP levels for the 16-36th week of pregnancy.

Analyte	Normal pregnancy	Pre-eclampsia	Power	Sample size
IL-6	0.93± 0.58 pg/mL	1.1±0.61 pg/mL	80%	37 per group
CRP	3.2±2.2 mg/L	5.1±2.5 mg/L	80%	26 per group

A minimum sample size of 74 participants (37 normal pregnancies and 37 preeclamptic pregnancies) was required to achieve a power of 80% and a significance level of 95%. We therefore, recruited 112 participants for the study.

3.1.4 SAMPLING PROCEDURE

The cases were consecutively sampled among consenting women while they were either attending antenatal clinic or on admission at the maternity unit of KBTH on account of PE. Controls were purposively sampled from the normotensive attendants with singleton gestations at the antenatal clinic of KBTH.

3.1.5 INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria for cases were consenting pregnant women with singleton gestations, diagnosed with preeclampsia from a gestational period of 20 to 42 weeks. Consenting normotensive women with singleton gestations at gestational age of 20 to 42 weeks were recruited as study controls. Women were not eligible to participate if they had a history of pre-gestational renal disease, hypertension induced by pregnancy, diabetes mellitus (DM) or gestational diabetes, heart disease, multiple gestations, history of epilepsy, or any other chronic end-organ dysfunction.

3.2 DATA COLLECTION APPROACH

Sociodemographic information was collected using a standardized questionnaire. Sleep quality was assessed by administering the Pittsburgh Sleep Quality Index (PSQI), and Epworth Sleepiness Scale (ESS) tools. These tools were used to assess the quality of sleep and chronotypes, respectively. Total sleep duration was computed as 5/7 (total hours of sleep on weekdays) + 2/7 (total hours of sleep on weekends). Participants had poor sleep quality if they had a PSQI score of >5 and daytime sleepiness as ESS>10.

The PSQI tool assesses bedtime sleep quality under seven components, namely subjective sleep quality, sleep latency, sleep disturbances, sleep efficiency, the use of sleep medication and daytime sleep dysfunction. Each component has a subset of questions which were administered. A scale of 0 to 3 is used to assess the level of difficulty or severity. All the components derive a global score ranging from 0 to 21, with higher scores (> 5) indicating poorer sleep quality.

The Epworth Sleepiness Scale was used to assess the tendency of the participants to feel sleepy in the daytime. It consists of 8 daily daytime activities and a scale of 0 to 3 that is used to assess the extent of the tendency of the participants to feel drowsy or sleepy. The

numbers of standardized scale are interpreted 0=no chance of dozing, 1= slight chance of dozing, 2= moderate chance of dozing and 3= high chance of dozing. A global score greater 10 indicates inadequate sleep quality and quantity worthy of medical attention.

3.2.1 Biochemical assays

About 5 ml of venous blood was aseptically sampled from the antecubital fossa of participants into labelled tubes containing ethylene diamine tetraacetate. Samples were transported under biosafety measures to the lab to be centrifuged at 4000G to collect the serum, and stored at -20ºC until assayed. Sandwich ELISA was used to measure IL-6 and CRP concentrations using a precoated 96-well commercially available ELISA kit (Biobase Biotech-Melson Shanghai Ltd, China). The protocol outlined by the manufacturer in the instruction manual was followed. The ELISA microplate reader (Synergy H1) was used to determine IL-6 and CRP concentrations at a wavelength of 450 nm. The laboratory work for ELISA was carried out at the Immunology unit of the central laboratory of the Kwame Nkrumah University of Science and Technology.

3.2.2 EEG recording and analysis

Resting-state EEG data were collected while each study participant was seated comfortably in a quiet office with the assistance of an EEG technician from the Department of Physiology. Resting-state EEG tracings were measured and recorded using 32 non-invasive elastic cap electrodes placed on the scalp, according to the international 10–20 system. Measurements were done in a quiet room using the KT 88 3200 amplifier (Contec Medical System, Hebei, China). Reference electrodes (A1 and A2) were placed on participants' ears and the impedance of each electrode was maintained below 5kΩ. The impedance between each electrode and the scalp was

between 100 Ω and 5000 Ω. First, a routine recording was performed for 1–2 min, followed by an eye opening and closing test, and lastly, 1 more minute of routine recording EEG activity of each brain area in the cerebral cortex. The tracings and participants were monitored to avoid artifacts from muscle contraction and EEG drowsiness.

EEG data were divided into 2 second EEG epochs and epochs with movement artifact, electrode artifact, eye blink storms, drowsiness, epileptiform discharges, and/or bursts of muscle activity were marked and to allow complete exclusion from subsequent analyses. After such visual inspection and treatment, data were low pass filtered below 50 Hz with an additional 60 Hz mains rejection notch filter. Remaining eye blink and eye movement artifacts, which may be surprisingly prominent even during the eyes closed state, were removed by utilizing the source component technique as implemented in the BESA (BESA GmbH, Freihamer Strasse 18, 82116 Gräfelfing - Germany) software package. These combined techniques resulted in EEG data that appeared largely artifact free, with rare exceptions of low level temporal muscle artifact and persisting frontal and anterior temporal slow eye movement, which remain capable of contaminating subsequent analyses.

The EEG data were divided into six bands: δ (0.3 to 3.5 Hz), θ (4 to 7.5 Hz), α1 (8 to 10 Hz), α2 (10.1 to 13 Hz), β1 (14 to 18 Hz), and β2 (18.1 to 30 Hz), and the absolute power values of each band was calculated. Power analysis of the waveform were performed using Welch's periodogram method in MATLAB, with nonoverlapping Hamming windows of 2s and log-transformed power spectra of the specific frequency band subsequently calculated. Furthermore, the underlying cortical sources of the frequency band were estimated using the EEGLAB and sLORETA software packages.

For resting state-EEG data, current densities from EEG electrodes were log-transformed and cross-spectral matrices for each participant were computed and then averaged as the input for the source analysis in the sLORETA system. The focus was on the 84 regions of interest (ROI) that may correspond to the 42 Broadman's areas of both hemispheres of the brain. Functional connectivity analysis was conducted using eLORETA to examine all connectivities between 84 ROIs (3486 connectivities) in the alpha band. Physiological measures of lagged linear connectivity were applied to eliminate instantaneous, non-physiological signal contamination due to volume conduction. Heat maps were generated from the decontaminated EEG data using sLORETA and presented as three-dimensional parametric heat maps showing differences in current densities and intensities between cases and controls. The maps also lateralize the sources to the brain hemispheres, aiding in their localization to regions of interest, and corresponding Brodmann areas of the brain. The reference heat map for the study is reported by Pal and her colleagues in (Pal et al., 2021)

3.3 QUALITY CONTROL MEASURES

All collected data were appropriately identified with assigned numbers; the data set for each patient bore the same number. EEG recordings were done under the supervision of a technician; continuous monitoring of the patients was done by the principal investigator. Collected blood samples were thoroughly mixed in the EDTA tubes, and the samples were delivered to the laboratory within one hour after collection and stored at -20 degrees Celsius to ensure that there are no false measurements for CRP and IL-6.

3.4 DATA ANALYSIS

Data was tested for normality and transformed if it is skewed. Summary statistics of sociodemographic and medical variables, inflammatory parameters, and sleep questionnaire scores are presented as mean and standard deviation for continuous variables with normal distribution, median and interquartile ranges for non-normally distributed data and counts/percentages for categorical variables. Comparison between normal and preeclamptic pregnancy with regards to various parameters was done using paired t-test for normally distributed continuous variables, Brunner-Manzel's test was done for non-normally distributed variables and chi-square for proportions.

Association between parameters of sleep quality, chronotype, markers of inflammation, and functional connectivity patterns from rsEEG were assessed using the generalized linear model with adjustment of sociodemographic and medical variables. All analysis were performed using IBM SPSS software and a p-value <0.05 was considered statistically significant.

The analysis of venous blood samples for IL-6 and CRP is described in the appendix and the results section of this manuscript.

Decontaminated epochs of EEG data will be filtered into respective bands, and transformed by the sLoreta software into three-dimensional voxels to be overlaid on a standard magnetic resonance template; comparing cases with controls. Warmer and more intense heat maps will imply higher current densities in cases than in controls while milder colours indicate lesser current densities in cases as compared to controls (Asadzadeh et al., 2020; H. M. Nguyen et al., 2014). Using its brain source localization algorithms, sLoreta compares the activities of spatiotemporal neuronal networks of the brain of preeclamptic women versus controls in the resting-state (Sohrabpour et al.,

2020). The images generated by the sLoreta programme will be a representation of areas of significant differences in current densities in preeclamptic versus normotensive pregnancies. sLoreta localizes the source of underlying brain electrophysiological activity in real time (Michel & Brunet, 2019) by conducting a comparative analysis of current densities; a voxel-by-voxel comparison of the cases and controls (Moon et al., 2022). Differences in current densities are displayed as colour scales or heat maps.

