EFFECT OF MATERNAL BLOOD HEAVY METAL LEVEL ON BRAIN-DERIVED NEUROTROPHIC FACTOR AND PREGNANCY OUTCOMES AMONG MYANMAR MIGRANTS IN SAMUT SAKHON PROVINCE, THAILAND

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ผลกระทบของระดับโลหะหนักในเลือดของมารดาต่อระดับโปรตีนเบรน-ดีไรฟ นิวโรโทรฟิค แฟคเตอร์ และผลกระทบของการตั้งครรภ์ในผู้อพยพชาวเมียนมา จังหวัดสมุทรสาคร ประเทศไทย

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เย เต็ด ซอว์ : ผลกระทบของระดับโลหะหนักในเลือดของมารดาต่อระดับโปรตีนเบรน-ดีไรฟ นิวโรโทรฟิค แฟคเตอร์และผลกระทบของการตั้งครรภ์ในผู้อพยพชาวเมียนมาจังหวัดสมุทรสาคร ประเทศไทย. (EFFECT OF MATERNAL BLOOD HEAVY METAL LEVEL ON BRAIN-DERIVED NEUROTROPHIC FACTOR AND PREGNANCY OUTCOMES AMONG MYANMAR MIGRANTS IN SAMUT SAKHON PROVINCE, THAILAND) อ.ที่ปรึกษาหลัก : ณัฏฐา ฐานีพานิชสกุล

ความเป็นมา: ตะกั่ว, ปรอท, แคดเมียมและสารหนูเป็นโลหะหนักที่มีความสำคัญด้านสาธารณสุขในประเทศกำลังพัฒนาการสัมผัสกับโลหะเหล่านี้อาจทำให้เกิดความบกพร่องทางสติปัญญาและความผิดปกติของการซึมเศร้าผ่านผลต่อ ระดับโปรตีนเบรน-ดีไรฟ นิวโรโทรฟิค แฟคเตอร์ (BDNF) ซึ่งเป็นดัชนีชี้วัดทางชีวภาพสำคัญในหญิงมีครรภ์ ผลกระทบของการตั้งครรภ์เช่น ภาวะครรภ์เป็นพิษ การคลอดก่อนกำหนดและน้ำหนักแรกเกิดต่ำ เป็นปัญหาด้านสาธารณสุขที่สำคัญสำหรับสุขภาพของมารดาและเด็ก แม้ว่าการศึกษาก่อนหน้านี้จำนวนหนึ่งได้ตรวจสอบผลกระทบของโลหะหนักต่อการตั้งครรภ์ แต่มีงานวิจัยเพียงเล็กน้อยที่มุ่งเน้นไปที่ประชากรผู้อพยพ การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อศึกษาความสัมพันธ์ระหว่างความเข้มข้นของโลหะหนักในเลือดของมารดาและโปรตีนเบรน-ดีไรฟ นิวโรโทรฟิค แฟคเตอร์ (BDNF) กับผลลัพธ์การตั้งครรภ์ของผู้อพยพชาวเมียนมาในประเทศไทย

วิธีการ: การศึกษาครั้งนี้เป็นการศึกษาแบบ COHORT ที่ดำเนินการที่คลินิกฝากครรภ์ของโรงพยาบาลตั้งแต่เดือนกรกฎาคม 2561 ถึงเมษายน 2562 จำนวนแรงงานผู้อพยพชาวเมียนมาที่ตั้งครรภ์ทั้งหมด 119 คน ทารกในครรภ์มีอายุครรภ์น้อยกว่า 14 สัปดาห์ เข้าร่วมการศึกษา ประเมินลักษณะทางสังคม - ประชากรและพฤติกรรมสุขภาพของผู้ป่วยโดยใช้แบบสอบถามด้วยตนเอง เก็บตัวอย่างเลือดในไตรมาสแรกและไตรมาสที่สาม ความเข้มข้นของโลหะหนักในเลือดของมารดา สารตะกั่ว (Pb) สารปรอท (Hg) สารแคดเมียม (Cd) และ สารหนู (As) ถูกวัดโดยใช้เครื่องสเปกโตรมิเตอร์มวลพลาสมาแบบเหนี่ยวนำคู่และการวัดระดับโปรตีนเบรน-ดีไรฟ นิวโรโทรฟิค แฟคเตอร์ (BDNF) ในพลาสมา โดยใช้เทคนิคเอนไซม์ลิงค์อิมมูโนซอร์เบนต์แอสเสย์ (ELISA) วิเคราะห์ผลด้วยการวิเคราะห์ถดถอยโลจิสติกไบนารีหลายตัวแปร และการถดถอยเชิงเส้นหลายค่าถูกสร้างแบบจำลอง

ผลการศึกษา: หญิงตั้งครรภ์ทั้งหมด 72 คน อยู่ในการศึกษาจนแล้วเสร็จ พบค่ามัธยฐานความเข้มข้นของโลหะหนักในเลือด (IQR) ดังนี้: BDNF: (64.60 [15.60] /18.27 [23.40]) μg / L , Pb: (27.40 [13.80] /19.90 [11.40]) μg / L , Hg: (6.20 [5.60], 2.60 [2.00]) μg / L , Cd: (0.91 [0.85] /1.06 [0.46]) μg / L และ As: (4.00 [1.10] /3.40 [1.40]) μg / L โดยสามารถแบ่งประเภทความเข้มข้นของโลหะหนักในเลือด เป็น 2 ระดับ คือระดับสูง (> มัธยฐาน) และระดับต่ำ (≤ มัธยฐาน) จากการวิเคราะห์การถดถอยโลจิสติกแบบไบนารีหลังปรับค่าตัวแปรกวนแล้ว พบว่าหญิงตั้งครรภ์ที่มีความเข้มข้นของสารหนู (As) ในเลือดสูงในไตรมาสแรกมีความเสี่ยงต่อการมีระดับ โปรตีนเบรน-ดีไรฟ นิวโรโทรฟิค แฟคเตอร์ (BDNF) ในพลาสม่าต่ำ เพิ่มขึ้น 2.6 เท่า (aOR = 2.603, 95% CI : 1.178, 5.751) นอกจากนี้ยังพบว่าความดันโลหิตไดแอสโทลิก ในไตรมาสที่สามสูงขึ้นในทุกหน่วยของความเข้มข้นของสารตะกั่ว (Pb) ในเลือดไตรมาสที่สามที่เพิ่มขึ้น (β = 2.766, 95% CI: 0.026, 5.506) อย่างไรก็ตามไม่พบความสัมพันธ์ระหว่างโลหะหนักกับ ภาวะครรภ์เป็นพิษ การคลอดก่อนกำหนด และน้ำหนักแรกเกิดต่ำ

สรุป: ผลการวิจัยแสดงให้เห็นว่าหญิงตั้งครรภ์ที่มีเข้มข้นของสารหนู (As) ในเลือดสูงมีแนวโน้มที่จะพบระดับ โปรตีนเบรน-ดีไรฟ นิวโรโทรฟิค แฟคเตอร์ (BDNF) ในพลาสมาลดลงในการตั้งครรภ์ระยะแรก และหญิงตั้งครรภ์ที่มีสารตะกั่ว (Pb) ในเลือดสูงมีความเสี่ยงต่อการเกิดความดันโลหิตสูงในการตั้งครรภ์ตอนปลาย ดังนั้นควรมีการจัดกิจกรรมให้ความรู้ด้านสาธารณสุขเรื่องอันตรายจากสารตะกั่ว (Pb) และ สารหนู (As) เพื่อส่งเสริมสุขภาพของแรงงานชาวเมียนมา

สาขาวิชา	สาธารณสุขศาสตร์	ลายมือชื่อนิสิต .....
ปีการศึกษา	2561	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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KEYWORD: Blood heavy metal level, Brain-derived neurotrophic factor, Pregnancy outcomes, Myanmar migrants

Ye Htet Zaw : EFFECT OF MATERNAL BLOOD HEAVY METAL LEVEL ON BRAIN-DERIVED NEUROTROPHIC FACTOR AND PREGNANCY OUTCOMES AMONG MYANMAR MIGRANTS IN SAMUT SAKHON PROVINCE, THAILAND. Advisor: Asst. Prof. NUTTA TANEEPANICHSKUL, Ph.D.

BACKGROUND: Lead, mercury, cadmium, and arsenic are the priority heavy metals of major public health concern in developing countries. Thailand is a newly industrialized country raising high human workloads of migrant workers form neighbored countries, mostly Myanmar. Exposure to these metals can cause cognitive impairment and depressive disorders through an effect on brain-derived neurotrophic factor (BDNF), which is an important biomarker of pregnancy. Pregnancy outcomes including preeclampsia, preterm birth and low birth weight are major burdens for maternal and child health. Although a number of prior studies have examined the effects of heavy metals on pregnancy, there are few studies focused on migrant population. The aim of this study was to examine the association between maternal blood heavy metals concentrations and BDNF levels and pregnancy outcomes among Myanmar migrants in Thailand.

METHODOLOGY: This study was a birth cohort study conducted at the antenatal care clinic of the hospital from July 2018 to April 2019. A total of 119 pregnant Myanmar migrants carrying a single viable fetus of less than 14 weeks of gestation who had stayed within the industrial plant at least 3 months before were recruited in first trimester. The socio-demographic characteristics and health behaviors of the patients were assessed using a self-report questionnaire. Blood samples were collected in first trimester and third trimester. Maternal blood heavy metal (Pb, Hg, Cd, As) concentrations were measured using an inductively coupled plasma mass spectrometer, and plasma BDNF levels were measured using an enzyme-linked immunosorbent assay. Multivariate binary logistic regressions and multiple linear regressions were modeled to evaluate the associations between these factors.

RESULTS: A total of 72 pregnant women were completed the study. Median (interquartile rank: IQR) concentrations were as follows: BDNF: (64.60 [15.60]/18.27 [23.40]) μg/L, Pb: (27.40 [13.80]/19.90 [11.40]) μg/L, Hg: (6.20 [5.60], 2.60 [2.00]) μg/L, Cd: (0.91 [0.85]/1.06 [0.46]) μg/L, and As: (4.00 [1.10]/3.40 [1.40]) μg/L. We categorized the concentrations into high (≥ median) and low (<median) groups for binary logistic regressions. After adjusting for potential confounders, patients with a high blood As in first trimester had a 2.6-fold increased risk (aOR = 2.603, 95% CI: 1.178, 5.751) of low plasma BDNF in early pregnancy. Diastolic BP in third trimester was higher in every unit of increased third trimester blood Pb concentrations (β = 2.766, 95% CI: 0.026, 5.506). However, there were no significant associations between heavy metals and preeclampsia, preterm birth or low birth weight.

Field of Study: Public Health Student's Signature .....

Academic Year: 2018 Advisor's Signature .....

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LIST OF ABBREVIATIONS

AchE	Acetyl cholinesterase
ANC	Antenatal care
As	Total arsenic
BBB	Blood brain barrier
BD	Bipolar disorder
BDNF	Brain-derived neurotrophic factor
BLL	Blood lead level
BMI	Body mass index
BP	Blood pressure
CBP	CREB-binding protein
Cd	Cadmium
CNS	Central nervous system
CP	Choroid plexus
CPE	Carboxypeptidase E
CREB	cAMP-response-element-binding protein
DAG	Diacylglycerol
DBP	Diastolic blood pressure
DIC	Disseminated intravascular coagulation
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
ER	Endoplasmic reticulum
ERK	Extracellular signal regulated kinase
GSH	Glutathione
Hg	Total mercury
IARC	International Agency for Research on Cancer
ICP-MS	Inductively coupled plasma mass spectrometer
IOC	Item-Objective Congruence Index
IPC	Inhibitory postsynaptic current
IQR	Interquartile range

IRS	Insulin receptor substrate
LBW	Low birth weight
LMP	Last menstrual period
MDD	Major depressive disorder
MEK	Mitogen-activated extracellular protein kinase
NMDA	N-Methyl-D-aspartic acid
OBGYN	Obstetrics and Gynecology
OR	Odd ratio
Pb	Lead
PE	Preeclampsia
PI3K	Phosphatidylinositol-3-kinase
PKC	Protein kinase C
PLC	Phospholipase C
PPD	Post-partum depression
SBP	Systolic blood pressure
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
TGN	Trans-golgi network
THB	Thai baht
TrB	Tyrosin kinase B
US EPA	United States Environmental Protection Agency
UTR	Untranslated region
WHO	World health organization

CHAPTER I

INTRODUCTION

1.1 Background information

Heavy metals are well-known environmental hazards and their toxicity is a major health threat. Since many decades, they had been utilized in agricultures, industries, domestic works, pharmaceutical products and other technological settings. Such an extensive use had induced the wide distribution of heavy metals in the environment (Tchounwou, Yedjou, Patlolla, & Sutton, 2012). Human can exposure to them through the environment in different routes including inhalation, ingestion of contaminated food or water and dermal contact (Rehman, Fatima, Waheed, & Akash, 2017). Their toxicological effects such as neurotoxicity, nephrotoxicity, fetotoxicity, genotoxicity and carcinogenicity had been identified (Tchounwou et al., 2012). Their toxicities depend on a variety of factors (e.g., dose, route of exposure, chemical species, age, gender, genetic, nutrition of the individuals). According to The World Health Organization (WHO), more than 25% of global burden of diseases is related with the environmental exposure to toxic heavy metals (WHO., 2010). Alongside industrialization, the utilization of heavy metals has found in a rapid growth and the possibility of human exposure to them increases in developing countries where both working population and general population residing near the industrial plant are at high risk. Heavy metals are becoming a significant public health problem with increased morbidity and mortality (Jan et al., 2015). Among them, lead (Pb), mercury (Hg), cadmium (Cd) and arsenic (As) are the priority metals of public health importance (WHO., 2017).

Prenatal exposure to these heavy metals grows as an important concern because of their effects on pregnancy resulting an array of health problems for both mother and child (Maekawa et al., 2017). They are well-known toxicants to cross the placenta and accumulate in the fetal tissues where their toxicokinetics such as uptake, biotransformation, distribution and toxicodynamics can occur to increase the risk of adverse outcomes (Gundacker & Hengstschläger, 2012). Furthermore, they can enter the systemic circulation through the different routes of exposure and reach the

central nervous system (CNS) from the blood by passing the blood-brain-barrier (BBB) or the choroid plexus (CP) (Yokel, 2006). The neurological effects of these heavy metals are most commonly found in the hippocampus region. Each of them have an individual effect as well as a common mode of action in a mixed-model fashion. Their mixture cause a dynamic interaction with neurochemicals in the hippocampus which can lead to oxidative stress. During oxidative stress, they induce an effect on a particular antioxidant, known as brain-derived neurotrophic factor (BDNF). Oxidative stress finally causes neuronal cell death, cognitive dysfunction and neuro-degerative outcomes (Ceccatelli, Daré, & Moors, 2010; Clarkson, 1987; Gavazzo, Zanardi, Baranowska-Bosiacka, & Marchetti, 2008).