3.5 ETHICAL CONSIDERATION

Ethical clearance was obtained from the Korle Bu Hospital Institutional Review Board (KBTH-IRB 000153/2023), the Korle Bu Hospital-Scientific and Technical Committee (STC/IRB/000153/2023) and the Ethical and Protocol Review Committee, College of Health Sciences, University of Ghana (IRB: 00006220). Written informed consent was obtained from the participants after a thorough discussion of the rationale, risks, and benefits of the study, as well as addressing all their concerns. The collected data was treated with confidentiality. Codes were used instead of names to de-identify participants, hard copies of data sheets were stored in a secured locker, and soft copies as password-protected files. Only the lead investigators could have access to participants' data. All the data collected from the study participants were used for this study only. Participants were not coerced or enticed by any means to consent to the study, and they were made to understand that they were at liberty to withdraw from the study at their own will without any repercussions.

3.6 QUESTIONNAIRE

The Epworth Sleep Scale (ESS) and the Pittsburg Sleep Quality Index (PSQI) questionnaire were administered. ESS assesses daytime sleepiness using 8 different scenarios of daily life. Using on a scale of 0-3 points, the chance of nodding off or dozing was scored. The PSQI is a tool made up of 19 questions for self-reported assessment of

sleep. Each tool was self-administered in under 5 minutes. Google Forms were also created to collect demographic data of patients as well as their medical and obstetric histories.

CHAPTER FOUR

4.0 RESULTS

Data was collected from 1st March to 30th May 2024. A total of 112 (59 cases and 53 controls) women consented to participate. Data was collected at the Korle Bu Teaching Hospital. Electroencephalography data and venous blood samples were collected from the participants who gave written informed consent. The Epworth Sleepiness scale and the Pittsburgh Sleep Quality Index were used to collect sleep data. Cases and controls are used interchangeably to refer to preeclamptic women and normotensive women, respectively.

4.1 DEMOGRAPHIC CHARACTERISTICS

Pregnant women with and without PE were similar in age, educational level, alcohol intake, smoking, gestational age, gravida, parity, abortion/miscarriages and prior hypertension. PE women were more likely to cohabit with their partners and had history of hypertension. When sleep indices were compared between women with and without PE, there were no difference in sleep duration, global PSQI domains, except habitual sleep efficiency, which was higher in non-PE women (Table 1).

Table 1. Demographic characteristics, parity, sleep scores of participants

	Preeclampsia (n=59)	Normal (n=53)	p
Age, years	29.8±6.1	31.7±6	0.107
Marital status, n (%)			0.026
Single	12 (20.3)	11 (20.8)	
Married	37 (62.7)	41 (77.4)	
Cohabitation	19 (16.9)	1 (1.9)	
Educational level, n (%)			0.328
Up to JHS/JSS	24 (40.7)	19 (35.8)	
SHS/vocational	16 (27.1)	10 (18.9)	
Tertiary	19 (32.2)	24 (45.3)	
Employment, n (%)			0.025
Formal	10 (16.7)	21 (39.6)	
Informal	36 (61)	25 (47.2)	
Unemployed	13 (22)	7 (13.2)	
Alcohol intake, n (%)	2 (3.4)	3 (5.7)	0.561
Smoking, n (%)	1 (1.7)	1 (1.9)	0.939
Gestational age, weeks	31.5±10.9	28.6±11.5	0.175
Gravida	2.8±1.5	3.2±1.7	0.185
Parity	1.4±1.4	1.4±1.3	0.87
Abortion/miscarriages	1.6±0.5	1.6±0.5	0.664
Previous preeclampsia	15 (25.4)	4 (7.5)	0.016
Prior hypertension	5 (8.5)	2 (3.8)	0.305
Sleep duration, hrs	6.2±2.4	6.2±2	0.491
Global PSQI	9.1±5.1	9.1±5.1	0.95
Subjective sleep quality	1.3±1.2	1.2±1.2	0.722
Sleep latency	1.7±1.2	1.5±1.2	0.359
Sleep duration	1.2±1.1	1.4±1.1	0.441
Habitual sleep efficiency	0.7±1.1	1.2±1.3	0.024
Sleep disturbances	1.9±0.7	1.8±0.5	0.626
Sleep medication	1.3±1.2	1.2±1.2	0.722
Daytime dysfunction	1.1±1	0.8±1	0.134

4.2 Sleep duration and prevalence of sleep disorders

When the pregnant women were compared based on the quality of sleep, there was no difference in the sleep quality between women with and without pre-eclampsia (Figure 3). Compared to non-PE women, PE women had a higher prevalence of short and long sleep durations (Figure 4).

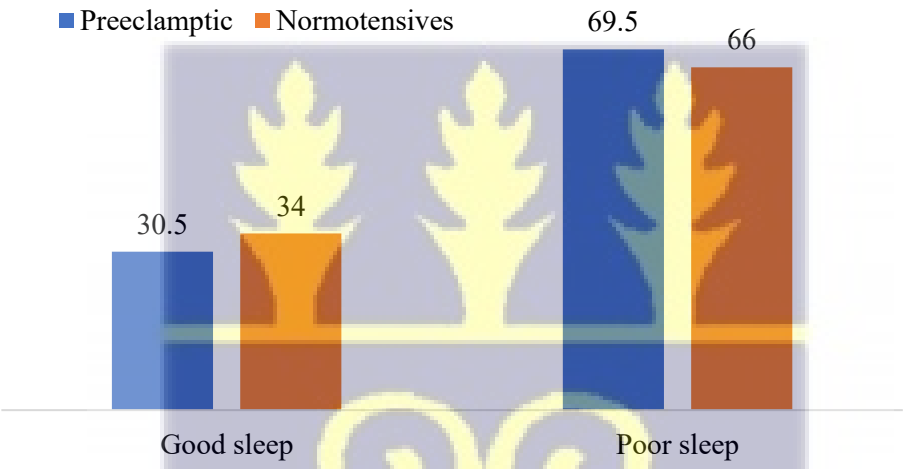

Figure 1 Prevalence of poor sleep quality in the study participants ($\chi^2 = 0.153$, $p = 0.696$)

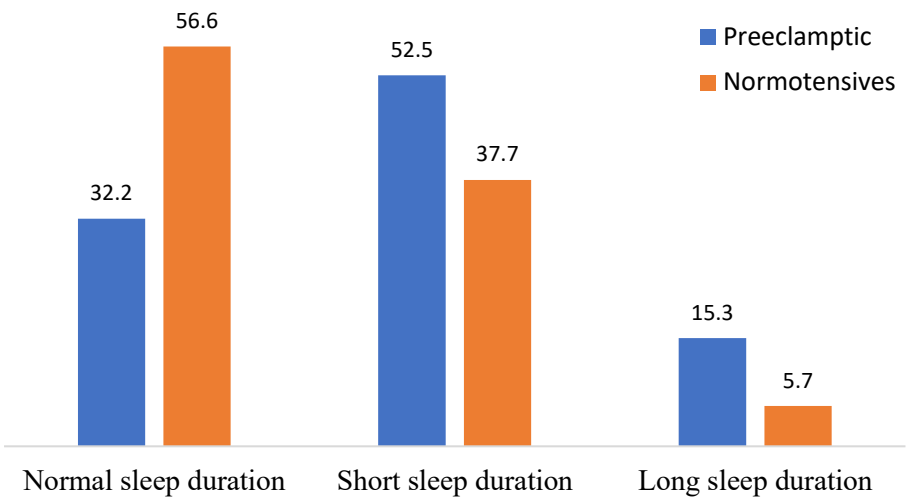

Figure 2 Sleep duration categorization of study participants ($\chi^2 = 7.54$, $p = 0.023$)

4.2 Levels of IL-6 and CRP in study participants by sleep quality status

As shown in Figure 5, women with good sleep quality had lower median IL-6 values [1.32 (1.16 – 1.37) vs 1.49 (1.39 – 1.6) µg/dl, p<0.001] compared to women with poor sleep (Figure 5). Similarly, women with good sleep quality had lower median CRP values [1.58 (1.27 – 1.67) vs 1.74 (1.64 – 1.91) mg/dl, p <0.001] compared to women with poor sleep (Figure 6).

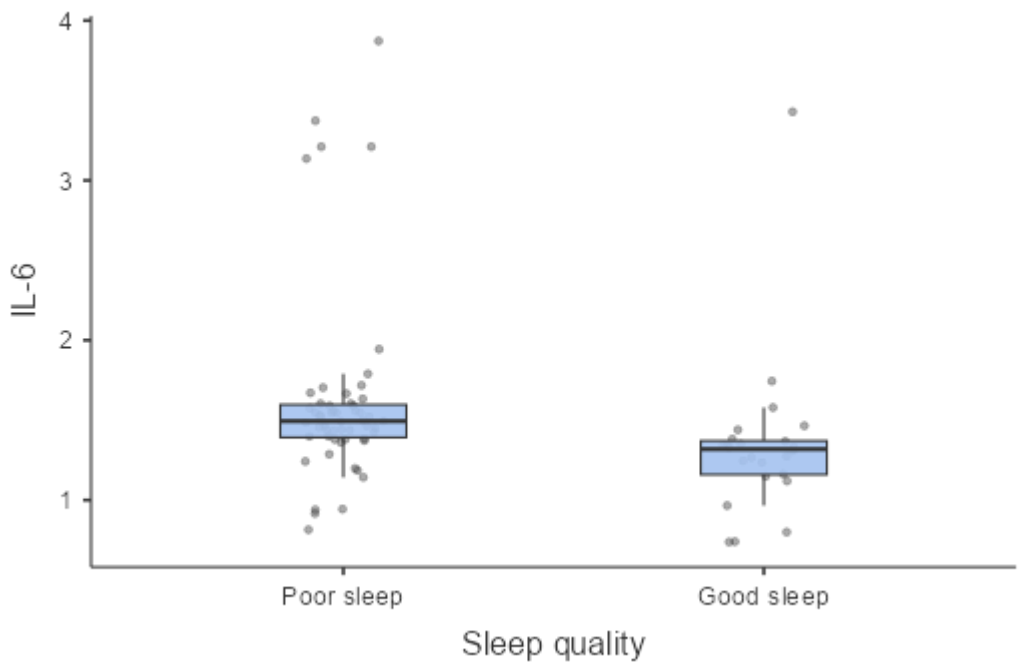

Figure 3 Distribution of IL-6 levels by their sleep quality status *[1.32 (1.16 – 1.37) vs 1.49 (1.39 – 1.6) µg/dl, p<0.001]*

Figure 4 Distribution of CRP levels by sleep quality status *[1.58 (1.27 – 1.67) vs 1.74 (1.64 – 1.91) mg/dl, p <0.001]*

4.3 Levels of IL-6 and CRP in study participants by sleep sufficiency status

Based on the responses from the Epworth Sleepiness Scale instrument, the participants were categorized as sleep sufficient and sleep insufficient groups. There were no association between sleep sufficiency and preeclampsia status ($\chi^2 = 0.036$, p = 0.85).

Women with normal sleep sufficiency had similar median IL-6 values [1.44 (1.34 – 1.59) vs 1.31 (1.12 – 1.53) µg/dl, p = 0.161] compared to women with insufficient sleep (Figure 7). Similarly, there was no difference in the levels of CRP between women with sufficient and insufficient sleep [1.7 (1.59 – 1.85) vs 1.61 (1.25 – 1.66) mg/dl, p = 0.194] (Figure 8).

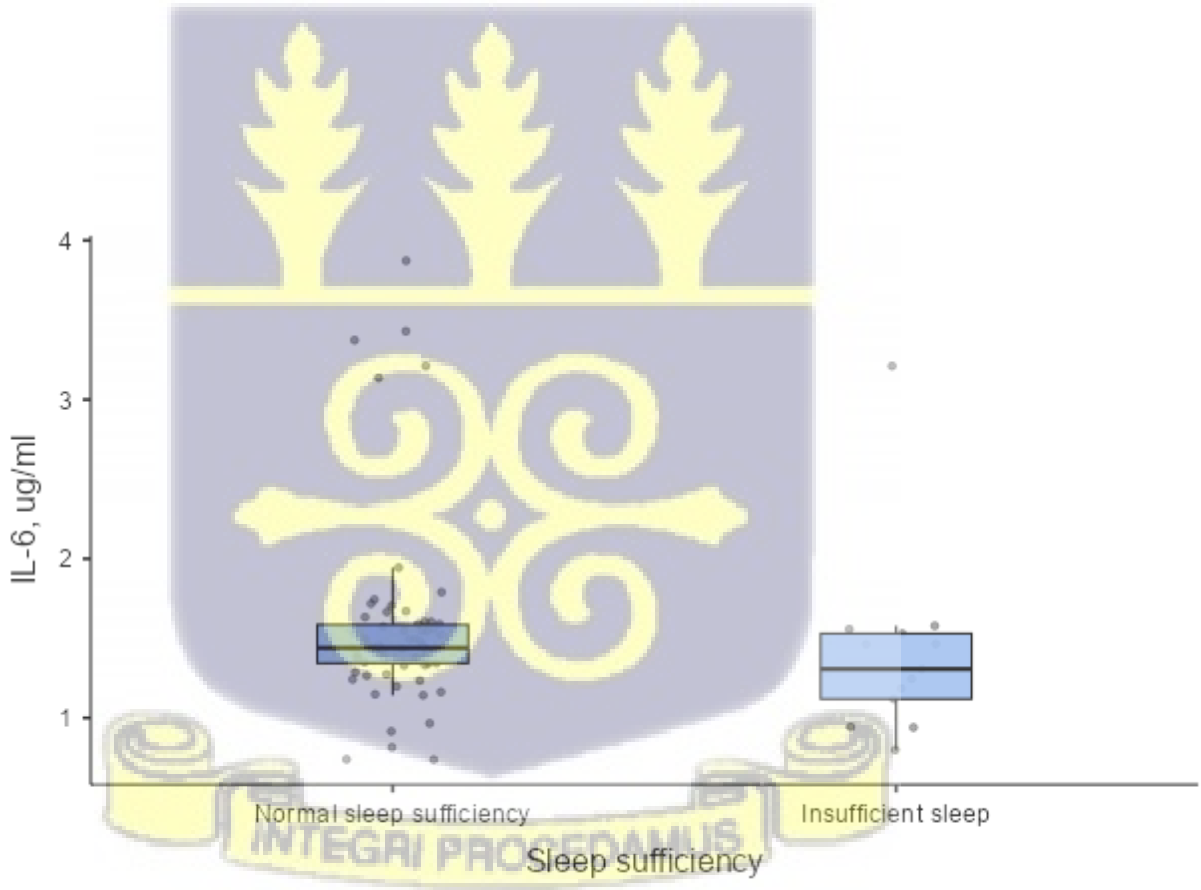

Figure 5 Distribution of IL-6 levels by sleep sufficiency status *values [1.44 (1.34 – 1.59) vs 1.31 (1.12 – 1.53) µg/dl, p = 0.161]*

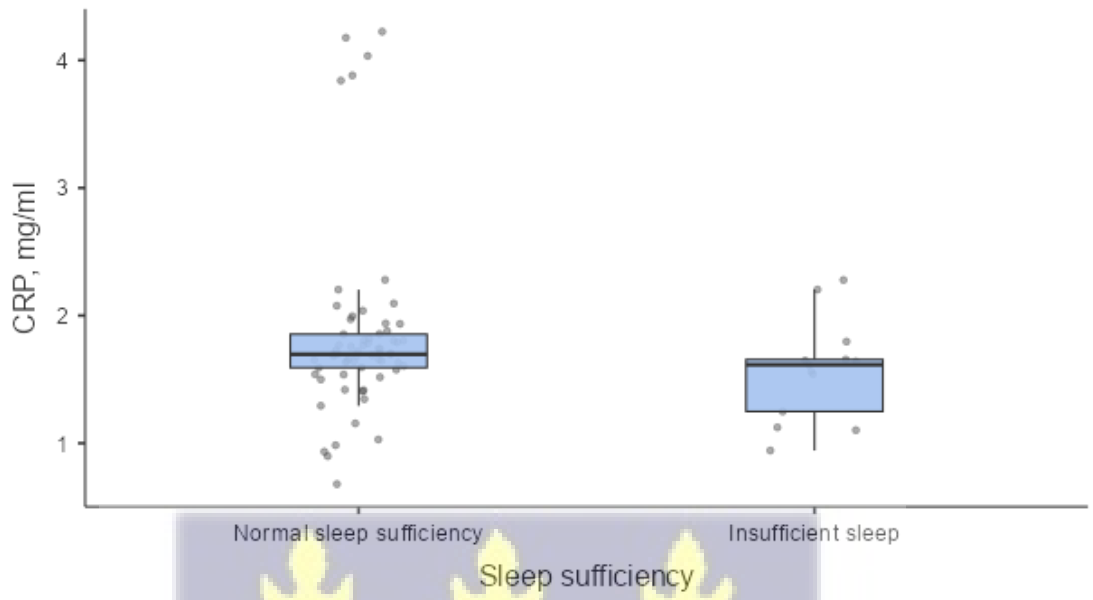

Figure 6 Distribution of CRP levels by sleep sufficiency status *[1.7 (1.59 – 1.85) vs 1.61 (1.25 – 1.66) mg/dl, p = 0.194]*

4.4 Independent factors associated with variations in IL-6 and CRP levels

The results of multiple linear regression analysis indicate that the quality of sleep was associated with a variation in IL-6 (Table 3) and CRP (Table 4) levels, accounting for 0.647 standard deviation in IL-6 variations.