Pb exposure during pregnancy is accounting for 12.4% of the global burden of idiopathic developmental disability (Institute for health Metrics and Evaluation, 2017) and it is also the significant maternal and child health burden (Renzetti et al., 2017). Previous studies have found that prenatal Pb exposure was significantly associated with preterm birth and low birth weight (LBW) (Gundacker & Hengstschläger, 2012; Liac et al., 2017). Identification of pregnant woman highly exposed to Pb is a particular issue for the prevention of adverse neurodevelopmental outcomes in newborns (S. Adrienne & Anne, 2010). The American College of Obstetricians and Gynecologists (ACOG) have recommended that pregnant women with whole blood Pb level of 5 μg/dL (50 5 μg/L) or higher should be identified to receive counselling on prevention of further exposures (CDC., 2010). Moreover, it was also found that prenatal Pb exposure has a significant association with preeclampsia (PE) (Bayat, Akbari, Dabirioskoei, Nasiri, & Mellati, 2016). Pb exposure contributes to an oxidative stress leading into a decrease in placental cell proliferation and cell death. Consequently, it impacts on the development of the placenta and endothelial cell dysfunction characteristic in PE (Fiore & Capasso, 2008).

Exposure to Hg can cause poor maternal health and decrease the placental and fetal growth (Harada, 1964; Mario et al., 2016). According to the previous studies, there are many adversities of Hg exposure for maternal and child health such as embryopathies, fetotoxicity, miscarriages, stillbirths, congenital craniofacial malformations including neural tube defects, brain damage and detrimental effects

in the older age (Hameed et al., 2018). It also impacts on the fetal health by interrupting the migration and maturation of fetal nerves cells causing oxidative stress, cell membrane damage and protein synthesis impairment (Reus, Bando, Andrés, & Cascales, 2003). It was found that the risk of high maternal blood Hg level has been identified as a particular issue for Korean population (Kim, Kim, Kwon, Kim, & Park, 2006).

Previous animal studies have found that Cd has both embryotoxic and teratogenic effects. Pregnant women are more vulnerable to suffer Cd burden than others because Cd can be highly absorbed in lower iron storage conditions (Ikeh-Tawari, Anetor, & Charles-Davies, 2013). Exposure to Cd mainly occurs through ingestion of contaminated food (e.g., cereals, seafood) and inhalation of tobacco smoke (Järup & Akesson, 2009). A study in Japan has mentioned that high maternal blood Cd concentration was significantly associated with preterm delivery of the baby (Tsuji et al., 2018). Another study in Bulgaria has found a significant relationship between exposure to Cd and adverse pregnancy outcomes such as threatened miscarriage, lipid peroxidation, toxemia and anemia among pregnant women living close to the copper smelter (Tabacova, Little, Balabaeva, Pavlova, & Petrov, 1994). In addition, perinatal exposure to Cd also has a significant association with PE (Vigeh et al., 2006).

Perinatal As exposure is a global health issue and it can cause subsequent effects on mother and fetus leading to long term negative health consequences (Bailey & Fry, 2014). As can readily cross the placenta and has significant associations with adverse birth outcomes such as LBW, decreased head and chest circumferences (Gilbert-Diamond, Emond, Baker, Korrick, & Karagas, 2016) (Anisur et al., 2009). It has been identified perinatal As exposure as a chronic burden for high risk of diseases in the adult life (e.g., cardiovascular diseases, diabetes, non-alcoholic fatty liver diseases and cancer) (Young, Cai, & States, 2018).

There is a growing evidence on the critical role of BDNF in depressive disorders and poor mental health during pregnancy (Karege et al., 2002). BDNF is a member of neurotrophins family which is important for neuronal health such as differentiation, maturation and survival of neurons (Acheson A et al., 1995; Binder &

Scharfman, 2004; Huang & Reichardt, 2001). Its particular functions for pregnancy has been found such as follicular development, oocyte maturation, implantation, proliferation within reproductive tissues and maturation of the fetus (Kawamura et al., 2009). Previous studies have examined the link between maternal blood BDNF and poor mental health outcomes in pregnancy. They have found that there was a significant association between maternal blood BDNF concentration and the incidence of maternal depressive disorders such as antepartum depression and post-partum depression (Fung et al., 2015; Gazal et al., 2012). Furthermore, decreased circulating BDNF in pregnancy also induces higher risk on neurodevelopmental development of the fetus (Deborah, Juan, Mary, Samuel, & Neill, 2012).

PE is one of the most common hypertensive disorders in pregnancy. It is also the major cause of maternal morbidity and mortality (American College of Obstetricians and Gynecologists, 2013). It was estimated that the rate of death due to hypertensive disorders in pregnancy is accounting 13% of all maternal deaths in which PE complicates approximately 2-3% (Carmen & Carla, 2003). Incidence of PE was found as 2.3% in developing countries and 0.8% in developed ones. It can be defined as hypertension of at least 140/90 mmHg recorded on at least two separate occasions, at least 4 hours apart and in the presence of at least 300 mg protein in a 24 hour collection of urine. Common risk factors include maternal age, body mass index (BMI), parity, multiple pregnancy, family history of preeclampsia, past history of hypertension, renal diseases and diabetes. It can be threatened systemic complications such as thrombocytopenia, acute pulmonary edema and disseminated intravascular coagulation (DIC) in mothers (Philip N & Louise K, 1917).

Preterm birth and LBW are the most common adverse birth outcomes related to critical determinants of child health such as disabilities. They have been identified as the leading causes of neonatal death which accounts for 40% of under-5 child mortality (WHO., 2005). Preterm birth is the delivery of an alive baby before 37 completed weeks of gestation. The common risk factors are poor socio-economic status, twin pregnancy, teenage pregnancy, smoking, poor nutrition, previous history of preterm birth and exposure to environmental hazards (Philip N & Louise K, 1917). An estimated 15 million babies are born preterm and approximately 1 million

children die every year due to its negative health consequences (L. Liu et al., 2016). LBW is the strong indicator of maternal and newborn health. Moreover, it is an important public health indicator for nutrition that is useful to predict growth and development outcomes of newborns in later life. It is defined as the weight at birth of less than 2,500 grams (or) 2.5 kilograms (or) 5.5 pounds. Risk factors derived from maternal influences such as age, ethnicity, height, pre-pregnancy weight, parity, multiple pregnancy, health behavior such as smoking and behavior predisposing exposure to environmental hazards (Philip N & Louise K, 1917). According to the previous reports, the highest incidence rate for both preterm birth (60%) and LBW (66%) was found in the South Asia (UNICEF., 2014).

Alongside globalization, economic diversification, variation in supply and demand of laborers across countries, migration is becoming a global phenomenon mainly in Asia and Pacific region. Migration impacts not only on an individual's physical health but also on mental health and social well-being (ILO., 2017). The great demand in feminized sectors (e.g., domestic work, manufacturing factory, textiles factory) develops into a high number of female migrants. Due to poor education, socio-economic status and access to information, migrants who stay and work in unhealthy environments such as industrial plant are at high risk of poor health. To date, Thailand is on the progress of a rapid industrialization and economic development. This situation leads to high human workload demand and attracts the migrants from neighboring countries; Cambodia, Laos and Myanmar. Among these countries, 80% of migrants are from Myanmar (International Organization for Migration, 2011). Previous studies have assessed the levels of heavy metals pollution in Thailand. A study of the workers from a battery manufacturing plant in Bangkok has found significantly high airborne Pb levels in the working environments (Lormphongs et al., 2003). Another study has analyzed the levels of Hg and As in fish samples from the industrial areas around the country. They found that heavy metals in some fish species collected near the industrial zone of Samut Sakhon province exceeded the standard United States Environmental Protection Agency (US EPA) levels (Jana, 2017). High Cd contamination has also been identified in a number of food items from the polluted areas in Thailand (Chunhabundit, 2016). However,

there are few studies on the association between biological monitoring of heavy metals and incidence of adverse pregnancy outcomes among migrants in Thailand.

Samut Sakhon is the second of top 10 provinces with largest Myanmar migrant population in Thailand (International Organization for Migration, 2011). It can be divided into 3 administrative districts: Amphoe Mueng Samut Sakhon, Ban Pheao and Krathum Baen. In this province, there is a river namely Tha Chin, a distributary of the Chao Pharya river flows through the province into the Gulf of Thailand. The surface water quality of the Tha Chin river has been rated as poor quality with heavy metals pollution (Bangkok: Pollution Control Department, 2015). It was also found that some crab species (e.g., *Sesarma mederi*) collected from these rivers have high Cd and Pb levels (Chaiyaraa, Ngoendeeb, & Kruatrachue, 2013). Among 77 provinces in Thailand, Samut Sakhon has been identified as a dense of industrial plant because of having a total of 6,000 factories and industries such as fisheries, food and beverage, plastic, rubber, packaging, dying and textiles factories. In these different factories and industries, the human workload for general works is composed of Myanmar migrants more than local Thai population. Most of Myanmar migrants workers receive daily wages of about 300 Thai Baht (10 USD) and it is (100-300 Thai Baht) lower than Thai minimum wages. A previous report has stated that most Myanmar migrants earn their monthly incomes and send back to their families. The educational level of Myanmar migrants was found as poor with unemployment backgrounds and most of them migrated from less developed areas of Myanmar (Chandravanshi, Gupta, & Shukla, 2018). In addition, a mixture of industrial and human activities can give rise to risks of heavy metals pollution in the environment. Poor educational background, lower income and the occupational status of Myanmar migrants may precede the higher risk of exposure to the environmental heavy metals and other hazards.

The effects of exposure to heavy metals on pregnancy outcomes have been examined in many previous studies. But there is lack of previous studies on the association between maternal heavy metals level and pregnancy outcomes such as preeclampsia, preterm birth and LBW among Myanmar migrants in Thailand. In addition, heavy metals induce an effect on mood disorder and depressive symptoms

(Karri, Schuhmacher, & Kumar, 2016). Previous studies have demonstrated a relationship between BDNF and depressive disorders (Licinio & Wong, 2002). Given the increased understanding of heavy metals exposure and BDNF level, it is crucial to gain a better understanding of decreased BDNF level in maternal blood and its relationship to heavy metal blood level through sharing a common effect on mood disorders pathway.

1.2 Research question

1.2.1 What is the association between maternal blood heavy metals (Pb, Hg, Cd, As) concentrations and BDNF levels among Myanmar migrants in Samut Sakhon Province, Thailand?

1.2.2 What is the association between maternal blood heavy metals concentrations and pregnancy outcomes including PE, preterm birth and LBW among Myanmar migrants in Samut Sakhon Province, Thailand?

1.3 Statistical hypothesis

1.3.1 Statistical hypothesis 1

Alternative hypothesis

There is an association between maternal blood heavy metals level and BDNF level among Myanmar migrants in Samut Sakhon Province, Thailand.

Null hypothesis

There is no association between maternal blood heavy metals level and BDNF level among Myanmar migrants in Samut Sakhon Province, Thailand.

1.3.2 Statistical hypothesis 2

Alternative hypothesis

There is an association between maternal blood heavy metals level and pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand.

Null hypothesis

There is no association between maternal blood heavy metals level and pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand.

1.4 Research objective

1.4.1 General objective

The main objective is to identify the association between maternal blood heavy metals level and BDNF and pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand.

1.4.2 Specific objective

1) To assess maternal blood heavy metals and BDNF concentrations among Myanmar migrants in Samut Sakhon Province, Thailand
2) To find the factors associated with heavy metals levels among Myanmar migrants in Samut Sakhon Province, Thailand
3) To describe the factors affecting pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand

1.5 Conceptual framework

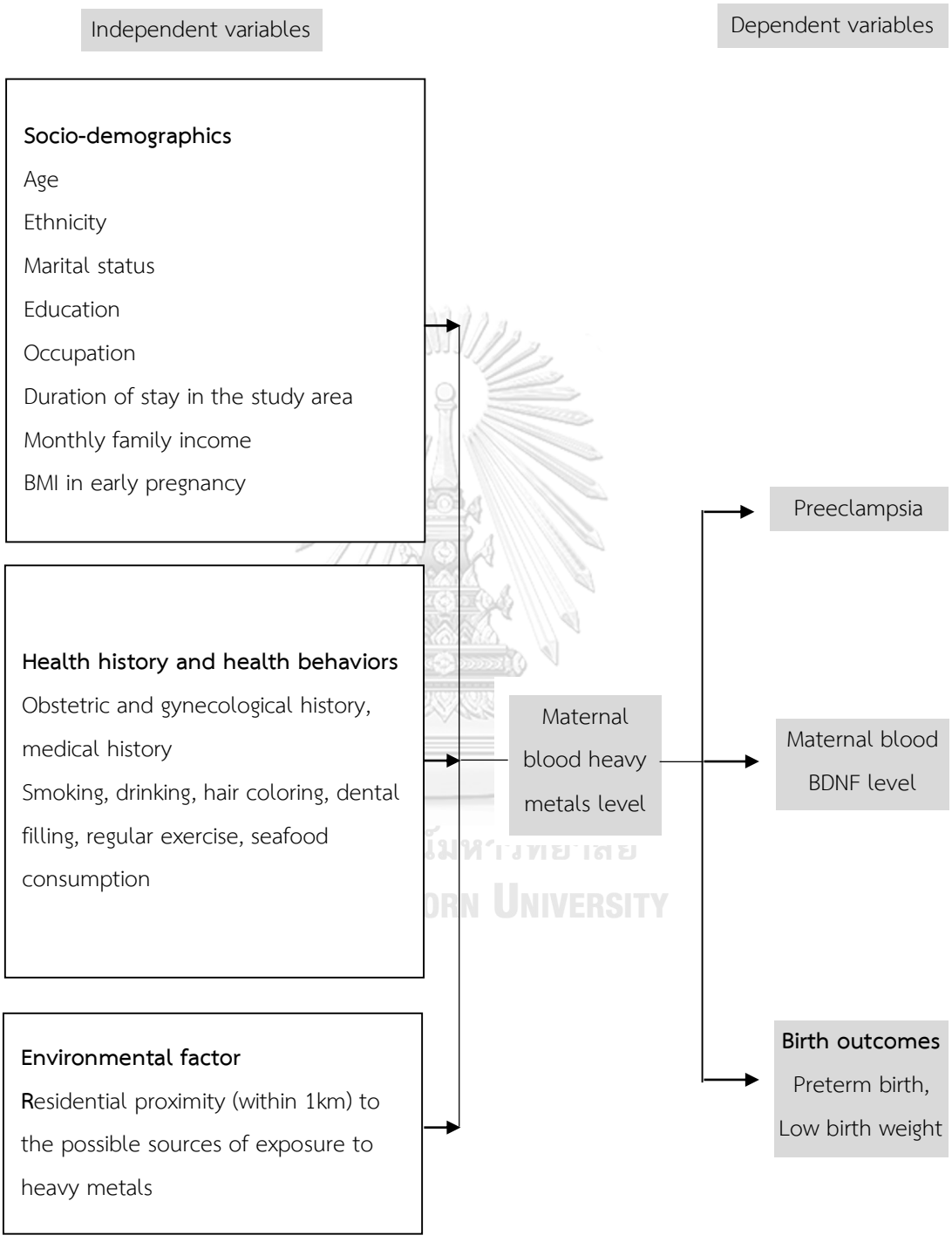


Figure 1 Conceptual framework

1.6 Operational definition

1.6.1 Maternal blood heavy metal level

It is the concentration of four heavy metals: Pb (μg/L), Hg (μg/L), Cd (μg/L), As (μg/L) in the whole venous blood of pregnant Myanmar migrant in first and third trimester.

1.6.2 Maternal blood BDNF level

It is the concentration of BDNF (μg/L) in the plasma of pregnant Myanmar migrant in first and third trimester.

1.6.3 Pregnancy outcomes

It include normal and adverse outcomes. Normal pregnancy outcomes are the absence of PE and normal birth outcomes such as full term birth and normal birth weight. Adverse pregnancy outcomes are the presence of PE and adverse birth outcomes such as preterm birth and LBW.

1.6.4 Preeclampsia

It is defined as the measurement of systolic and diastolic blood pressure (SBP/DBP) more than 140/90 mmHg in first and third trimester ANC visits.

1.6.5 Preterm birth

It is defined as the live born infant delivered before 37 weeks gestation.

1.6.6 Low birth weight

It is defined as the weight of newborn at birth less than 2500 grams (or) 2.5 kilograms.

1.6.7 Myanmar migrant

It represents a registered Myanmar migrant with pregnancy.

1.6.8 Socio-demographics

It include age, ethnicity, marital status, education, occupation, monthly family income, duration of stay in the study area and BMI in early pregnancy.

1) Age: is the completed age of pregnant woman in years.
2) Ethnicity: means the most common ethnicity of Myanmar migrants in Thailand such as Burmese, Karen and Mon.

3) Marital status: means the pregnant woman who is officially married (or) single (or) separated/ divorced (or) stay together without married (or) widowed.
4) Education: means the education of pregnant woman who is able to read and write (or) primary school (or) secondary school (or) high school and above.
5) Occupation: means the occupational status e.g., employed (or) unemployed and type of occupation during the present pregnancy, e.g., industrial sector (or) agricultural sector (or) construction (or) domestic sector (or) others.
6) Monthly family income: is defined as an average monthly family income in Thai Baht.
7) Duration of stay in the study area: means the total duration of pregnant woman's stay in Samut Sakhon province.
8) BMI in early pregnancy: means the body mass (kilogram) divided by the square of the body height (meter) measured at the first trimester ANC visit.

1.6.9 Health history and health behavior

It includes health history; obstetric and gynecological history, medical history and health behavior; smoking, drinking, hair coloring, dental filling, regular exercise and seafood consumption.

1) Obstetric and gynecological history: includes whether have been pregnant, the total number of previous child and history of past gynecological diseases.
2) Medical history: includes the history of hypertension before pregnancy and family history of hypertension and depression.
3) Smoking history: includes the history of smoking, e.g., current (or) not current (or) never and history of secondhand smoke exposure during the current pregnancy.
4) Drinking history: means the history of alcohol drinking, e.g., current (or) not current (or) never.
5) History of hair coloring: means the history of coloring the hair or uses of hair dyes during the present pregnancy and 3 months prior the present pregnancy.
6) History of dental filling: means the history of taking amalgam filling treatment during the present pregnancy and 3 months prior the present pregnancy.

7) History of regular exercise: means the history of taking walking exercise at least 20 minutes per day during the present pregnancy.
8) History of seafood consumption: means the history of consuming behavior of fish and seafood during the present pregnancy, e.g., less than once a week (or) once a week (or) 2-3 times per week (or) more than 3 times per week.

1.6.10 Environmental factor

It means the history of staying the residence within 1 kilometer proximity to the possible sources of exposure to heavy metals during the present pregnancy and 3 months prior the present pregnancy. Possible sources include a variety of industries (e.g., alloy production factory, battery manufacturing factory, ceramic manufacturing factory, electronics manufacturing factory, glass manufacturing factory, insecticide/ pesticide manufacturing factory, metal pipe production factory, paints production factory, paper manufacturing factory, pigments manufacturing factory, plastics manufacturing factory, textile factory) and others (e.g., construction sites, farm using insecticides/ pesticides and solid waste combustion site).

CHAPTER II

LITERATURE REVIEW

The literature review consists of both theoretical background and researches relating with:

1) Heavy metals; Pb, Hg, Cd, As
2) Brain-derived neurotrophic factor
3) Pregnancy outcomes including preeclampsia, preterm birth and low birth weight
4) Myanmar migrants in Thailand and
5) Heavy metals contamination in Thailand.

2.1 Heavy metals

They are naturally occurring elements composed of a high atomic weight or a density at least 5 times greater than water (Fergusson, 1990). They include the transition metals, metalloids, lanthanides and actinides. They can be found throughout the earth's crust but most of human exposure and environmental contamination emanated from anthropogenic activities such as mining and smelting, industrial production and use, domestic, agricultural and pharmaceutical uses (He, Yang, & Stoffella, 2005). Weathering and volcanic eruptions are also included in the main sources of heavy metals pollution (Bradl, 2002; Nriagu, 1989; Shallari, Schwartz, Hasko, & Morel, 1998). Other sources of environmental contamination are metal corrosion, atmospheric deposition, soil erosion of metal ions, sediment re-suspension and metal evaporation from water sources to soil and ground water. Heavy metal pollution and contamination is a crucial problem because of their disadvantageous effects on human health (Nriagu, 1989). They have different toxicological properties which affect the functions of human body system such as neurology, nephrology and embryology. Moreover, the US EPA and the International Agency for Research on Cancer (IARC) have classified them as known or probable human carcinogens based on the significant findings of epidemiological and experimental studies (Tchounwou et al., 2012). Among these heavy metals, Pb, Hg, Cd and As have been classified as the priority heavy metals of public health concerns (WHO., 2017). Previous studies

have found that exposure to these heavy metals is a potentially hazardous for the pregnant mother and the developing fetus resulting a number of adverse outcomes. This study focused on the outcomes including preeclampsia, preterm birth, low birth weight and BDNF which is a particular biomarker of cognitive dysfunction leading mental health problems in pregnancy.

1) Lead

Global production and consumption of Pb has increased in the past decade and is expected to be continued. It is among the most extensively recycled of any comorbidity metal. The extensive use of Pb causes negative effects on the environment and humans (WHO., 2010). Exposure to Pb is approximated to account for 0.6% of the global burden of diseases and the highest Pb burden is particularly seen in the developing countries (WHO., 2009). Although reduction the uses of Pb in some sectors have been achieved, the source of Pb exposure still remains as an important role for environmental and human health (Fewtrell, Kaufmann, & Pruss-Ustun, 2003). Pb is physically a bluish or silvery gray metal. Atomic number in periodic table is 82. Relative atomic mass is 207.19 and specific gravity is 11.34. Melting point is 327.5℃ and boiling point is 1740℃ at atmospheric pressure. Oxidation state in inorganic compounds is +2 (IPCS., 1995). Occupations with potential to expose Pb are battery manufacturing, ceramic manufacturing, construction, manufacturing of industrial machinery and equipment, paint and pigment manufacturing, plastics manufacturing, printing, solid waste combustion, and use of Pb based paints (John & Gary, 2001).

Inhalation and ingestion of Pb are the primary routes of absorption. Kinetics and metabolism is influenced by the physical and chemical states and also host factors including age, physiological state, nutritional status and genetic factors. In workplace, approximately 35-40% of inhaled Pb is ultimately absorbed to the bloodstream. Absorption from air to blood consists of two main processes; deposition of airborne Pb particles in the respiratory tract and absorption and clearance from the respiratory tract into the blood circulation. In case of non-occupational exposure, Pb is absorbed by the gastrointestinal system where dietary

factors and nutritional status are also influencing the absorption. Dermal absorption of Pb through unabraded human skin is considered to be in minimal level. The initial distribution of Pb in human body relies on the rate of blood delivery to the various organs. Approximately 99% of Pb binds to the erythrocytes and only 1% remains in the plasma. Pb is distributed to the soft tissues such as blood, liver, kidney and mineralizing systems such as bone and teeth. Three pools of blood, bone and soft tissues have identified with distinct half-lives respectively. Among them, blood Pb is recommended as the most liable compartment with 36 days of half-life in human. It is eliminated in urine, feces, bile, skin, nails, sweats, and breast milk, but approximately 70% is via the urine (Rabinowitz, Wetherill, & Kopple, 1976).

Pb has been found as able to cross the blood-placenta barrier by passive diffusion. It can be readily transferred from mother to the fetus and accumulate in the fetal bone tissues. Oxidative stress in trophoblastic placental tissue plays an important role in the biochemical mechanism of preterm birth. Pb-induced oxidative stress is becoming increasingly concerned for preterm birth. Researchers proposed that Pb could enhance the lipid peroxidation in the placenta through promotion of membrane physical changes which leads to oxidative stress. Some assumed that Pb directly reacts with GSH through the mechanism of oxidative stress to occur the significant effect on preterm birth (Ahamed, Mehrotra, Kumar, & Siddiqui, 2009). In placental tissue, there is a redox system in which Glutathione (GSH) is the first line of defense against oxidative damage (Hayes & McLellan, 1999). Regarding the role of Pb in LBW, it is well-known that Pb can accumulates in many parts of the body and mostly in the bones (Chuang et al., 2001). The body burden of Pb stored in the maternal bones can be released in pregnancy and then contribute to impact on the fetus (Al-Saleh, Shinwari, Mashhour, Mohamed Gel, & Rabah, 2011).

There are a number of previous studies on the relationship between prenatal Pb exposure and adverse pregnancy outcomes such as gestational hypertension, spontaneous miscarriage, preterm birth, intrauterine fetal growth restriction, low birth weight and neurodevelopment (Andrews, Savitz, & Hertz-Picciotto, 1994; Angell & Lavery, 1982; Falcon, Vinas, & Luna, 2003). Whole blood Pb concentration is the utmost useful laboratory test to confirm whether acute or chronic exposure (Joseph

& Robert, 2014). Previous studies which proved the significant association between maternal Pb exposure and pregnancy outcomes are shown in the table 1.

Table 1 Related studies on the association between maternal Pb exposure and pregnancy outcomes

No.	References	Study population	Sample collection	Findings
1.	(Disha. et al., 2019), Taiwan	67 pregnant women from the OBGYN outpatient department, 23 (PE cases), 44 (healthy controls)	Maternal whole blood samples	Higher blood Pb level (BLL) is significantly associated with increased risk of PE, mean BLL: 3.42 ± 2.18 ug/dL (cases), 2.38 ± 2.43 ug/dL (controls), (p-value = 0.0132), DBP was significantly higher in cases, (102.95 ± 13.34 mmHg) than controls (65.54 ± 7.9 mm Hg) (p-value < 0.001)

Table 1 continued

No.	References	Study population	Sample collection	Findings
2.	(Obadia et al., 2018), DR Congo	80 pregnant women who came to gve birth at the hsopital, 40 (PE cases), 40 (controls)	Whole blod samples and spot urine samples before delivery	A significant association between high maternal BLL and PE (p-value = 0.001), mean BLL: 6.7 μg/dL (cases), 5.1 μg/dL (controls)
3.	(Bayat et al., 2016), Iran	158 pregnant women, aged 15-40 years, a singleton pregnancy (cases: ≥ 20th weeks of gestation admitted to the hospital with a diagnosis of PE), (controls: without PE)	Whole blood samples	A significant relationship between maternal BLL and PE (p-value = 0.028), mean BLL: 8.04 ± 3.4 μg/dL (cases), 6.24 ± 1.74 μg/dL (controls)

Table 1 continued

No.	References	Study population	Sample collection	Findings
4.	(Vigeh et al., 2006), Iran	396 pregnant women, absent history of chronic diseases (heart diseases, diabetes, cancer and renal failure)	Umbilical cord blood samples at delivery, maternal whole blood samples within 24 hours after delivery	Mean cord BLL were significantly higher in PE cases (4.30 ±2.49 μg/dl), a significant association between environmental exposure to Pb and risk of PE (OR: 12.96, 95% CI 1.57: 107.03, p-value <0.05)
5.	(Luo et al., 2017), North California, US	1,700 pregnant women who attended to ANC clinic, English or Spanish speaking, age ≥ 18 years, 18th weeks gestation	310 whole blood samples during 1st trimester	A significant association between maternal BLL and LBW

Table 1 continued

No.	References	Study population	Sample collection	Findings
6.	(Taylor, Golding, & Emond, 2014), UK	14,541 pregnant women	4,285 whole blood samples during early pregnancy	Mean Pb: 3.67 ± 1.47 μg/dl, median Pb: 3.42 μg/dl, a significant association with preterm birth (adjusted OR 2.00, 95% CI 1.35, 3.00)
7.	(Perkins et al., 2014), Eastern Massachusetts, US	949 mother-child pairs during 1st prenatal visit to the hospital, English speaking, a singleton pregnancy, < 22 weeks gestation	Whole blood samples at a mean of 27.9 weeks gesteation	A significant association between maternal Pb exposure (at very low levels) and preterm birth among male newborns (OR: 5.51, 95% CI: 1.21, 25.15), mean BLL: 1.2 μg/dL, mean birth weight: 3505 g

Table 1 continued

No.	References	Study population	Sample collection	Findings
8.	(Xie et al., 2013), China	252 mother-infant pairs, age ≥ 18 years, plan to deliver at the research hospital, residence > 3 years in the research area	Maternal whole blood samples during admission for delivery, cord blood samples at birth	An increased maternal exposure to Pb was associated with decreased birth weight (OR: −148.99; 95% CI: −286.33, −11.66), median: 3.20 μg/dL
9.	(McMichael, Vimpani, Robertson, Baghurst, & Clark, 1986), Australia	749 pregnant women from longstanding Pb pollution suffered community	Maternal whole blood samples at 4-0 weeks, 32 weeks and delivery	A significant association between maternal BLL at delivery and preterm birth

2) Mercury

Different forms of Hg had been used for distinct purposes in industrial sectors because of their property acting as a cathode in the electrolysis of sodium chloride. The resultant chemicals are contaminated with Hg and their use in other industrial activities contaminates to other products. Hg was used in gold extraction, electrical products manufacturing industry, laboratory, medical instruments and some therapeutic medical treatment such as dental silver amalgams (IPCS., 1991). There are three forms of Hg; elemental form (metallic form), inorganic form (Hg chloride), and organic form (methyl Hg and ethyl Hg). In physical appearance, it is a slivery white metal. Atomic number in periodic table is 80. Relative atomic mass is 200.59 and specific gravidity is 13.633. Melting point is -38.83°C and boiling point is 356.7°C at atmospheric temperature. The usual oxidation state of three forms are; 2 for elemental Hg, 1 for inorganic Hg and -2 for organic Hg respectively (Bose-O'Reilly, McCarty, Steckling, & Lettmeier, 2010).

According to previous studies, human exposure to Hg can occur mainly through the consumption of contaminated fish or seafood. Occupations related with batteries, ceramics, dental medicine, electroplating, disinfectants, wood preservatives, paints and dyes, fungicides, insecticides and paper manufacturing are at high risk of exposure (Joseph & Robert, 2014). Inhalation of Hg vapor is the main route of elemental Hg intake. The uptake of metallic Hg vapor from inspired into the blood depends on the dissolution of Hg vapor in the blood because it passes through the pulmonary circulation (WHO., 1976). Absorption of inorganic Hg from the contaminated food was found to be about 7% in average. Use of skin-lightening cosmetics which contains inorganic Hg can be absorbed through the skin but little is known about dermal absorption of inorganic Hg (Hursh, Clarkson, Miles, & Goldsmith, 1989). Small amount of absorbed inorganic Hg is exhaled as metallic Hg vapor in urine and feces (WHO., 1976) .