Table 2. Multiple linear regression of the factors associated with variations in logarithm-transformed IL-6 levels

Predictor	Estimate	p	Stand. Estimate	Lower	Upper
Intercept	0.065	0.401			
Poor sleep quality	0.086	0.010	0.647	0.157	1.137
Insufficient Sleep	-0.05	0.278	-0.377	-1.064	0.311
Preeclampsia	-0.023	0.446	-0.174	-0.628	0.279
Age	0.001	0.586	0.074	-0.197	0.346
Gravidity	0.006	0.582	0.083	-0.216	0.381
Smoking	-0.074	0.537	-0.559	-2.358	1.240
Alcohol	-0.06	0.445	-0.446	-1.604	0.712

Table 3. Multiple linear regression of the factors associated with variations in logarithm-transformed CRP levels

Predictor	Estimate	p	Stand. Estimate	Lower	Upper
Intercept	0.082	0.315			
Poor sleep quality	0.078	0.028	0.572	0.065	1.081
Insufficient Sleep	-0.053	0.267	-0.392	-1.09	0.307
Preeclampsia	-0.013	0.673	-0.099	-0.564	0.366
Age	0.003	0.255	0.159	-0.118	0.436
Gravidity	0.003	0.760	0.047	-0.258	0.351
Smoking	-0.027	0.827	-0.201	-2.03	1.629
Alcohol	-0.029	0.723	-0.2100	-1.387	0.967

4.5 Origin of brain waves from EEG analysis

Electroencephalography data were bandpass filtered into 7 frequency bands; delta (δ):0.5-4 Hz, theta (θ): 4-8 Hz, alpha-1 (α1): 8-10 Hz, alpha-2 (α2): 10-13Hz, beta-1 (β1): 12-16.5Hz, beta-2 (β2): 12.5-20, and beta 3 (β3): 20.5-30Hz.

The current densities of various frequencies at different Brodmann areas of the brain were compared between women with and without pre-eclampsia, and the results are shown in Table 5. The overall current density distribution were different between women with and without pre-eclampsia. When the various frequency bands were compared, there was a significant difference in the current density of the frequency bands within the β2 and β3 domains originating from Brodmann areas 19 and 8, respectively (Table 5).

Table 4. Frequency Bands and Corresponding Brodmann Areas

Threshold Frequency (TF)	Frequency bands	Broadmann Area	p-value
1	δ	10	0.533
2	θ	27	0.402
3	α1	30	0.336
4	α2	23	0.239
5	β1	23	0.147
6	β2	19	0.041
7	β3	8	0.049
8	Ω	30	0.091
	overall		0.041

Heat mapping is a 3-D data visualization method of presenting data as 2-D models and colours (Freedman & Osicka, 2008). The use of heatmaps depicts the intensity of activity in brain regions. More intense colours (such as red) represent higher and positive connectivity, while milder colours, such as blue, represent reduced/negative activity (to no activity) and connectivity in neural cell populations (Lejap et al., 2024). The reference template heat map for the study is reported by Pal and her colleagues in (Pal et al., 2021)

Figure 9 depicts the heat map showing the origin of the difference in δ frequency between women with and without pre-eclampsia. The δ frequency band was different mostly in the Brodmann area 10 which corresponds to the superior frontal gyrus in the frontal lobe of the brain.

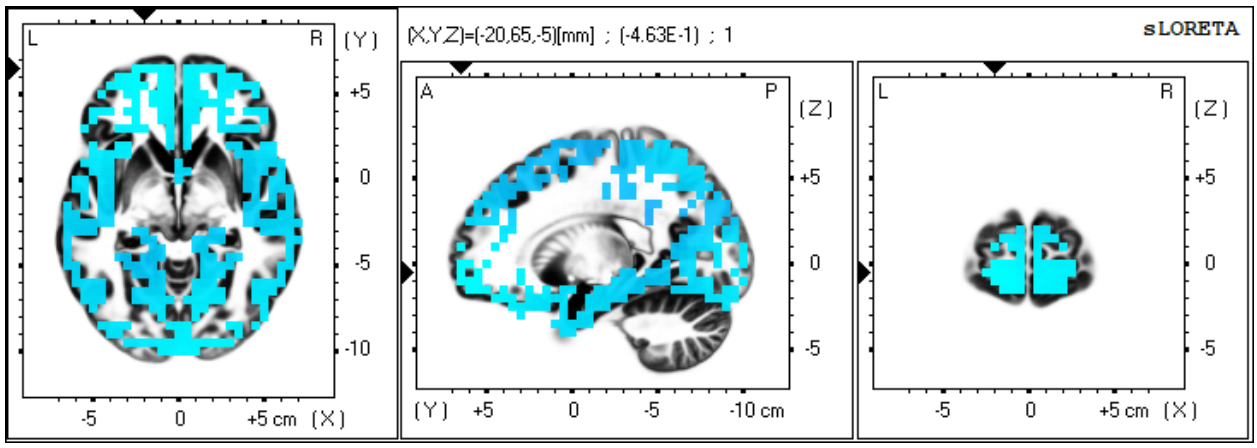

Figure 7 Heat map showing the origin of the difference in δ frequency between women with and without pre-eclampsia.

Figure 10 depicts the heat map showing the origin of the difference in θ frequency between women with and without pre-eclampsia. The θ frequency band was different mostly in the Brodmann area 27 which corresponds to the Parahippocampal gyrus in the limbic lobe of the brain.

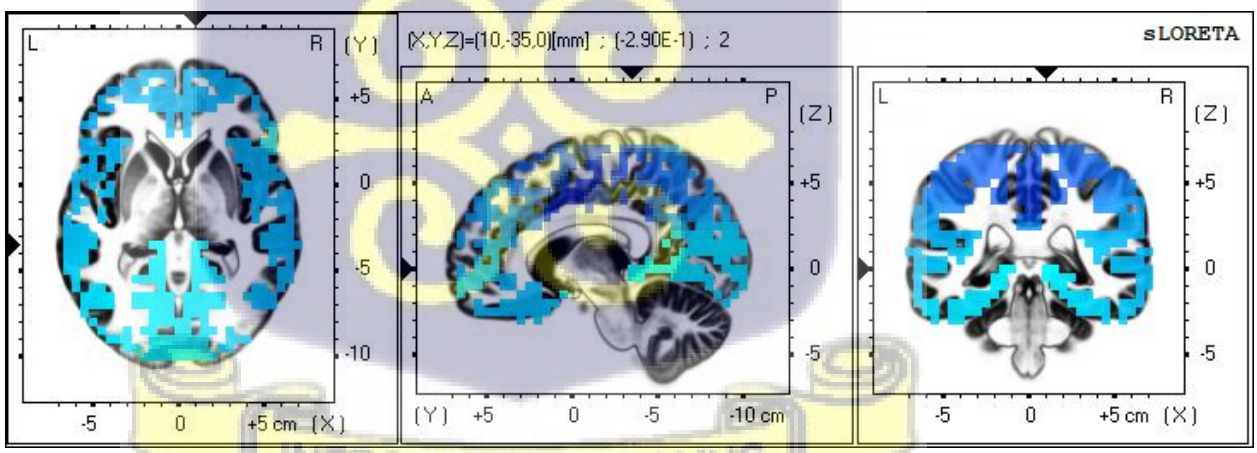

Figure 8 Heat map showing the origin of the difference in θ frequency between women with and without pre-eclampsia.