Human health effects include both acute and chronic onsets. Acute effect includes local skin irritation, vomiting, stomach pain, bloody diarrhea, acute respiratory distress and intentional tremor. Chronic effect includes paresthesia in fingers, tongue and face, dysphagia, salivation, restlessness, insomnia, visual and

auditory disturbances, mental disturbances, proximal tubular damage with proteinuria and renal failure (Morton, 2006). Hg can also transfer the neurotoxic effect from mother to fetus providing prolonged burden on neurological development of the child (Bose-O'Reilly et al., 2010). Biological monitoring of Hg can be assessed in whole blood, exhaled air, urine and hair. Whole blood Hg is a good indicator of acute and chronic exposure to methyl Hg or Hg vapor. (Boerleider, Roeleveld, & Scheepers Paul, 2017). Previous studies examining the association between maternal Hg exposure and pregnancy outcomes are shown in the table 2.

Table 2 Related studies on the association between maternal Hg exposure and pregnancy outcomes

No.	References	Study population	Sample collection	Findings
1.	(Kobayashi et al., 2019), Japan	15,444 pregnant women in early pregnancy form the obstetrics facilities or local government offices	Maternal whole blood samples during 2nd and 3rd trimesters	No association between blood Hg level and birth weight, median (IQR): 3.66 (2.59-5.18) ng/g
2.	(Vigeh et al., 2018), Japan	334 mother-child pairs from early pregnancy (12 weeks gestation) to delivery, well communicated, age ≥20 years, a singleton pregnancy, planned to undergo prenatal care and delivery at the research hospital, free from chronic conditions (hypertension, diabetes, cancer)	Maternal whole blood samples at 1st, 2nd and 3rd trimesters, umbilical cord blood samples at delivery	A negative correlation between total blood Hg in early pregnancy and birth weight (OR: – 0.170, p-value = 0.006), mean blood Hg in 1st trimester were higher than US EPA recommended level (5.8 μg/L), Hg exposure at the early stages of pregnancy may be a risk factor for LBW

Table 2 continued

No.	References	Study population	Sample collection	Findings
3.	(Mario et al., 2016), Spain	2,644 pregnant women during 1st ANC visit of early pregnancy from primary health care centres or public hospitals	1,869 cord blood samples at delivery	Prenatal Hg exposure may be associated with decreased fetal growth, fish consumption should be considered as an important confounder
4.	(Tang et al., 2016), China	120 pregnant Chinese women living on Shengsi Island, an area of high heavy metals contamination	Umbilical cord samples from mother-newborn pairs (n= 103) at delivery	Maternal exposure to Hg was assocaited with decreased birth weight in fish consuming pregnant women
5.	(Bashore et al., 2014), US	191 pregnant women from Brooklyn Prenatal Clinic and follow up until delivery (aged 18–45 years)	Urine samples during the 6th to 9th month of pregnancy, cord blood samples at delivery	No association between maternal Hg exposure and either LBW or preterm birth

Table 2 continued

No.	References	Study population	Sample collection	Findings
6.	(Ding et al., 2013), China	258 mother–infant pairs from the rural northern China in the southern coastal area of Laizhou Bay of the Bohai Sea	Maternal whole blood samples at adimission for delivery, cord blood samples at delivery	Hg exposure levels were much lower than those reported in previous studies, mean maternal blood Hg: 0.84 μg L^{-1}, no significant association between maternal blood Hg and birth weight

3) Cadmium

Cd is an electropositive metal. It is commonly present in zinc, Pb and copper cores and produced as a by-product of the smelting and refining of these ores. Extensive usage of Cd is in electroplating. Cd alloys are used in high speed bearings, solder and jewelry. Cd sulfides and selenides are used as pigments in rubber, plastics, paint, textiles and ceramics (Joseph & Robert, 2014). Regarding physical appearance, it is a soft bluish-white solid. Atomic number in periodic table is 48. Relative atomic mass is 112.40 and specific gravity is 8.65. Melting point is 321.01°C and boiling point is 767°C at atmospheric temperature. The usual oxidation state of Cd is +2 but it also exists in +1 state (Weast, 1974).

Occupational exposure to Cd can be occurred in the production of alloy, battery, electrical contact, paint, pesticide and plastic, dry color formulation, electroplating and textile printing. Food contamination risk is high if the storage was done in ceramic containers glazed with Cd. In general population, Cd exposure mainly occurs through contaminated food such as liver and meat by-products, shellfish and vegetables. Tobacco plant can be accumulated with environmental Cd and cigarette smoking is an also a well-known exposure (Joseph & Robert, 2014). Cd is primarily absorbed by inhalation (10-40%) and ingestion (5%). Dermal absorption is negligible under ordinary circumstances.

It was mentioned that Cd cannot easily cross the placental barrier, however, adverse effects of Cd on placental functions, fetal growth and development had been identified in previous studies (Iyengar & Rapp, 2001; K. Yang, Julan, Rubio, Sharma, & Guan, 2006). Cd concentration can be measured in whole blood and blood Cd level provides useful information on Cd absorption from different parts of the body. In occupational exposure cases, blood Cd concentration can be interrupted if the exposure pattern is ascertained, whether recent or past. Therefore, other information such as the diet, smoking, personal hygiene at workplace are also required (W. Thomas, Lars, Gunnar, & Rolly, 1988). Previous studies which proved the significant association between maternal Cd exposure and pregnancy outcomes are shown in the table 3.

Table 3 Related studies on the association between maternal Cd exposure and pregnancy outcomes

No.	References	Study population	Sample collection	Findings
1.	(F. Wang et al., 2018), China	132 pregnant women at the research hospital (51 PE cases, 51 healthy controls)	Maternal whole blood samples during 28-40 weeks gestation, placental tissue samples within 10 minutes after delivery, BP measurement and two mid-stream urine samples during each prenatal visits	Median blood Cd: 1.21 μg/L (0.76–1.84 μg/L) in cases and 1.09 μg/L (0.72–1.31 μg/L) in controls], a statistically significant higher blood and placental Cd levels in PE cases than healthy controls (OR: 7.83, 95% CI: 1.64, 37.26)
2.	(Tsuji et al., 2018), Japan	14,847 pregnant women in early pregnancy from obstetrics facilities or local government offices	Maternal whole blood samples in 2nd and 3rd trimesters	Median Cd: 0.66 ng/g, a significant association between Cd level and early preterm birth (OR 1.91, 95% CI: 1.12, 3.27, p-value=0.018)

Table 3 continued

No.	References	Study population	Sample collection	Findings
3.	(Luo et al., 2017), North California, US	1,700 pregnant women who attended to prenatal clinic, English or Spanish speaking, age ≥ 18 years, 18th weeks gestation	310 whole blood samples during 1st trimester	A significant association between maternal blood Cd and LBW
4.	(Wai, Mar, Satoko, Mitsutoshi, & Chiho, 2017), Myanmar	419 pregnant women during 3rd trimester, age ≥ 18 years, resdience > 6 months in the research area	419 maternal spot urine samples in 3rd trimester	A significant association between prenatal Cd exposure and LBW (OR 1.10, 95% CI : 1.0, 1.21, p-value = 0.043)
5.	(H. Wang et al., 2016), China	3,254 pregnant women	Maternal serum samples (1,122 in 1st trimester, 2,132 in 2nd trimester)	Mean serum Cd: 0.89 μg/L, median: 0.79 μg/L, a positive association with preterm birth (OR 2.86, 95%CI: 1.95, 4.19, p-value < 0.001)

Table 3 continued

No.	References	Study population	Sample collection	Findings
6.	(C.M. Taylor, J. Golding, & A.M. Emond, 2016), UK	4,191 mother-child pairs	Maternal whole blood samples in early pregnancy (median of 11 weeks gestation)	Mean blood Cd: 0.56 ± 0.62 μg/L, median: 0.29 μg/L, an adverse association between blood Cd level and birth weight (OR: -62.7g, 95% CI: -107.0, -18.4)
7.	(J. Yang et al., 2016), China	5,364 pregnant women from the prospective healthy baby cohort (a single gestation and live birth, well communicated in Chinese language)	Mid-stream urine samples during admission for delivery	An increased urinary Cd was associated with likelihood of preterm (OR: 1.78; 95% CI: 1.45, 2.19), no association with LBW

4) Arsenic

As is a natural metalloid and occurs in a variety of chemical forms such as elemental, organic and inorganic forms. Elemental form seldom exits in the nature and is of low suability. That form rarely causes human toxicity. Inorganic As is encountered in commerce predominantly as trivalent or pentavalent oxides, sulfides or salts. Organoarsenicals occurs in the nature and have many synthetic forms varying widely in the toxicological attributes. As is used in the industrial settings as minor constituent of metal alloys (e.g., the hardening of Pb in battery grids, bearings, ammunition and the manufacture of certain types of glass). It is used in domestic sector as a pesticide or herbicide in the past but most of them had been continued except some herbicides (Joseph & Robert, 2014). In physical appearance, it is different depending upon the specific gravity such as yellow colored As with specific gravity of 1.97 and gray or metallic with specific gravity of 5.73. Atomic number in periodic table is 33. Relative atomic mass is 74. 922. Melting point is 817° C and boiling point is 613°C at atmospheric pressure. It has totally thirty isotopes including 75, 74, 76, 82, 77, 73, 79, 78, 72, 64, 81, 90, 80, 87, 92, 63, 66, 61, 68, 83, 62, 71, 67, 91, 84, 70, 60, 65, 88 and 89 (Joseph & Robert, 2014).

Occupational exposure to As can be found in animal food additives, microelectronic manufacturing, pesticide spraying, phosphate detergents and smelting of nonferrous ores (John & Gary, 2001). General population expose inorganic As primarily through ingestion of food that contain As as a consequence of natural crustal occurrence or anthropogenic contamination. In different parts of the world, inorganic As of geologic origin may be found in artesian well water that exceeds USEPA standard. Seafood such as fish, mollusks, and seaweeds may often contain naturally occurring nontoxic organoarsenicals (Joseph & Robert, 2014). The main routes of exposure are inhalation and ingestion. Absorption greatly depends upon its chemical and physical form. After inhalation of airborne As particles, they are deposited in the upper respiratory tract and swallowed by mucociliary clearance, then resulting in gastrointestinal absorption (National Academy of Sciences, 1977). Approximately 80 % is absorbed by the gastrointestinal tract (Fowler, Ishnishi,

Tsuchiya, & Vahter, 1979). Dermal absorption of As can be seen by the occurrence of systemic toxicity after accidental topical exposure to As acid. But the information about significant skin absorption is limited (National Academy of Sciences, 1977). After absorption, As is bound to proteins in the blood and redistributed to the liver, spleen, kidneys, lungs and gastro-intestinal tract within 24 hours. Negative effects can be released via multiple modes of action including inhibition of enzymes essential for cell metabolism, induction of oxidative stress and alterations in gene expression and cell signal transduction (John & Gary, 2001). It is excreted primarily by the renal system as inorganic form (Lugo, Cassady, & Palmisano, 1969).

As was found as able to readily cross the placenta led to transfer of exposure effects from mother to fetus inducing adverse outcomes. Significant association of maternal As exposure with adverse pregnancy outcomes such as LBW, preterm birth had been studied. For example, a study in an arseniasis-endemic area of northeastern Taiwan (C. Y. Yang et al., 2003) compared the risk of adverse pregnancy outcomes including preterm birth and LBW between an area with historically high As-exposed area and non-As-exposed area. They showed an association between As exposure from drinking well water and risk of preterm (OR: 1.10 (95% CI 0.91–1.33) although not significantly. They also identified the evidence for the role of As exposure in increasing risk of LBW. Measurement of As concentration in the urine is useful to confirm recent exposure (Joseph & Robert, 2014). Blood analysis of As is also helpful to diagnose acute intoxication and whole blood As level may be elevated in that conditions (John & Gary, 2001). Previous studies which proved the significant association between maternal As exposure and pregnancy outcomes are shown in the table 4.

Table 4 Related studies on the association between maternal As exposure and pregnancy outcomes

No.	References	Study population	Sample collection	Findings
1.	(Farzan et al., 2015), US	514 pregnant women from The New Hampshire Birth Cohort at ANC clinics during 24-28 weeks gestation, age 18-45 years, a singleton pregnancy, no plan to move residence before delivery	Maternal spot urine samples at enrollment, BP measurement at each prenatal visits	Both SBP and DBP increased during pregnancy, mean BP was highest in 3rd trimester SBP: 112.9 ± 9.8 (1st), 112.5 ± 8.2 (2nd), 115.3 ± 8.4 (3rd), DBP: 68.4 ± 7.7 (1st), 67.0 ± 6.0 (2nd), 69.4 ± 6.2 (3rd), each 5-μg/L increase in urinary As was associated with a 0.15-mmHg greater monthly increase in SBP (95% CI: 0.02, 0.29; p-value = 0.022), As exposure was associated with greater increases in BP over the course of pregnancy

Table 4 continued

No.	References	Study population	Sample collection	Findings
2.	(H. Wang et al., 2018), China	3,194 mother-infant pairs from a sub-study of the China-Anhui Birth Cohort	Maternal serum samples at the beginning and middle of the pregnancy (4–27 weeks gestation)	Maternal As exposure increases the risks of moderate-to-late preterm birth, incidence of preterm birth was elevated in high As-exposed group compared to low As-exposed group (7.0% vs 4.8%, p-value = 0 .016), adjusted OR: 1.47 (95%CI: 1.03,2.09; p-value = 0.034)
3.	(H. Liu et al., 2018), China	1,390 pregnant women at 1st prenatal visit (no plan to move, a singleton baby <16 weeks, plan to deliver at the research hospital)	Spot urine samples during prenatal visits in 1st, 2nd, 3rd trimesters	Urinary As levels in 3rd trimester were associated with decreased birth weight 24.27 g (95% CI: -46.99: - 1.55)

Table 4 continued

No.	References	Study population	Sample collection	Findings
4.	(Liao et al., 2018)	130 pregnant women (22-45 years old)	Maternal urine samples in all trimesters	Mean urinary As: 41.8 μg/L (1st trimester), 40.0 μg/L (2nd trimester), 40.6 μg/L (3rd trimester), 2nd trimester urinary As level was associated with decreased birth weigh (OR: -173.26 g, p-value < 0.01)
5.	(Rahman et al., 2017), Bangladesh	1,180 pregnant women for drinking water As exposure, 1,093 pregnant women for maternal toenail As exposure from a longitudinal birth cohort study in Banglades(age ≥ 18 years, a singleton pregnancy of ≤16 weeks gestation	Dirnking water samples from tubewells, maternal toenails samples (all 10 toenais) at ≤ 1 month post-partum	A causal relationship between prenatal As exposure and LBW, shortening gestation and possibily IUGR likely to play an important role in the causal pathway

Table 4 continued

No.	References	Study population	Sample collection	Findings
6.	(Claus et al., 2016), US	622 mother-infant pairs residing near mining-related Superfund site in Northeast Oklahoma during ANC visits or at delivery from the research hospital (giving birth at the hospital, plan to live in the research area for next 2 years)	Maternal whole blood and umbilical cord blood samples at delivery	Median blood As: 1.94 (0.97, 2.3) μg/L, high maternal As exposure (Q 4) was significantly associated with decreased birth weight (OR: -142.5, 95% CI: -252.9: -32.2)
7.	(Huyck et al., 2007), Bangladesh	57 pregnant women through community meetings with health care workers, age ≥18 years, a singleton pregnancy of < 28 weeks gestation, utilized the same primary drinking water source for at least 6 months before pregnancy	Maternal hair, toenail, and drinking water samples at the 1st ANC visit and within 2 weeks after delivery	A negative association between As exposure and birth weight, a significant association beteween hair As level in early pregnancy and decreased birth weight (OR: -193.5 ± 90.0 g, p-value = 0.04)

2.1.5 Relationship between heavy metals and BDNF

Previous animal studies had examined that heavy metals can negatively impact cognitive function through down regulation of BDNF. All of lead, mercury, cadmium and arsenic share the common pathway to produce oxidative stress where pro-oxidant elements and antioxidants including BDNF become lack of balance (Karri et al., 2016). Their common mode of actions in the hippocampus of the brain was shown in the following figure. It was proved the links between lead, mercury, cadmium, arsenic and cognitive dysfunction. For example, lead intervene the Glu transmission and interrupt the expression of NMDA in synaptic and extra synaptic region. Mercury has high affinity to Na^{+} /K^{+}-ATPase enzyme, extra synaptic NMDA receptor, Glu and biological Ca^{+2}. Cadmium interfere with Na^{+} /K^{+}-ATPase and biological Ca^{+2}. Arsenic has the property bind AchE and GAD. Then the functional interaction of them induces common adverse effect under influencing the anti-oxidant elements status. Moreover, the dynamic interaction between heavy metals and neurochemicals alters the integrity of neuronal cell by down-regulation of BDNF and other elements. Finally common susceptibility factor provides the oxidative stress which leads to programmed neuronal cell death resulting cognitive dysfunction (Ceccatelli et al., 2010; Gavazzo et al., 2008; Stackelberg, Elizabeth, Tian, & Birgit, 2013).