Figure 11 depicts the heat map showing the origin of the difference in α1 frequency between women with and without pre-eclampsia. The α1 frequency band was different mostly in the Brodmann area 30, which corresponds to the retrosplenial area of the posterior cingulate gyrus.

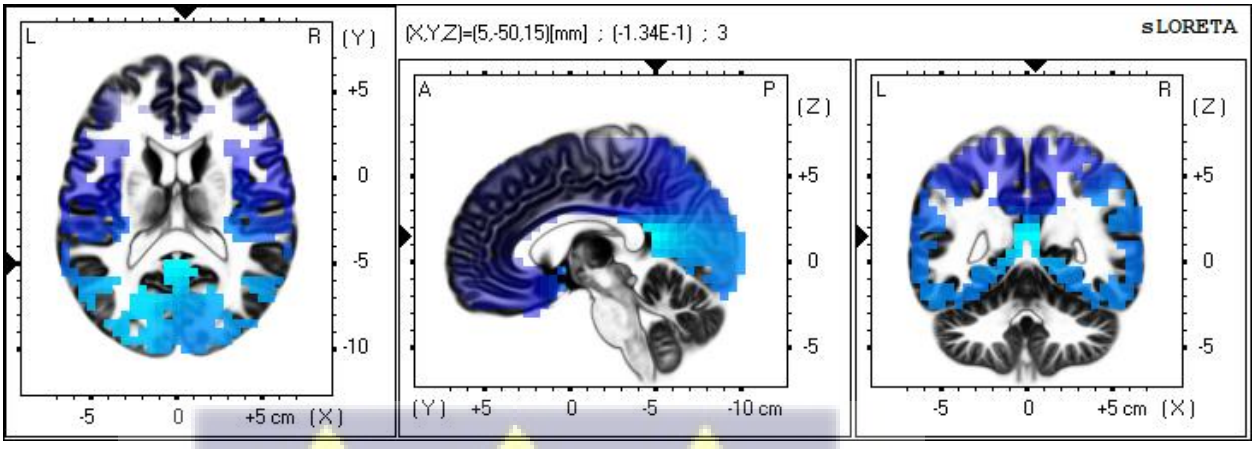

Figure 9 Heat map showing the origin of the difference in α_1 frequency between women with and without pre-eclampsia.

Figure 12 depicts the heat map showing the origin of the difference in α2 frequency between women with and without pre-eclampsia. The α2 frequency band was different mostly in the Brodmann area 23, which corresponds to the posterior cingulate gyrus in the limbic lobe of the brain.

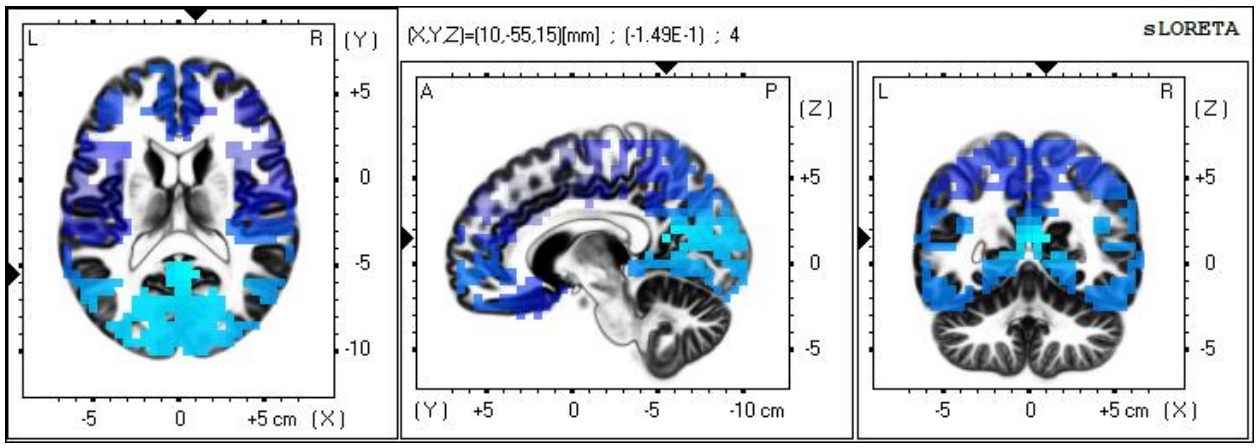

Figure 10 Heat map showing the origin of the difference in α2 frequency between women with and without pre-eclampsia.

Figure 13 depicts the heat map showing the origin of the difference in β1 frequency between women with and without pre-eclampsia. The β1 frequency band was different mostly in the Brodmann area 23 which corresponds to the posterior cingulate gyrus in the limbic lobe of the brain.

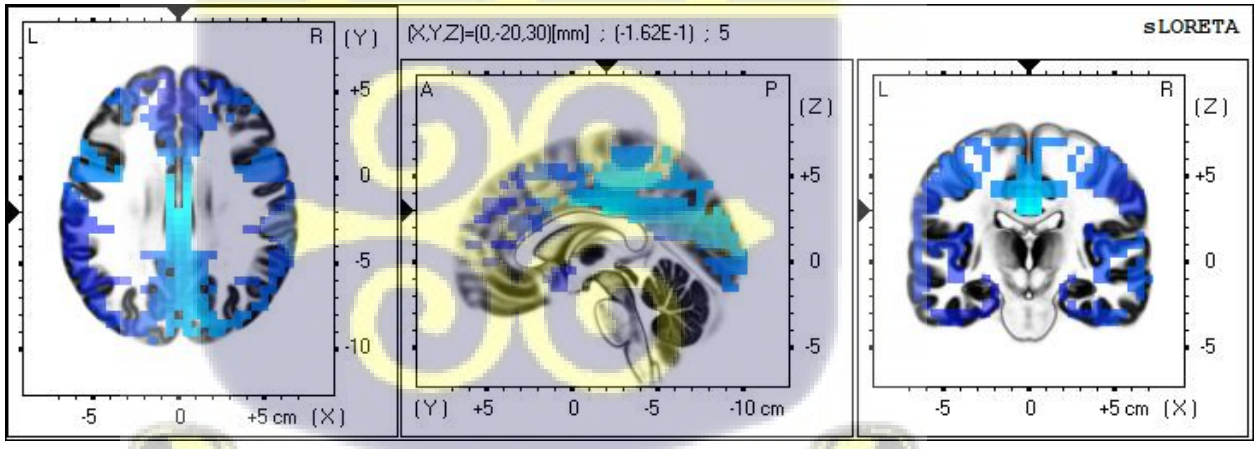

Figure 11 Heat map showing the origin of the difference in β1 frequency between women with and without pre-eclampsia.

Figure 14 depicts the heat map showing the origin of the difference in β2 frequency between women with and without pre-eclampsia. The β2 frequency band was different

mostly in the Brodmann area 19 which corresponds to the cuneus in the occipital lobe of the brain.

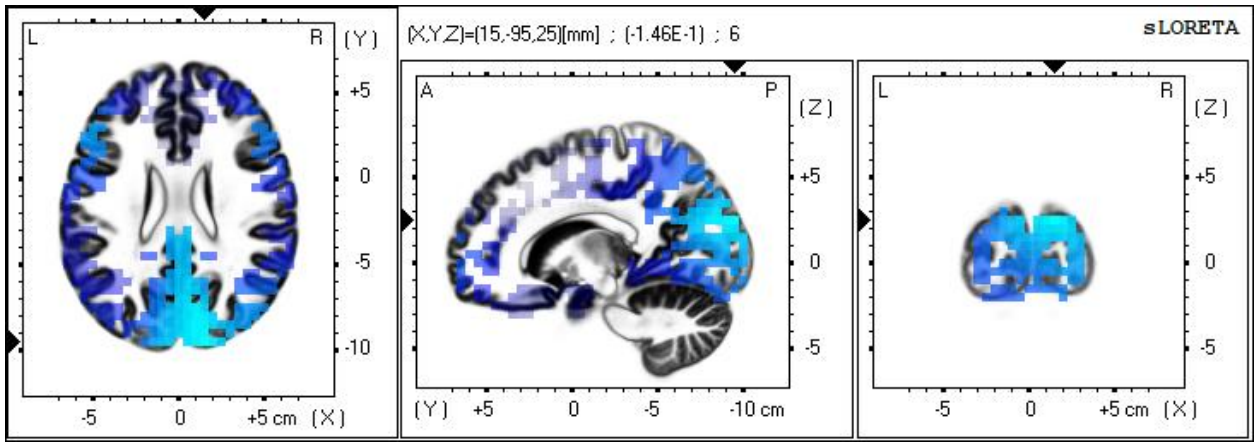

Figure 12 Heat map showing the origin of the difference in β2 frequency between women with and without pre-eclampsia.