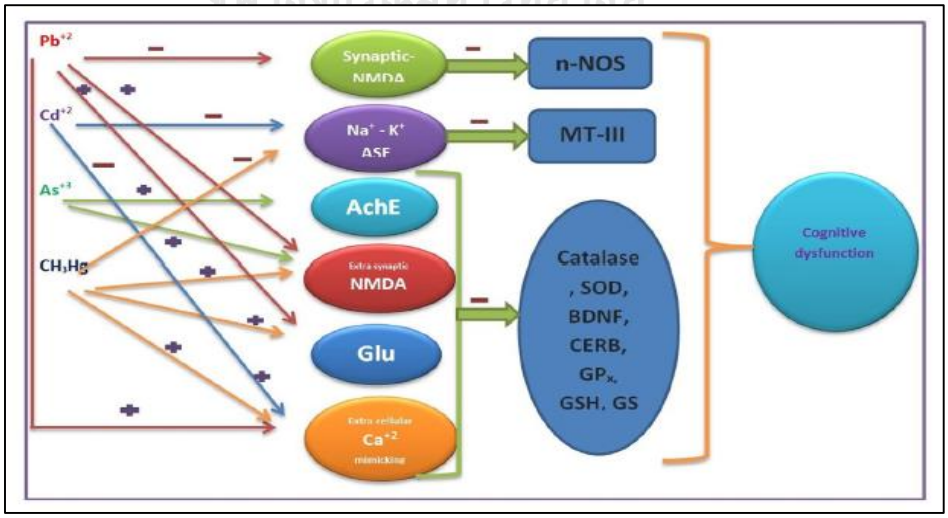


Figure 2 Common mode of actions of heavy metals on BDNF
(Karri et al., 2016)

2.2 Brain-derived neurotrophic factor

It is the 2nd discovered member of neutrophins family and essential for the development and survival of neurons, synaptic plasticity and cognitive functions. Sources of secretion are neurons and peripheral cells such as leukocytes, endothelial cells, and platelets. It has a capability of crossing the blood-brain barrier (Endling, Nanavati, Johnson, & Tuohy, 2004; Nakahashi et al., 2000; Pan, Banks, Fasold, Bluth, & Kastin, 1998). It is important for adult neurogenesis in which neural stem cells and progenitor cells generate the neurons (Travaglia & La Mendola, 2017). It is located on the short arm of chromosome 11 and consists of 9 exons and 9 promoters which organize the transcription of BDNF (Binder & Scharfman, 2004). Additionally, BDNF is the result of translation of minimally 34 mRNA transcripts from alternative splicing of totally 11 upstream exons (1-9a) where each exon is coding for the 5′ untranslated region (5′UTR), spliced to a common downstream exon 9 that encodes the protein and two different 3′UTR sequences (Pruunsild, Kazantseva, Aid, Palm, & Timmusk, 2007). Gene structure of human BDNF was mentioned in the figure 3 in which open boxes are representatives of exons. Lines are connecting two exons. Arrows indicate alternative polyadenylation sites (PolyA) in the 3′UTR and internal alternative splice sites in exons 2, 6, 7 and 9a (letters a, b, c and d). Exons are drawn to scale (Gabriela & Tongiorgi, 2009).

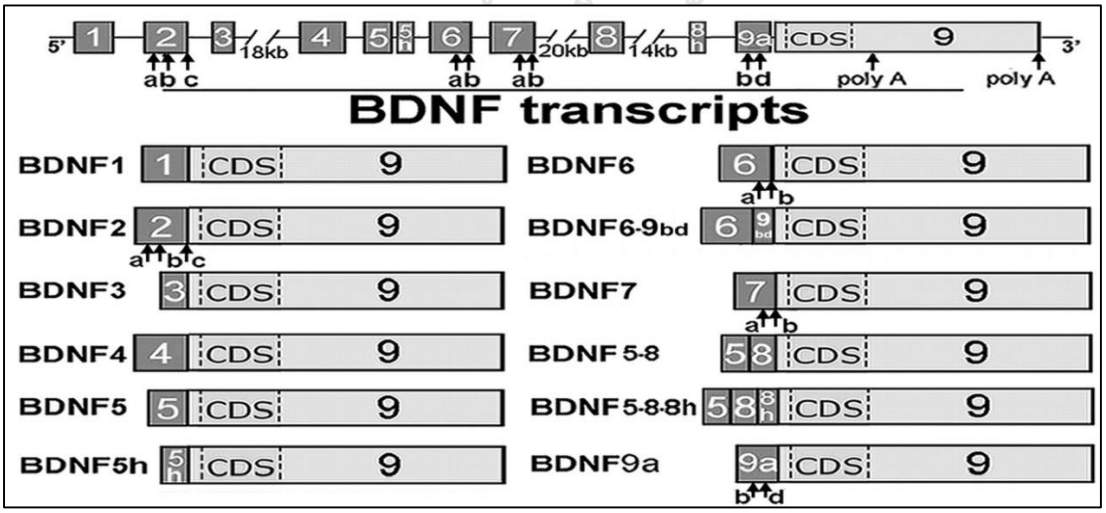


Figure 3 Human BDNF gene structure and its splicing variants
(Gabriela & Tongiorgi, 2009)

Neuronal synthesis, processing, sorting, transport and secretion of BDNF was shown in the figure 4. BDNF protein is primarily synthesized in the endoplasmic reticulum (ER) as a pro BDNF. Then it reaches into the Trans Golgi network (TGN) via the Golgi apparatus from where it moves onwards to the constitutive and regulated secretory pathways. The process of BDNF binding to the lipid-raft-associated sorting receptor carboxypeptidase E (CPE) in the TGN is essential for sorting into secretory vesicles of the regulated pathway in which the vesicles are subsequently transferred into suitable sites for activity-dependent secretion. Afterwards CPE is internalized and transported back to the TGN through the endocytic recycling compartment. The obvious protein convertases within the TGN and secretory vesicles of the regulated pathway divide the amino-terminal pro-domain of pro BDNF for the production of mature BDNF. Mature BDNF undergoes the interaction with both pre- and post-synaptic TrkB receptors in order to activate intracellular secondary messenger cascades (K. Thomas & Davies, 2005).

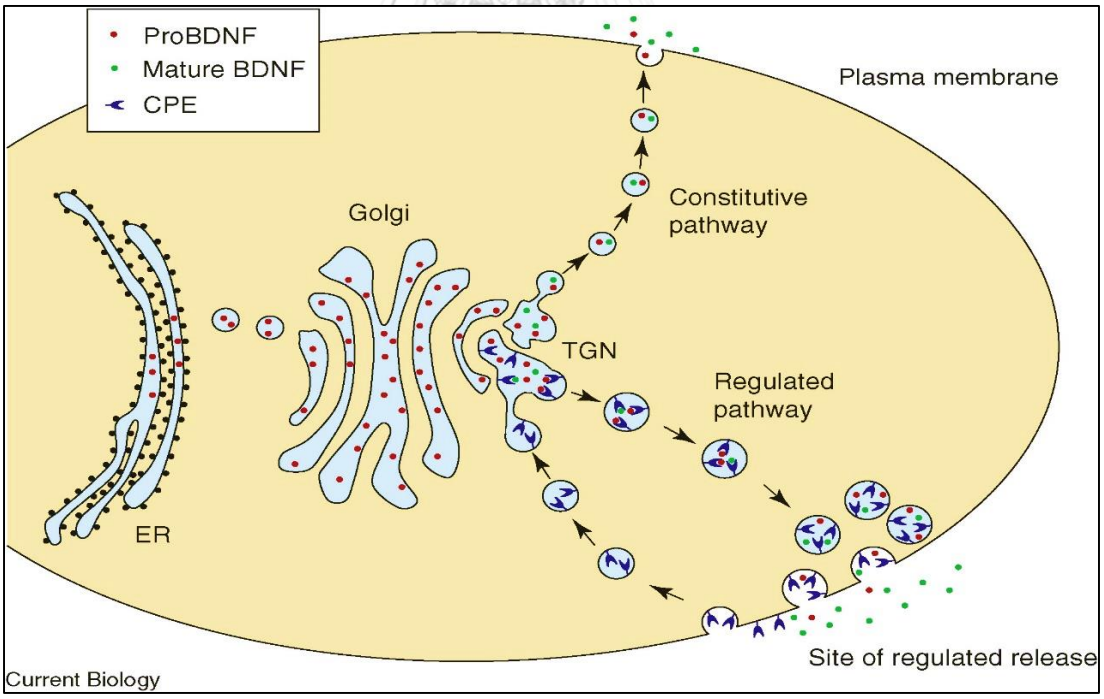


Figure 4 BDNF synthesis, processing, sorting, transport and secretion in neurons (K. Thomas & Davies, 2005)

Signaling pathway of BDNF was shown in the figure 2.4. It binds to its high-affinity receptor namely tyrosine kinase B (TrkB) which led to the recruitment of proteins for the activation of three signal transduction cascades. The first cascade contains sequential activation of "insulin receptor substrate-1 (IRS-1/2), phosphatidylinositol-3-kinase (PI-3K) and protein kinase B (Akt)". The second cascade is the activation of "Shc/Grb2, Ras, Raf, mitogen-activated protein kinases (MEKs) and extracellular signal regulated kinases (ERKs)". The third cascade involves "phospholipase C (PLC), inositol (1,4,5)-trisphosphate [Ins(1,4,5)P3], diacylglycerol (DAG) and protein kinase C (PKC)". BDNF signaling pathways activate one or more transcription factors "(cAMP-response-element-binding protein (CREB) and CREB-binding protein (CBP)" that regulate expression of genes encoding proteins involved in neural plasticity, stress resistance and cell survival (Bathina & Das, 2015).

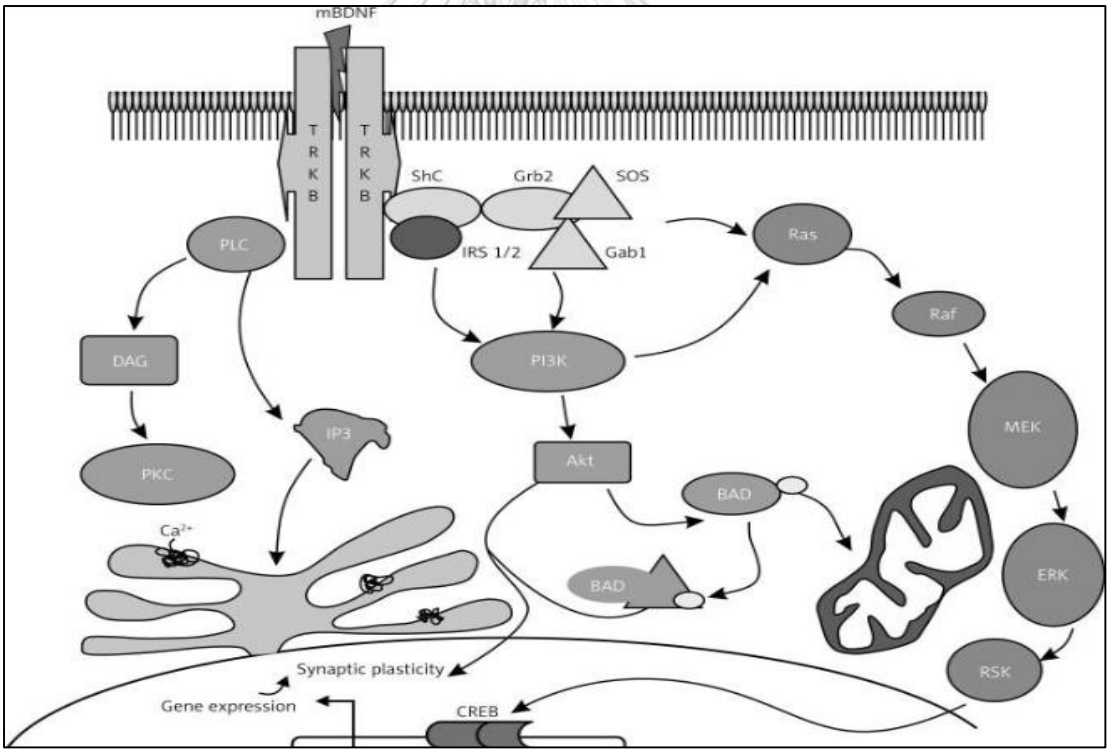


Figure 5 Signaling pathway of BDNF
(Bathina & Das, 2015)

Bio specimens such as whole blood, plasma, serum or blood cells can be used for assessment of BDNF (Radka, Holst, Fritsche, & Altar, 1996). Serum BDNF level is responsible for the concentration platelet pool and plasma levels might reflect the immediately delivered amount to the nervous system (Tamura et al., 2012). A number of studies had stated the critical role of BDNF for cognitive function, stress and mood disorders. They showed that BDNF can provide the protection of neurons against chemical stress. Mechanism of BDNF effect was mentioned as the significant decrease in stimulus-evoked inhibitory postsynaptic currents (IPSCs) on hippocampal CA1 pyramidal cells (Frerking, Malenka, & Nicoll, 1998).

BDNF is relatively important for pregnancy because of its peculiar role for follicular development, embryo implantation, placentation and fetal maturation (Kawamura et al., 2007) (Kawamura et al., 2009) (Mayeur et al., 2010). Maternal BDNF concentration influences the neurodevelopment of embryo in embryonal hippocampal neurogenesis. It was found that BDNF plays a critical role in the embryonal neurodevelopment of essential neurons such as dopaminergic, noradrenergic and serotonergic neurons (Glenn et al., 2007). Moreover, previous studies had investigated that serum BDNF is significantly low in pregnant mothers comparing to non-pregnant women in follicular phase even in the absence of any metal problems. However, the knowledge on the mechanism of decreased peripheral BDNF levels during pregnancy is still limited. It was mentioned that hemodilution, fetal sequestration and platelets changes might be the possible causes (Deborah et al., 2012). Significant association between low maternal BDNF concentration and socio demographic factors and health behaviors such as age, early pregnancy BMI and regular aerobic exercises during early pregnancy also had been examined (N. Yang et al., 2017). Decreased circulating BDNF in pregnancy induces higher risk on affective or neurodevelopmental disturbances and it becomes awakened for maternal and child health (Deborah et al., 2012).

The role of BDNF in depression has grown in great attention because of significant evidences in many pre-clinical and clinical studies. A study by (Karege et al., 2002) shown that serum BDNF levels of depressed patients was significantly lower than that of healthy controls. They also found that female depressed patients were

more severe in depressive symptoms and released less BDNF than male patients. Animal studies had examined that behavioral phenomenon related with depression could include modulation of BDNF expression (Duman, Malberg, Nakagawa, & D'Sa, 2000). Pathophysiology of BDNF role in depression had been identified as the relationship between depression and disturbance in structural and synaptic plasticity which are the major functions of BDNF (Duman, 2002). Clinical studies also proved the significant response of BDNF in depressed patients before and after antidepressant medication. For example, (Chen B, Dowlatshahi D, MacQueen GM, Wang JF, & Young LT, 2001) described that BDNF expression is elevated in the postmortem brain of depressed subjects treated with antidepressant medications in comparing with those who were not under antidepressants. In addition, there are a number of previous studies which investigated the link between maternal blood BDNF concentration and mental health during pregnancy. They could conclude the significant relationship between maternal blood BDNF level and the incidence of maternal depressive disorders within perinatal period (Fung et al., 2015). A Chinese cohort study hypothesized whether serum BDNF concentration after delivery of the baby is associated with development of postpartum depression or not. They found the strong association between decreased serum BDNF concentration at admission and the incidence of post-partum depression (PPD) after 3 months follow up (Gao, Wang, Yao, Cai, & Cheng, 2016). A recent study examined BDNF levels across the pregnancy including post-partum period and concluded that decreased serum BDNF levels in the late pregnancy correlates with increased depressive symptoms (Christian, Mitchell, Gillespie, & Palettas, 2016).

2.3 Pregnancy outcomes

2.3.1 Preeclampsia

It was defined as hypertension of at least 140/90 mmHg recorded on at least two separate occasions, at least 4 hours apart and in the presence of at least 300 mg protein in a 24 hour collection of urine. It complicates approximately 2-3% of pregnancies and incidence varies depending on the exact definition used and the population characteristics. (Philip N & Louise K, 1917). A number of studies have

identified common risk factors of PE in pregnancy. For example, risk of PE was 4.1% in first pregnancy and it was 2.76% higher than in second pregnancy (Cho et al., 2015; Hernández-Díaz, Toh, & Cnattingius, 2009). Twin pregnancy or multiple pregnancy also causes nearly a fourfold increased risk of PE independent of race and parity (Coonrod, Hickok, Zhu, Easterling, & Daling, 1995). Another study found that PE risk in second pregnancy was 13.3% among those who had the history of PE in the first pregnancy and 0.85% for those who had absence of past history (Cho et al., 2015). Age was also included as significant factor because risk of PE in pregnant women with advanced age was 9.4% and those in younger ones was 6.4% (Lamminpää, Vehviläinen-Julkunen, Gissler, & Heinonen, 2012). By comparing risk of PE between pregnant women with overweight and those with normal BMI, it can be concluded pre-pregnancy BMI and gestational weight gain as significant risks. (Shao et al., 2017). Furthermore, previous studies also examined the significant relationship between gestational PE and family history or personal history of hypertension (Tessema, Tekeste, & Ayele, 2015). Its complications can affect both mother and newborns. Maternal complications are abruption placenta, disseminated coagulopathy (DIC), pulmonary edema, acute renal failure, eclampsia, liver failure, stroke, long term cardiovascular morbidity and death. Neonatal complications are preterm birth, IUGR, hypoxia-neurologic injury and even perinatal death (Philip N & Louise K, 1917).

During normal pregnancy, the villous cytotrophoblast invades into the inner third of the myometrium and spiral arteries lose their endothelium and muscle fibers. Those structural modifications are related to functional alterations, such that spiral arteries become low-resistance vessels, and thus less sensitive, or even insensitive, to vasoconstrictive substances. Pathophysiology of preeclampsia is complex and poorly understood. Previous studies have demonstrated that the primary cause may be related to abnormal placentation. Defective invasion of the spiral arteries by cytotrophoblast cells is observed during preeclampsia (Uzan, Carbonnel, Piconne, Asmar, & Ayoubi, 2011).

In public health perspectives, preeclampsia has remained a significant public health threat in both developed and developing countries contributing to maternal and perinatal morbidity and mortality globally. But the impact of its consequences is

more severe in developing countries (Igberase & Ebeigbe, 2006). A previous study has mentioned that the problem of preeclampsia is confounded by the continued mystery of the etiology and the unpredictable nature of the disease (Duley, 2003).

The incidence of preeclampsia globally ranges between 2% and 10% of all pregnancies. WHO estimates the incidence of preeclampsia to be seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%) (WHO., 2005). It is a well-known precursor to eclampsia. The incidence of eclampsia in the developed nations of North America and Europe is similar and estimated to be about 5–7 cases per 10,000 deliveries. But, the incidence of eclampsia in developing nations varies widely, ranging from 1 case per 100 pregnancies to 1 case per 1700 pregnancies (WHO., 2004). In Myanmar, eclampsia is the third leading cause of maternal mortality (11.3%) and the government sectors effort on the promotion of antenatal care services to prevent preeclampsia and its consequences (Thein et al., 2012). In Thailand, the incidence of preeclampsia was 2.2% and severe preeclampsia 10.1 per 1,000 deliveries (Abalos et al., 2014).

2.3.2 Preterm birth

In obstetrics, the meaning of term is referred to the gestational period from 37^{+0} to 41^{+6} weeks and the meaning of preterm is the period between 24^{+0} and 36^{+6} weeks. According to The WHO, preterm birth is defined as live born infants delivered before 37 week from the first day of the last menstrual period (Philip N & Louise K, 1917).

Preterm birth remains a leading cause of neonatal morbidity and mortality worldwide, accounting for 60 to 80% infant death without congenital abnormalities. Neonatal morbidities related to preterm birth can induce many complications including growth failure, cerebral palsy, cognitive disorders and others which remain as significant public health problems (Richard, Avory, & Michele, 2015). Risks of preterm birth include non-modifiable and modifiable factors. Non-modifiable factors are ethnicity, low education and socio economic status, parity 0 or >5, adolescent pregnancy, twin pregnancy, past history of preterm birth, uterine anomalies, cervical anomalies, abdominal surgery, present pregnancy conditions such as recurrent

antepartum hemorrhage and intercurrent illness. Modifiable factors are **s**moking, poor nutrition, absence or inadequate antenatal care, BMI < 20 , closed inter-pregnancy interval (<1 year) (Philip N & Louise K, 1917). A study in Brazil mentioned that adolescent pregnancy, low education, advanced maternal age, multiple pregnancy and inadequate prenatal care were associated with spontaneous preterm birth. It was found that maternal age >30 years and short maternal stature also had a significant risk on preterm birth among Tanzanian population (Muhihi et al., 2016). Another study in Kenya concluded that maternal age ≤20 years, parity> 4, twin pregnancy, urinary tract infections, pregnancy induced hypertension, antepartum hemorrhage and prolonged rupture of membranes were significantly associated with the risk of preterm birth (Wagura, Wasunna, Laving, Wamalwa, & Ng'ang'a, 2018). Moreover, improper antenatal care, short inter pregnancy interval and underweight mother with inadequate weight gain were included in common risks of preterm birth according to previous study. In Myanmar, Infant Mortality Rate was 25.9 (urban) & 27.4 (rural) in 2011. Preterm birth rate was 12.4% of total live births in 2010. In Thailand, IMR was 10.5 in 2016. Preterm birth rate was 12 % of total live births in 2010 (Blencowe et al., 2013).

2.3.3 Low birth weight

According to the WHO, LBW is defined as a newborn weight of less than 5 pounds 8 ounces (or) 2,500 grams (or) 2.5 kilograms. Measuring weight at birth is very important for the infant's life and it influences on both infant mortality and morbidity. The risk of infant mortality is 20 times higher for LBW babies when compared to normal weight babies (Hussaini, Holley, & Ritenour, 2011).

A number of maternal factors can impact on birth weight of newborn and the most common ones are maternal age (both old and young), ethnicity, height, pre-pregnancy weight and parity (Philip N & Louise K, 1917). Previous studies have examined that non-modifiable factors of the mother such as age < 20 years, twin pregnancy, low education and history of chronic diseases were significantly associated with the incidence of LBW (Gebremedhin, Ambaw, Admassu, & Berhane, 2015). Presence of history of medical diseases: hypertension, lungs diseases (e.g.,

cystic fibrosis) or cardiac diseases (e.g., cyanotic heart diseases) can cause poor placental function which results maternal hypoxia and decreased fetal weight (Philip N & Louise K, 1917). It had been examined that maternal behaviors potential to expose environmental hazards significantly influences the fetal weight and growth. For example, health related behaviors such as smoking, poor antenatal care visit and poor nutrition impact on fetal weight and growth. Mothers who smoke during pregnancy deliver babies up to 3 kg lighter than non-smoking mothers (da Fonseca, Strufaldi, de Carvalho, & Puccini, 2012) (Miyake, Tanaka, & Arakawa, 2013) (Ward, Lewis, & Coleman, 2007). Previous studies have also found the significant relationship between exposure to heavy metals and the reduced birth weight of newborns.

It was demonstrated that LBW babies suffer long term consequences on chronic diseases such as hypertension, type 2 diabetes and cardiovascular diseases. They have a poor cognitive function and academic performance in comparison with normal birth weight babies (Hack et al., 2002). In Myanmar, incidence of LBW is 2.1 % in 2016 (Ministry of Health and Sports, 2017). In Thailand, LBW is 10.4% in 2014 and it is also the leading cause of under-5 child mortality (Ei EA, Nuttapat M & Kanitta B, 2018).

2.4 Myanmar migrants in Thailand

Push factors including rural poverty, fragile livelihoods, unemployment and poor economic opportunity predispose Myanmar people especially rural residents who live near borderline areas to migrate internally or externally. Thailand becomes a destination country with open economy and job opportunities for migrants of neighboring countries; Laos, Myanmar and Cambodia. Of these 3 countries, migration from Myanmar is the highest and increasing progressively. It was reported that 70% of Myanmar migrants living abroad are in Thailand. They work in various labor intensive industries, agriculture, trading and services. The educational background of Myanmar migrants in Thailand was found in the previous reports as no schooling (9.8%), elementary (or) primary school level (26.3%), secondary school level (32.8%) and high school (12.7%) (Chantavanich & Vungsiriphisal, 2012). In Thailand, there are top 10 provinces with the highest Myanmar migrant population mentioned as in the table

2.5 (Chantavanich S & Vunsiriphisal P, 2012). The largest numbers are employed in constructions (16.6%), fishery and fishery related work (15.6%), and agriculture/ animal husbandry related (12.5%) respectively (Euan, Pukchanok, & Premjai, 2015).

Table 5 Top 10 provinces with largest Myanmar migrant population in Thailand

No.	Province	Population
1.	Bangkok	101,489
2.	Samut Sakhon	73,225
3.	Tak	35,653
4.	Samut Prakan	28,128
5.	Ranong	22,988
6.	Pathum Thani	22,591
7.	Surat Thani	21,228
8.	Songkla	19,306
9.	Phuket	19,235
10.	Chon Buri	18,425

(Chantavanich S & Vunsiriphisal P, 2012)

2.5 Heavy metals contamination in Samut Sakhon Province

Samut Sakhon Province is situated at the mount of the Tha Chin River, a distributary of the Chao Phraya River, to the Gulf of Thailand. It is subdivided into 3 districts such as Mueang Samut Sakhon, Krathum Baen, and Ban Pheao. The districts are further subdivided into 40 communes (tambon) and 288 villages (muban). Neighboring provinces are Samut Songkhram, Nakhon Pathom and Bangkok. It is also a part of Bangkok Metropolitan Region. Obviously it is a dense of industrial plant with a total of about 6,000 factories including fisheries, food and beverages, plastic, rubber, painting, packaging, dying, textiles and others. Rapid increase of population with industrialization and economic development in the coastal areas combined with insufficient environmental protection measures may led to elevated levels of heavy metal pollution in Thailand (Hungspreugs, Utoomprurkporn, Dharmvanijj, & Sompongchaiyakul, 1989). Chao Phraya River, Tha Chin River and Mae Klong River are

regarded as heavy metals contaminated estuarine areas (Polprasert, 1982). They flow through the densely populated central plain of Thailand before discharging into the Gulf of Thailand. Because of nutrient-rich, shallow waters and confined nature, the ecosystems are vulnerable to human activities. However, detrimental effects of pollution on these ecosystems are believed to have an increased significant amount of toxic metals (Suvapepun, 1991). A study in the upper Gulf of Thailand had examined the significant accumulations of lead and cadmium concentrations. This leads to a long term impact on the aquatic environment through precipitation of metals to the bottom sediments and bioaccumulation and bio-magnification of metals in various food chains (Schwartz, Rajan, Askury, Putthapiban, & Djaswadi, 1995).