Figure 15 depicts the heat map showing the origin of the difference in β3 frequency between women with and without pre-eclampsia. The β3 frequency band was different mostly in the Brodmann area 8 which corresponds to the superior frontal gyrus in the frontal lobe f the brain.

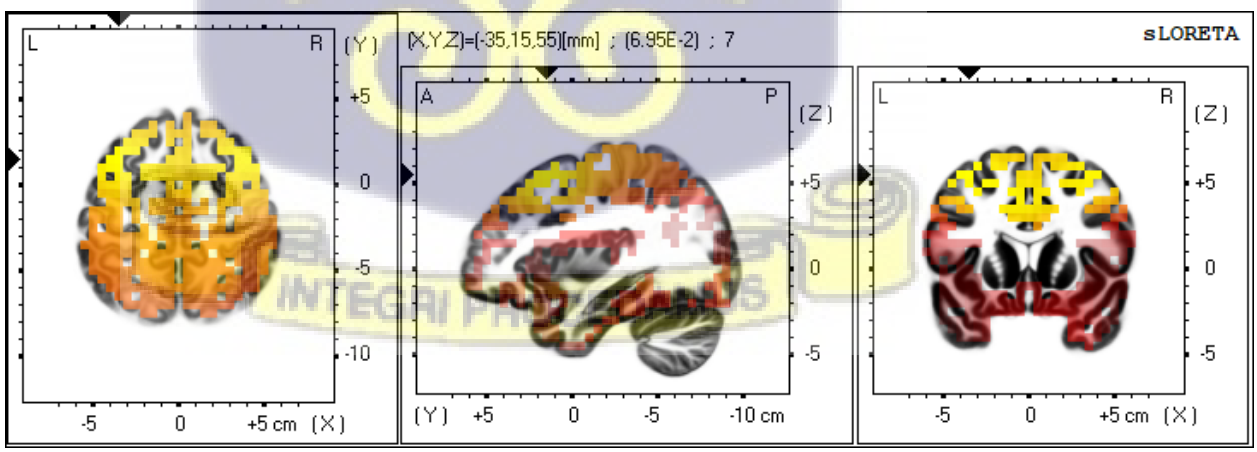

Figure 13 Heat map showing the origin of the difference in β3 frequency between women with and without pre-eclampsia.

Figure 16 depicts the heat map showing the origin of the difference in Ω frequency between women with and without pre-eclampsia. The Ω frequency band was different mostly in the Brodmann area 30, which corresponds to the posterior cingulate gyrus of the limbic lobe.

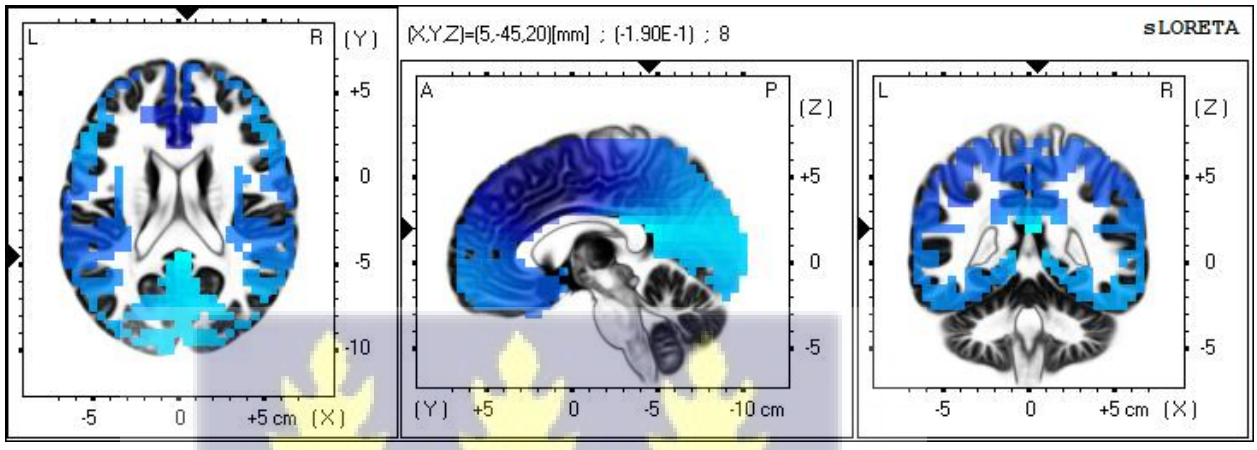

Figure 14 Heat map showing the origin of the difference in Ω frequency between women with and without pre-eclampsia.

CHAPTER FIVE

5.0 DISCUSSION, LIMITATIONS, RECOMMENDATION AND CONCLUSION

5.1 DISCUSSIONS

The study assessed sleep quality among pregnant women using sleep quality assessment tools, which, to the best of our knowledge, have not been used to assess sleep disorders among pregnant women in Ghana. The study compared the brain functional connections of 50 pregnant women with and without preeclampsia. The study identified significant differences in the functional connectivity in many cortical areas. The Pittsburgh Sleep Quality Index tool is recognized as a gold standard in the multi-dimensional assessment of sleep quality (Albqoor & Shaheen, 2021a; Manzar et al., 2018). Several sleep studies have been conducted in Ghana (Agyekum et al., 2023; Cole et al., 2017; Kundel et al., 2022; Owusu-Sarpong et al., 2024) with only a few focusing on pregnant Ghanaian women. These include the assessment of post-natal depression among adolescent pregnant women (Asante et al., 2024), sleep posture as a predictor of maternal and neonatal outcomes, (Coleman et al., 2019; O'Brien & Warland, 2014) and snoring during sleep as an independent risk for preeclampsia among pregnant women in Ghana (Owusu et al., 2013). Our study will therefore be adding on to the body of knowledge of sleep disorders among Ghanaian pregnant women.

There was no significant difference in the global PSQI scores for both controls and cases. Subjective sleep quality, sleep latency and sleep duration were similar in both groups. This is possibly attributable to the anatomical and physiological changes of pregnancy which were present in both are reported to change sleep quality. These include weight gain of pregnancy, frequent nocturnal awakenings to micturate, a higher incidence of gastroesophageal disease and uncomfortable bedtime sleep positioning due to the gravid

uterus (Kazma et al., 2020b; Sedov et al., 2018). These findings are consistent with other studies (Takmaz et al., 2022) which report a high prevalence of sleep disorders in both normal and preeclamptic gestations. Sleep duration and sleep sufficiency can be improved if sleep habits are altered to allow early bedtime while avoiding procrastinating bedtime (Magalhães et al., 2020). Our data also demonstrates that improving sleep efficiency could contribute to the prevention of preeclampsia. Sleep efficiency is the ratio of nocturnal sleep hours to the number of hours spent in bed (Y.-Q. Lin et al., 2021). From our study, women with preeclampsia spent more hours at night being unable to sleep compared to women without PE, which was statistically significant (p=0.024). Habitual sleep inefficiency has been associated with depression, neurocognitive decline and adverse cardiometabolic outcomes (Halson et al., 2022). Though both controls and cases had poor sleep quality, the higher prevalence of habitual sleep inefficiency among the cases could have contributed to the incidence of PE in this group. Sleep efficiency is associated with a controlled stress response and cytokine synthesis (Macdonald et al., 2025) and a lesser incidence of preeclampsia (Saraei et al., 2024).

Prolonged paternal sperm exposure has an inverse relationship with the incidence of PE (Di Mascio et al., 2020)(Zhu et al., 2021). This may account for the high incidence of PE among nulliparous women compared to multiparous women (Al-Rubaie et al., 2020; Bdolah et al., 2014; Chang et al., 2023). From our study, marital status was associated with a statistically significant risk of developing PE among women who were co-habiting. Though there was no significant difference in parity between cases and controls. The cases generally had lower gravidity than the controls. This may support the theory that prolonged paternal sperm exposure contributes to the immune tolerance of the growing foetus and confers protection against preeclampsia (Kenny & Kell, 2018; Lokki et al., 2018). However, we did not assess how long the participants had been with their partners,

the number of lifetime partners and whether or not their current partners were responsible for their previous pregnancies.