Figure 6 Geographical distribution of Chao Phraya River and Tha Chin River (http://www.maproom.psu.edu/dcw/ Digital Chart of the World)

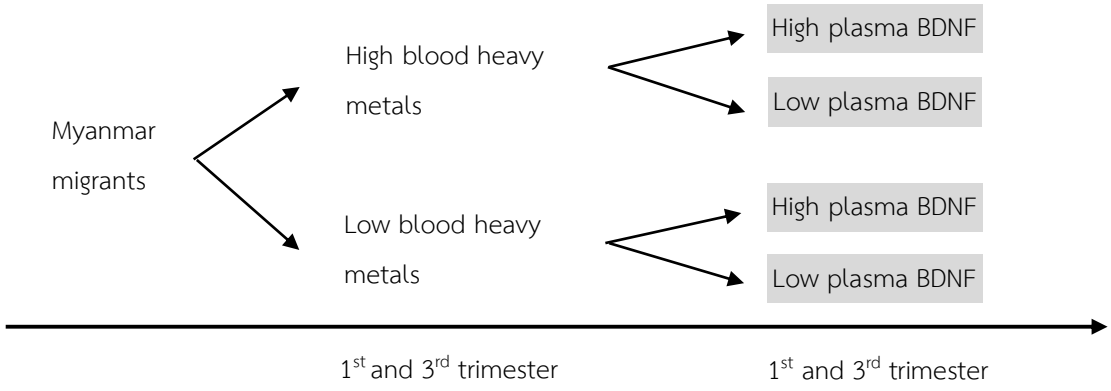
CHAPTER III

RESEARCH METHODOLOGY

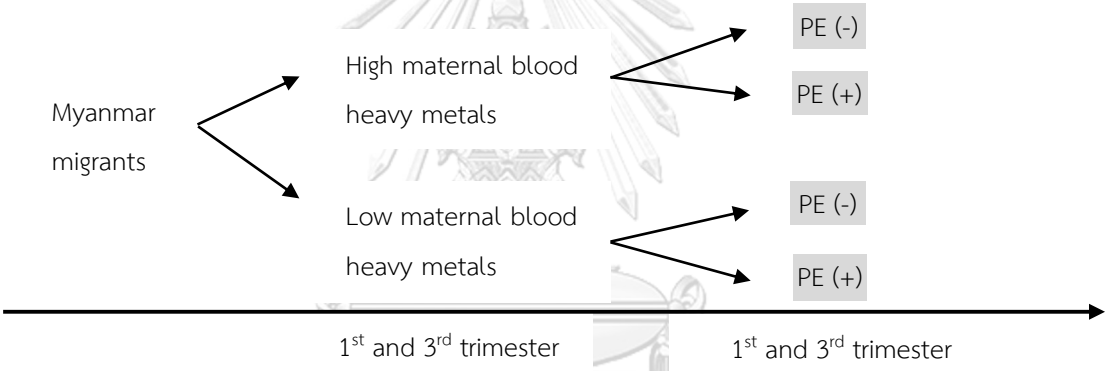
3.1 Study design

This study aimed to identify the association between maternal blood heavy metals and BDNF and pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand. A birth cohort design was used in which Myanmar migrants with pregnancy were recruited during first trimester gestation and followed up throughout pregnancy. Interested outcomes were: high (or) low maternal plasma BDNF level, preeclampsia (or) no preeclampsia, normal birth outcomes (full term birth and/ or normal birth weight) (or) adverse birth outcomes (preterm birth and/or LBW). Study was carried out from June 2018 to April 2019. Data collection was done based on the routine ANC procedures of the hospital; first trimester (baseline), second trimester, third trimester and delivery of newborn baby. Blood sample collection was done two times in first trimester and third trimester.

Outcome 1: Maternal plasma BDNF



Outcome 2: Preeclampsia



Outcome 3: Birth outcomes

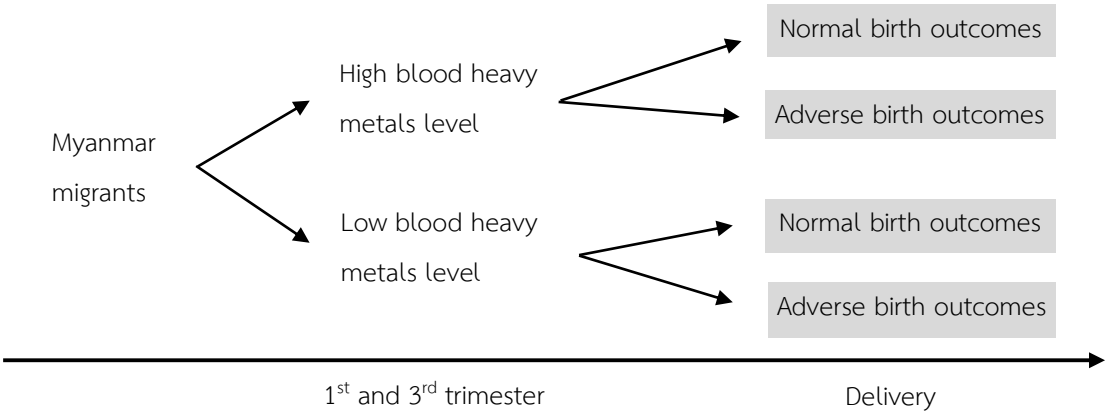


Figure 7 Myanmar migrant birth cohort

3.2 Study area

The study area was Samut Sakhon Province which is the second of top ten provinces with largest Myanmar migrants. It was recognized as a dense of industrial plant with a total of about 6,000 factories manufacturing mainly food and beverages, plastic and plastic products, rubber and rubber products, jewelry and textiles. It is situated at the mouth of the Tha Chin River which is one of the distributaries of the Chao Phraya River to the Gulf of Thailand. There were three administrative divisions in Samut Sakon province; Amphoe Mueang Samut Sakhon, Ban Pheao and Krathum Baen.

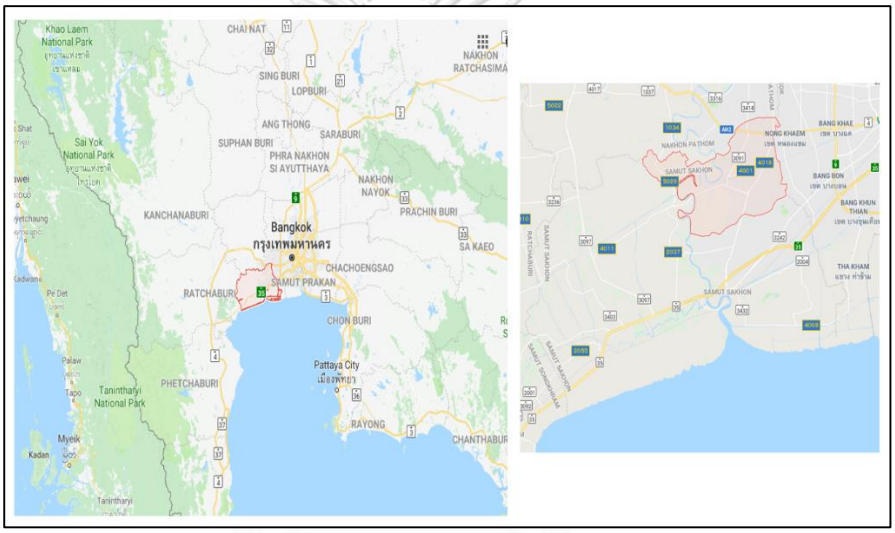


Figure 8 *Samut Sakhon Province*
(https://www.google.com/maps/place/Samut+Sakhon)

3.3 Study population

Participants were the registered Myanmar migrants in Samut Sakhon Province, Thailand.

3.3.1 Inclusion criteria

1) Those who visited ANC clinic of the hospital within first trimester gestation
2) Those who stayed in the study area at least three months before
3) Those who aged between 18 to 35 years
4) Those who planned to deliver the baby at the study hospital
5) Those who could read, write and communicate in Myanmar language
6) Those who were willing to participate

3.3.2 Exclusion criteria

1) Those who was multiparous with more than five parities
2) Those who had less than one year inter-pregnancy interval
3) Those who was confirmed as multiple pregnancy by ultrasound
4) Those with history of PE, preterm birth, LBW and depression

3.4 Sample size calculation

The following formula was used to calculate the sample size for this study (Bernad, 2000; Fleiss, Levin, & Paik, 2003; Ngamjarus & Chongsuvivatwong, 2014). A total sample size calculated was 124 to identify as high exposure and low exposure towards heavy metals. The participants were divided into two groups; group with high maternal blood heavy metals level (high exposure, n= 62) and group with low maternal blood heavy metals level (low exposure, n= 62).

$$n_{exposure} = \left[\frac{z_{1-\frac{\alpha}{2}} \sqrt{\bar{p}\bar{q}\left(1+\frac{1}{r}\right)} + z_{1-\beta} \sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]^2$$

$$p_1 = P(outcome|exposure), q_1 = 1 - p_1$$

$$p_2 = P(outcome|unexposure), q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + p_2 r}{1+r}, \bar{q} = 1 - \bar{p}, r = \frac{n_{unexposure}}{n_{exposure}}$$

Where,

P (outcome/ unexposed) = 0.210 (C.M. Taylor et al., 2016)

P (outcome/ exposed) =0.460 (C.M. Taylor et al., 2016)

Ratio (r) =1.000

Alpha (α) = 0.05, z (0.975) = 1.9559964, Beta (β) = 0.20, z (0.800) = 0.841621

Exposed = 54, Unexposed = 54,

By a continuity correction,

High exposed (Exposed) = 62, Low exposed (Unexposed) = 62

3.5 Sampling method

In Thailand, there are totally 77 provinces. Among them, Sumut Sakhon Province was purposively selected based on its characteristics of greater possibilities for heavy metals pollution. In Samut Sakhon province, there are three administrative districts: Amphoe Mueang Samut Sakhon, Ban Pheao and Krathum Baen. Among them, Krathum Baen district was selected purposively and Krathum Baen hospital was also selected by purposive sampling. Participants were collected on the basis of inclusion and exclusion criteria at the registration of regular ANC clinic.

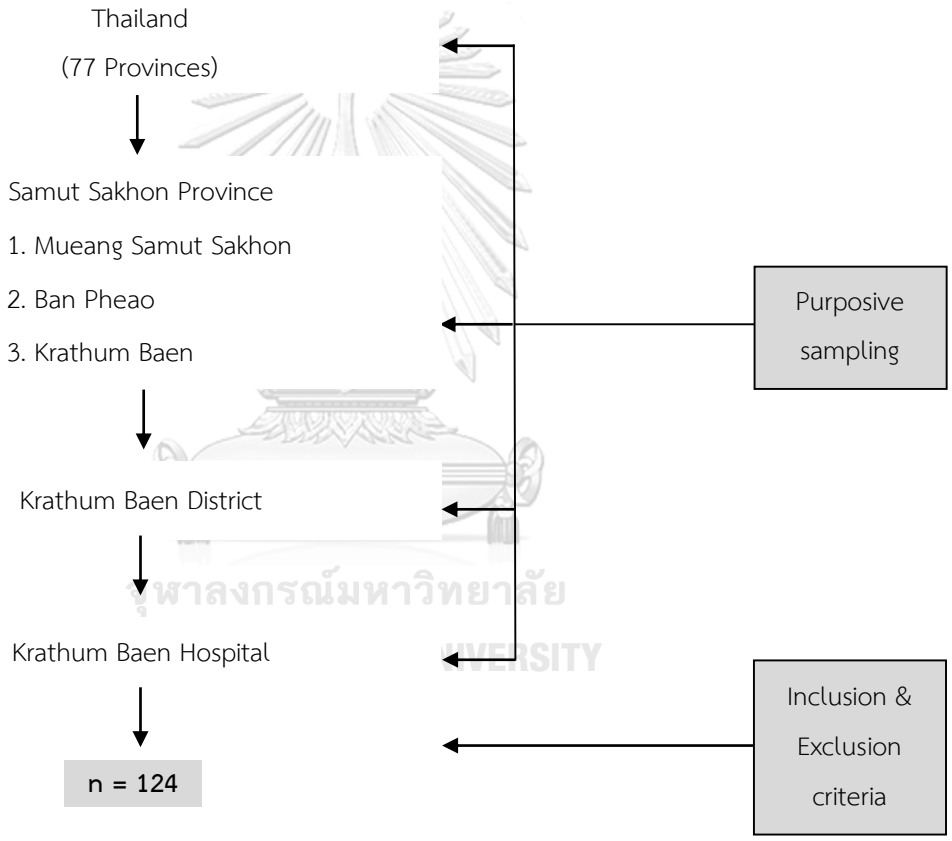


Figure 9 Sampling method

3.6 Measurement tools

3.6.1 Questionnaires

1) Self-reported questionnaires for first trimester

Socio-demographics: age, ethnicity, marital status, education, occupation, monthly family income, duration of stay in the study area

Health history and health behaviors: obstetric and gynecological history, history of hypertension, family history of hypertension and depression, history of smoking including secondhand smoke exposure, history of drinking, history of hair coloring, dental filling, regular exercise, and seafood consumption

Environmental factors: residential proximity within 1 kilometer to the places of high risk of heavy metals exposure such as alloy production factory, battery manufacturing factory, ceramic manufacturing factory, electronics manufacturing factory, glass manufacturing factory, insecticide/ pesticide manufacturing factory, metal pipe production factory, paints production factory, paper manufacturing factory, pigments manufacturing factory, plastics manufacturing factory, textile printing factory, other factories, construction sites, farm using insecticides/ pesticides, solid waste combustion site

2) Self-reported questionnaires for second trimester

Health behavioral change

Occupation change

Residence change

3) Self-reported questionnaires for third trimester

Health behavioral change

Occupation change

Residence change

3.6.2 Clinical records

1) ANC card

Height (centimeters), Weight (kilograms)

Systolic and diastolic BP (mmHg)

Ultrasound findings

2) Delivery note

Gestational age at delivery (weeks)

Birth weight of newborn (grams)

3.6.3 Laboratory tools for blood analysis

1) Inductively coupled plasma mass spectrometer (ICP-MS) was used for whole blood heavy metals analysis

2) Sandwish Enzyme-linked Immunosorbent Assay (ELISA) kit (RayBio, USA) was used for plasma BDNF analysis.

3.7 Validity of the questionnaires

The Item-Objective Congruence Index (IOC) was analyzed for questionnaires' content validity testing by the following experts:

1) Dr. May Thu Htun, MBBS, MMed Sc

Senior Assistant Surgeon, Obstetrics and Gynecology Specialist

Central Women Hospital, Yangon, Myanmar

2) Dr. Pokkate Wongsasuluk, Ph.D

College of Public Health Sciences, Chulalongkorn University

3) Dr. Wandee Sirichokchatchawan, Ph.D

College of Public Health Sciences, Chulalongkorn University

The IOC of the questionnaires from three experts was 0.84 and the content validity of the questionnaires used in this study was approved for measuring.

3.8 Data collection

Permission was asked from the local authorities and the study hospital. A research team was organized and it included one research assistant (to facilitate the participants in providing questionnaires), three trained nurses (to facilitate the participants at ANC clinic, to collect blood samples and to collect clinical records) and one experienced laboratory technician (to perform laboratory analysis). The research assistant was a Myanmar nationality migrant from the local migrants' health volunteered group who had well Myanmar language proficiency. The trained nurses were Thai Nationalities and recruited from the corresponding departments of the hospital: ANC clinic, laboratory department and delivery room. Before data collection, an orientation session for the nurses was given by the researcher to standardize their performances. The laboratory technician was requested from the standard toxicological laboratory. The appropriate time for data collection was planned according to the information of ANC clinic schedule of the hospital. An appropriate plan for blood collection including management of complications, storage and transportation of blood samples was prepared.