Statistically significant differences in the history of previous preeclampsia and marital and employment status between cases and controls were observed. The difference was in favour of women who had preeclampsia. Previous history of preeclampsia is associated with a 13.8% risk of recurrence according to a meta-analysis of 99,415 women with a history of hypertensive disorders of pregnancy (van Oostwaard et al., 2015). This is also confirmed by our results, which show high recurrence rates for women with a history of preeclampsia. The incidence of PE is known to increase in an ascending order when the number of previous preeclamptic pregnancies also increases (Hernandez-Diaz et al., 2009).

IL-6 is a robust marker of inflammation in pregnancy (Scholaske et al., 2018) while CRP is also a marker of systemic inflammation. IL-6 and CRP are assessed because the former induces the expression of the latter by the liver (Ngwa et al., 2022). This sequential biochemical relationship also underlies why both of them were assayed in this study. From our study, poor sleep quality was associated with a statistically significant variation in the serum levels of IL-6 and CRP. This demonstrates a strong positive relationship between poor sleep and the serum IL-6 and CRP levels. This relationship has been reported in other sleep studies, which have demonstrated a positive correlation between poor sleep and higher levels of IL-6 in body fluids (Alqaderi et al., 2023a; Koreki et al., 2024; Reinhardt et al., 2019) as well as CRP (Alqaderi et al., 2023b; Iyegha et al., 2019). This also further buttresses how sleep disorders dysregulate circadian rhythms and increase the expression of pro-inflammatory cytokines such as IL-6 and CRP. The role of IL-6 and CRP in preeclampsia is also widely reported. Our study will also add to the knowledge that underpins PE is an uncontrolled inflammatory state.

This study also demonstrates considerable differences in the brain functional connectivity between women with and without PE. Reduced functional connectivities were observed in δ frequency in Brodmann Area 10 (the superior frontal gyrus). The frontal lobe of the cerebral cortex is associated with executive functions such as memory, cognition, attention and problem-solving abilities (Jones & Graff-Radford, 2021). The superior frontal gyrus of the frontal lobe of the cerebral cortex processes sensory information from neuronal networks for working memory (Boisgueheneuc et al., 2006). Our study is therefore consistent with findings of impaired working memory and long-term cognitive impairment in women with a history of PE (Elharram et al., 2018). Cognitive dysfunction continues up to two decades after an episode of PE (Alers et al., 2023) and women with PE have premature atrophy of the brain (Raman et al., 2017). The frontal lobe is also the lobe that is most commonly affected (60-67%) cortical white matter lesions observed in PE (Soma-Pillay et al., 2017).

Differences in functional connectivity in θ frequency were also observed between cases and controls in Brodmann area 27, corresponding to the parahippocampal gyrus. The heat maps show reduced connectivity in the parahippocampal gyrus, which is known to process new memories (Webb, 2017). The parahippocampal gyrus is also a part of the limbic system and participates in other executive functions, such as learning, visuospatial information processing and memory (D. Gupta, 2017; Y.-H. Lin et al., 2021). Preeclampsia causes systemic vascular endothelial dysfunction, which affects the parahippocampal arteries, predisposing the hippocampus to hypoxic-ischaemic injury. The hippocampus is more susceptible to vascular dysfunction than other parts of the cerebral cortex (Johnson et al., 2022).

The bands for α1 frequencies differed between cases and controls in Brodmann area 30, corresponding to the retrosplenial area of the posterior cingulate gyrus. The retrosplenial

area and the posterior cingulate gyrus are involved in cue-based learning and the retrieval of autobiographical memory (Daviddi et al., 2023). These areas are also involved in imagination and planning (Vann et al., 2009). They also have functional connections with the parietal lobes and the hippocampus, and in the processing of emotions and memory by serving as an input system to the hippocampal memory system (Rolls, 2019).

The β2 frequency band was different between cases and controls in the Brodmann area 19, which corresponds to the cuneus or the lingual cortex of the occipital lobe. The lingual lobe is a part of the secondary visual cortex and participates in the processing of complex visual stimuli . It is particularly vulnerable to sleep disorders and atrophies with prolonged sleep deprivation (C. Wang et al., 2021). Our findings of decreased functional connectivity in this area are also similar to the reports of decreased cortical thickness, reduced neural activity, and impaired visual short-term memory in this area following sleep deprivation (Weng et al., 2025).

Increased activity was observed in Brodmann Area 8 and accounted for the differences in the β3 frequency between women with and without pre-eclampsia. Brodmann area 8 is a part of the prefrontal cortex that lies anterior to the premotor cortex (Dadario et al., 2023). Aside its involvement in motor, language and cognitive functions, Brodmann area 8 is activated during decision making driven by uncertainty, and the functional connectivity of the area increases with the increasing degree of uncertainty (Feng et al., 2022; Volz et al., 2004). A diagnosis of preeclampsia often leads to prolonged admission for feto-maternal monitoring, catastrophic medical expenses, disruption of family life and emergency caesarean deliveries, the outcomes of which may be unpredictable (Fox et al., 2017; Xing et al., 2021). The fear of ambiguity and unpredictable outcomes of a preeclamptic pregnancy may underlie the high prevalence of postpartum depression in preeclampsia (Caropreso et al., 2020; L. Roberts et al., 2022) and the increased activity

observed in Brodmann area 8. Vascular endothelial dysfunction and uncontrolled inflammation are common to both preeclampsia and depression and may be what associates both diseases (M. Yuan et al., 2022).

Between cases and controls, Ω frequency band was different mostly in the Brodmann area 30 which corresponds to the posterior cingulate, limbic lobe.

5.2 LIMITATION

Self-reported sleep data may be subjective as compared to other objective methods of assessing sleep quality, such as actigraphy and polysomnography. Polysomnography is able to detect the state of sleep, the different stages of sleep, other sleep disorders such as restless leg syndrome and sleep apnoea and changes in physiological parameters (Ibáñez et al., 2018).Constraints of time, logistics, and funding prevented the use of polysomnography or actigraphy to assess sleep quality. More so, the patients were not in their natural environment at the time of the study. Sleep studies assessing sleep quality by comparing PSQI and actigraphy, among 47 healthy volunteers, yielded similar, comparable results, indicating that are results are reliable (Forner-Cordero et al., 2018). Infections are common in pregnancy due to physiological adaptations which suppress the immune system in order not to reject the foetus as an allograft (Kumar et al., 2022). This results in asymptomatic bacterial and parasitic infections, especially of the urinary tract, whose causatives also elevate serum levels of inflammatory cytokines (Cotton et al., 2024; Robert-Gangneux & Dardé, 2012). Our research design did not include specific tests to rule out asymptomatic infections, which could have confounded our results for C-RP and IL-6.

Unlike resting-state encephalography, functional magnetic resonance imaging (fMRI) offers a better spatial resolution, although the latter has a better temporal resolution (Menon & Crottaz-Herbette, 2005). fMRI is also able to capture functional connectivity

in subcortical structures, unlike resting-state EEG (Deligianni et al., 2014). While resting-state encephalography may have limited our results, studies which concurrently assess functional connectivity using fMRI and resting-state EEG report that both modalities capture a unique connectome with an overlap/similarities in connectivity organization and are best used as complementary methods (Heugel et al., 2019; Menon & Crottaz-Herbette, 2005).

5.3 RECOMMENDATIONS

Survivors of pre-eclampsia have to recognize the increased risk of developing neurocognitive dysfunction and an increased risk of neurodegenerative diseases. These can be mitigated by engaging in activities that improve neuroplasticity to recover and preserve cognitive function. Dietary supplements like thiamine and omega-3 polyunsaturated fats (Listabarth et al., 2023; Sasaki et al., 2024), exercise and good sleep all contribute to restoring cognition. The guidelines of the International Group of Cognition Researchers and Clinicians, on the rehabilitation of attention and memory, recommend the retraining of affected persons using their daily tasks as well as pharmacological interventions (Ponsford et al., 2023). Lastly, healthcare workers and the relatives of patients with preeclampsia have to provide emotional support for patients.

5.4 CONCLUSION

In conclusion, sleep disorders are major contributors to an uncontrolled maternal immune response, evidenced by elevated serum IL-6 and C-RP levels, which, among others, mediate vascular endothelial and multi-organ dysfunction in preeclampsia.

The resting-state encephalogram showed differences in overall current density distribution between women with and without pre-eclampsia in the β2 and β3 frequency domains originating from Brodmann areas 19 and 8.

Optimizing sleep in pregnancy not only translates into the prevention of preeclampsia but also into improved functional connectivity of the brain and the preservation of its function. Pregnant women need to be educated on the role of sleep quality in good maternal and neonatal outcomes. Clinicians will need to emphasize emotional and psychological support aside from the medical and surgical management of preeclampsia.

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APPENDIX: 1. LAB PROTOCOLS FOR C-RP AND IL-6

INTERLEUKIN 6 (IL-6)

1. Dilute Standard following the table below:

40 pg/ml	Standard 5	150 ul of original density + 150 µl standard diluent
20 pg/ml	Standard 4	150 ul of standard 5 + 150 µl standard diluent
10 pg/ml	Standard 3	150 ul of standard 4 + 150 µl standard diluent
5 pg/ml	Standard 2	150 ul of standard 3 + 150 µl standard diluent
2.5 pg/ml	Standard 3	150 ul of standard 2 + 150 µl standard diluent

2. Set blank wells separately (for blank well do not add sample and HRP conjugate; each other step operation is same).
3. Add 50 µl of each of standard 1 to 5 to standard wells
4. For sample testing wells, add 40 µl of sample diluent to each well and 10 µl of sample to each well in the micro-ELISA stripplate and mix gently.
5. Close plate with plate-closure membrane and incubate for 30 minutes at 37°C.
6. Dilute was buffer with distilled water between 20 to 30 folds.
7. Uncover closure-membrane, discard liquid and swing to dry. Add wash buffer to each well still for 30 seconds and drain. Repeat the washing procedure 5 times and dry.
8. Add 50 µl HRP-conjugate reagent to each well in the exception of the blank well.
9. Incubate following step 5
10. Wash after incubation following step 7
11. Add 50 µl of chromogen A and 50 µl of chromogen to each well and evade the light preservation for 10 minutes at 37°C.
12. Stop the reaction by adding 50 µl of 'stop solution' (blue colour will change to yellow)
13. Read absorbance at 450 nm after adding Stop Solution within 15 minutes (Take absorbance of blank well as zero).

C-REACTIVE PROTEIN

1. Dilute Standard following the table below:

40 pg/ml	Standard 5	150 ul of original density + 150 µl standard diluent
20 pg/ml	Standard 4	150 ul of standard 5 + 150 µl standard diluent
10 pg/ml	Standard 3	150 ul of standard 4 + 150 µl standard diluent
5 pg/ml	Standard 2	150 ul of standard 3 + 150 µl standard diluent
2.5 pg/ml	Standard 3	150 ul of standard 2 + 150 µl standard diluent

2. Set blank wells separately (for blank well do not add sample and HRP conjugate; each other step operation is same).
3. Add 50 µl of each of standard 1 to 5 to standard wells
4. For sample testing wells, add 40 µl of sample diluent to each well and 10 µl of sample to each well in the micro-ELISA stripplate and mix gently.
5. Close plate with plate-closure membrane and incubate for 30 minutes at 37°C.
6. Dilute was buffer with distilled water between 20 to 30 folds.
7. Uncover closure-membrane, discard liquid and swing to dry. Add wash buffer to each well still for 30 seconds and drain. Repeat the washing procedure 5 times and dry.
8. Add 50 µl HRP-conjugate reagent to each well in the exception of the blank well.
9. Incubate following step 5
10. Wash after incubation following step 7
11. Add 50 µl of chromogen A and 50 µl of chromogen to each well and evade the light preservation for 10 minutes at 37°C.
12. Stop the reaction by adding 50 µl of 'stop solution' (blue colour will change to yellow)
13. Read absorbance at 450 nm after adding Stop Solution within 15 minutes (Take absorbance of blank well as zero).

APPENDIX 2: PSQI TOOL

APPENDIX 3: EPWORTH DAYTIME SLEEPINESS SCALE

APPENDIX 4: DEMOGRAPHIC DATA SHEET

SOCIO-DEMOGRAPHIC DATA SHEET

PART A: DEMOGRAPHY

1. Age: .....yrs Weight:…… kg Height:……..cm
2. Marital status: [ ] Married [ ] Single [ ] Separated/Divorced
[ ] Cohabiting [ ] Other (Specify)……
3. Educational level completed:
[ ] No education [ ] Primary/Elementary [ ] Junior High School
[ ] Senior High School/O-A Level [ ] Tertiary and above
4. Occupation: (Specify)……
5. Place of residence: …….
6. Religion: [ ] Christianity [ ] Islam [ ] Traditional
[ ] Other (Specify)……

PART B : PAST OBSTETRIC HISTORY

7. Gravidity: …… Parity: .....
8. History of previous abortion/miscarriage: [ ] Yes [ ] No [ ] If Yes, how many?: ……

PART C: MOTHER'S MEDICAL HISTORY

9. When were you diagnosed or informed of your pre-eclampsia status?
If yes to above: a) --Patient can provide date of diagnosis (provide date below).
b) --Participant cannot provide date of diagnosis.

PART D: MEDICAL HISTORY

10. Do you smoke cigarette(s)? [ ] Yes [ ] No
If YES, how many packs per day do you smoke?_____
12. Do you consume alcohol? [ ] Yes [ ] No
If YES, specify the amount taken per day:
13. Have you been told by your healthcare provider that you had hypertension BEFORE you become pregnant? [ ] Yes [ ] No
14. Have you been told you had pre-eclampsia or high blood pressure during your PREVIOUS pregnancy? [ ] Yes [ ] No

15. Do you have diabetes? [ ] Yes [ ] No

APPENDIX 5: PARTICIPANT INFORMATION SHEET AND CONSENT FORM

Title: "ASSOCIATION BETWEEN SLEEP QUALITY AND COGNITIVE FUNCTION BY RESTING STATE ELECTROENCEPHALOGRAM IN PREECLAMPSIA"

Investigator: Dr. Ebenezer Amofa, Department of Physiology, University of Ghana Medical School, College of Health Science, University of Ghana.

Dear volunteer,

This consent form contains information about the research titled: "Association between sleep quality and cognitive function by resting state electroencephalogram in preeclampsia." To be sure that you are duly informed about your participation in this research, we are asking you to read (or have read to you) this consent form. You will also be asked to indicate Yes: I agree to participate No: I don't agree t participate and submit before you participate.

Objective: We wish to ask you to take part in this study to investigate associations between sleep problems and brain activity amongst pregnant women with high blood pressure and some problems with organs such as the kidney and liver (preeclampsia). We are interested in your opinion because you are receiving care at the Korle-Bu Teaching Hospital and we wish to find ways to help improve early detection and management of preeclampsia.

Possible benefits: There are no direct benefits to you from this study. However, your participation will add more knowledge on sleep and brain function which may, in the long run, contribute to new and more effective preventive measures as well as a better management system to help women deliver healthy babies as well as stay healthy after delivery. You will not be paid for participation in this study and you are also not expected to pay anything. However, if during the study we detect any condition that needs prompt attention, you will be referred for investigation and management.

Possible Risks: This research presents minimal risk to you or your baby. The main risks include psychological distress from discussing potentially upsetting issues and loss of confidentiality, though none of the data to be collected are highly sensitive. Confidentiality will be protected as described in the following section.

Confidentiality: All information gathered would be treated in strict confidentiality. We will protect information about you taking part in this research to the best of our ability. You will not be named in any reports. If you have any questions, please feel free to ask.

Withdrawal from the study: We would like to stress that this study is strictly voluntary. Should you decide not to participate in the study it will have no consequences for you. Should you at any point during the study decide that you do not wish to participate any further; you are free to terminate your participation, effective immediately. Any such decision will be respected without any further discussion. Your decision will not affect the health care you would normally receive.

Contacts: If you have any questions about the research study or study-related problems, you may contact the principal investigator or the Ethics Board:

Dr. Ebenezer Amofa, Department of Physiology, University of Ghana Medical School, College of Health Science, University of Ghana

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Ethical and Protocol Review Committee
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PARTICIPANT AGREEMENT

The above document describing the benefits, risks, and procedures for the research, titled: "Association between sleep quality and cognitive function by resting state electroencephalogram in preeclampsia" has been read and explained to me. I have been allowed to have any questions about the research answered to my satisfaction. I agree to participate as a volunteer.

---------- ----------

Date Signature or Thumbprint
(of the volunteer)

If a volunteer cannot read the form themselves, a witness must sign here:
I was present while the benefits, risks, and procedures were read to the volunteer.
All questions were answered and the volunteer has agreed to take part in the research.

---------- ----------

Date Signature or Thumbprint
(of the witness)

I certify that the nature and purpose, the potential benefits, and possible risks associated with participating in this research have been explained to the above individual.

---------- ----------

Date Signature
(of the person who obtained the Consent)

APPENDIX 7: ETHICAL APPROVAL DOCUMENTS