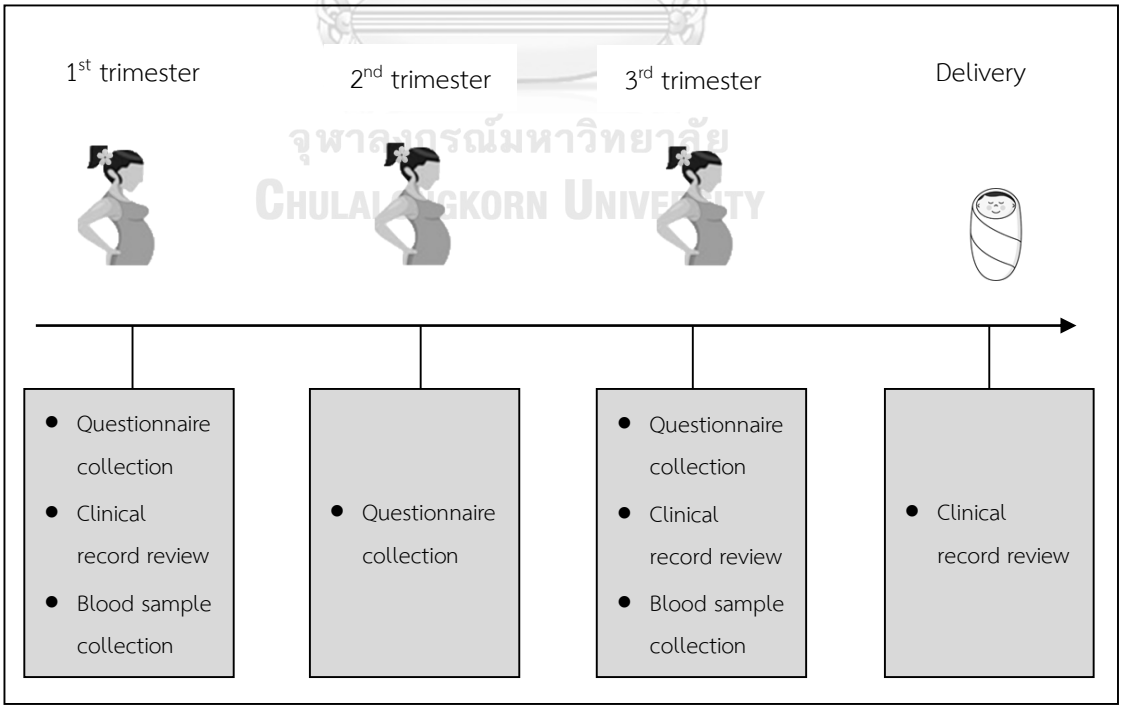


Figure 10 Flow of data collection

3.8.1 First trimester (baseline)

1) Questionnaires collection

It was carried out at the ANC clinic. Eligible participants were recruited from the registration records by inclusion and exclusion criteria. Adequate information including the objectives, methods, benefits and risks of the study, rights of the participants was properly provided to the participants. Informed consent was also obtained. Self-reported questionnaires were collected after their appointments with the obstetrician and it took about 10 minutes to complete all components. The researcher and the research assistant facilitated in the questionnaires collection. After completing the questionnaires, they were sent to the laboratory department to collect blood samples alongside routine investigation procedures.

2) Clinical record review

The ANC card of participant was reviewed by the nurse from ANC clinic. Information including height, weight, systolic/ diastolic BP, and ultrasound findings were noted.

3) Blood sample collection

It was carried out at the laboratory department. The trained nurse drew blood (total 5 ml) into 2 separated EDTA tubes (2.5 ml each); 1 tube was to analyze whole blood heavy metals and another tube was to analyze plasma BDNF. The sample tubes were properly labelled with hospital number and name of the participant and also included the purpose to analyze. All sample tubes were stored at 4°C before transfer to the laboratories.

3.8.2 Second trimester

1) Questionnaires collection

It was performed during second trimester ANC visit. The pregnant women answered the self-reported questionnaires for second trimester which contained health related behavioral change, occupation change and residential change. It was taken about 3 minutes.

3.8.3 Third trimester

1) Questionnaires collection

It was carried out during third trimester ANC visit. The participants answered the self-reported questionnaires for third trimester which contained health related behavioral change, occupational change and residential change. It was taken about 3 minutes.

2) Clinical record review

ANC cards review was done by the nurse from ANC clinic. Information including systolic/ diastolic BP and ultrasound findings were noted.

3) Blood sample collection

It was performed by the trained nurse at the laboratory department. Totally 5 ml of maternal whole blood was drawn into two separated EDTA tubes (2.5 ml each); one tube was to analyze whole blood heavy metals and another tube was for plasma BDNF analysis. Sample tubes were properly labelled with hospital number and name of the participant and also included the purpose to analyze. All samples were stored at 4°C before transferring to the laboratories.

3.8.4 Delivery

1) Clinical record review

Delivery notes review was done by the nurse from the delivery room. Interested birth outcomes; type of delivery, gestational week at birth and birth weight of the newborn were noted.

3.9 Data analysis

3.9.1 Statistical analysis

In this study, IBM SPSS Software Version 22 for Windows supported by Chulalongkorn University was used to analyze the data. Appropriate statistical tests were used based on the objectives. For the homogeneity of pregnant women in first trimester and delivery, general characteristics of them were compared by using independent t-test for continuous variables and Chi-square test of homogeneity for categorical variables.

Table 6 Statistical methods

Objective		Statistical methods
Main	To identify the association between maternal blood heavy metals level and BDNF and pregnancy outcomes	Linear regression models for continuous variables Independent variable: blood heavy metals concentrations (Pb, Hg, Cd, As) Dependent variable: systolic/ diastolic BP, gestational age at delivery, birth weight of newborn Logistic regression models for categorical variables Independent variable: blood heavy metals levels (Pb, Hg, Cd, As) Dependent variable: plasma BDNF levels

Table 6 Continued

Objective		Statistical methods
Specific	To assess maternal blood heavy metals and BDNF concentrations	Descriptive analysis Mean (± SD), Median (IQR)
	To find the factors associated with heavy metals levels	Independent t-test for continuous variables, Chi-square test of association for categorical variables, Fisher's exact test Independent variable: general characteristics of pregnancy Dependent variable: blood heavy metals levels (Pb, Hg, Cd, As)
	To describe the risk factors affecting pregnancy outcomes	Independent t-test for continuous variables, Chi-square test of association for categorical variables, Fisher's exact test Independent variable: general characteristics of pregnancy Dependent variable: PE, preterm birth, LBW

3.9.2 Whole blood heavy metals analysis

A total of 5 ml of maternal whole blood was collected from each participant in 2 separate ethylenediaminetetraacetic acid (EDTA) coated tubes by a trained nurse. One tube (2.5 ml) was used to analyze whole blood heavy metal concentrations, and the second tube (2.5 ml) was used to measure plasma BDNF concentrations. Samples were sent to a standard toxicology laboratory for heavy metal analysis. In summary, each blood sample was washed in purified water and a 2% nitric acid solution. Digested samples were quantitatively analyzed using an inductively coupled plasma mass spectrometer (ICP-MS).

The detection limits were mentioned as follows.

First trimester

1) Pb: 12.00 μg/L
2) Hg: 1.00 μg/L
3) Cd: 0.18 μg/L
4) As: 2.70 μg/L

Third trimester

1) Pb: 6.00 μg/L
2) Hg: 1.20 μg/L
3) Cd: 0.17 μg/L
4) As: 2.00 μg/L

Limits of detection (LOD) was calculated by SD*3 and limits of quantitation was calculated by SD*10.

3.9.3 Plasma BDNF analysis

It was performed two times in first trimester and third trimester. Maternal plasma BDNF concentration was measured using the quantitative ELISA kit (RayBio, USA) in accordance with manufacturer's protocols. All reagents and samples were bought to room temperature before use. Sample dilution of antibody cocktails and serial dilution for standard solution were prepared according to the procedures. Flat bottom 96-well plates coated with anti-Human BDNF were used to analyze BDNF absorbance. All samples were assayed in duplicate. The immobilized antigen and antibody were incubated with 70 µl of antibody cocktail containing biotinylated anti-Human BDNF and concentrated HRP-conjugated streptavidin for 10 minutes. After incubation, 50 µl of each standard and sample were added into the appropriate wells followed by incubation for 2 hours. The solutions were discarded by adding and washing with 300 µl of wash buffer into 4 times. After washing, 100 µl of tetramethylbenzidine (TMB) one-step substrate reagent was added to each well and incubation at dark room was done for 30 minutes by gentle shaking. Color development was stopped by the addition of 0.2 M sulfuric acid, then the absorbance of 450nm of each well contents was measured immediately by a Microplate Reader. All incubations were performed under room temperature and it took 2 hours and 40 minutes for total assay time excluding washing process. BDNF concentrations were expressed as µg/ml.

Figure 11 A quantitative sandwich ELISA kit (RayBio, USA)

3.10 Identification of heavy metals exposed groups

Heavy metals exposed groups were identified according to the median concentrations of each heavy metals because of non-normal distribution of their concentrations by the test of normality. Those whose heavy metals concentrations equal to and above median levels were identified into high exposed groups and those whose heavy metals concentrations less than median levels were identified into low exposed groups.

The cut-off points for each heavy metals exposed group were as follows.

1) Pb: 27.40 μg/L (first trimester), 19.90 μg/L (third trimester)
2) Hg: 6.20 μg/L (first trimester), 2.60μg/L (third trimester)
3) Cd: 0.91 μg/L (first trimester), 1.06 μg/L (third trimester)
4) As: 4.00 μg/L (first trimester), 3.40 μg/L (third trimester)

3.11 Ethical consideration

This study was reviewed and approved by:

1) The Research Ethics Review Committee for Research Involving Human Research Participants, Health Sciences Group, Chulalongkorn University (RECCU) (COA No. 251/2018)
2) The Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects, Krathum Baen Hospital, Ministry of Public Health

CHAPTER IV

RESULTS

A migrant birth cohort study was conducted among registered Myanmar migrants residing in Samut Sakhon Province, Thailand. The study period was June 2018 to April 2019 and a total of 119 pregnant women were recruited to participate in this cohort.

The results of this study were presented in five parts as the followings

4.1 General characteristics of pregnant Myanmar migrants in Thailand

4.2 Maternal blood biomarkers

4.3 Factors affecting maternal blood heavy metals levels

4.4 Factors affecting pregnancy outcomes

4.5 Effect of maternal blood heavy metals level on BDNF

4.6 Effect of maternal blood heavy metals level on pregnancy outcomes

4.1 General characteristics of pregnant Myanmar migrants in Thailand

At baseline, 119 registered Myanmar migrants, aged 18-35 years who visited the clinic within the first trimester gestation were recruited. In first trimester, the heavy metals exposure groups were identified according to the median values: high exposed groups (≥ median) and low exposed groups (< median) as follows.

a) 60 low exposed and 59 high exposed for Pb exposure (median = 27.40)

b) 62 low exposed and 57 high exposed for Hg exposure (median = 6.20)

c) 60 low exposed and 59 high exposed for Cd exposure (median = 0.91)

d) 64 low exposed and 55 high exposed for As exposure (median = 4.00)

In third trimester data collection, there were 103 pregnant women completed the questionnaires data collection. But only 72 pregnant women of them completed blood samples collection. All of them have also taken their delivery at the study hospital. Therefore, there were a total of 72 pregnant women completed the study including first trimester, second trimester, third trimester and delivery of the newborn. In third trimester, the heavy metals exposure groups were identified

according to the median values: high exposed groups (≥ median) and low exposed groups (< median) as follows.

a) 36 low exposed and 36 high exposed for Pb exposure (median = 19.90)

b) 39 low exposed and 33 high exposed for Hg exposure (median = 2.60)

c) 37 low exposed and 35 high exposed for Cd exposure (median = 1.06)

d) 38 low exposed and 34 high exposed for As exposure (median = 3.40)

In this study, 47 pregnant women were lost and excluded from the study as followings.

a) 1 case of completed miscarriage

b) 1 case of intrauterine fetal growth restriction

c) 5 pregnant women who moved ANC to the other hospitals

d) 15 pregnant women who went back to delivery in Myanmar

e) 25 pregnant women who did not complete blood samples collection

Flow of the participants in this cohort was demonstrated in the following figure 12.

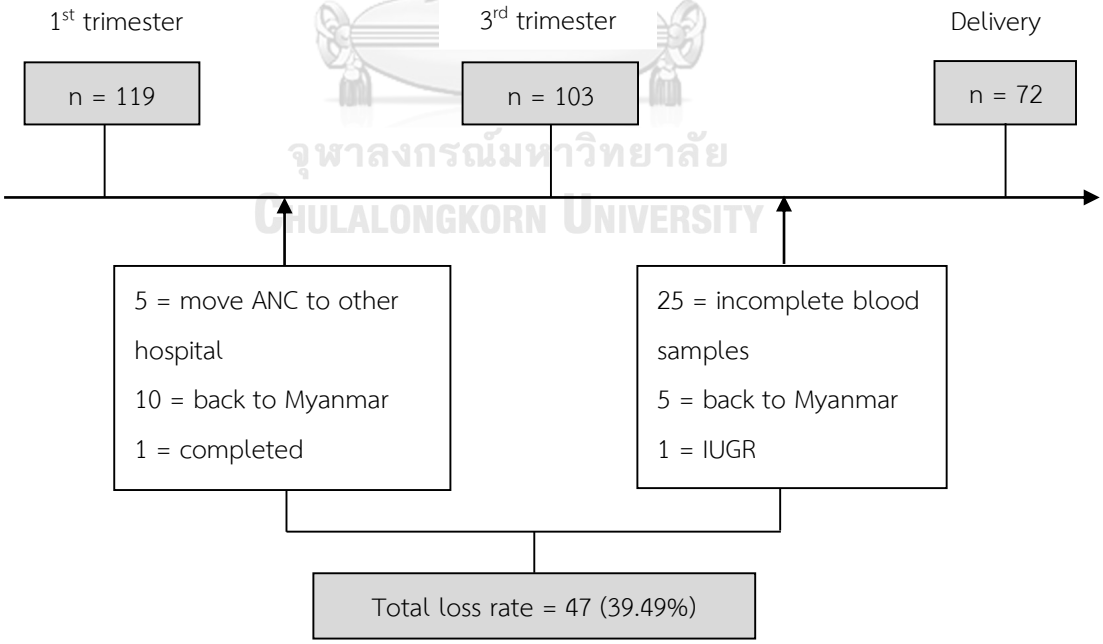


Figure 12 Flow diagram of participants

Baseline data collection was participated by 119 pregnant women and delivery of newborn was completed by 72. There was no significant difference for general characteristics of pregnancy between first trimester (n= 119) and delivery (n= 72). The average age (± SD) was 28.05 ± 4.22 (years) for first trimester and 28.79 ± 4.09 (years) for delivery. The average BMI in early pregnancy (± SD) was 23.64 ± 3.78 (kg/m^2) in first trimester and 23.73 ± 3.93 (kg/m^2) at delivery. Regarding monthly family income, the average (± SD) was 15400.00 ± 5303.22 (THB) in first trimester and 15534.72 ± 5181.20 (THB) at delivery. The average duration of residence in the study area (± SD) was 5.25 ± 2.81 (years) in first trimester and 5.82 ± 2.98 (years) at delivery. Regarding the ethnicity, Burmese was the most common group, 52 (43.7%) in first trimester and 28 (37.8%) at delivery. All of pregnant women in this cohort reported that they were officially married. Most of them had finished their secondary school education 44 (37.0%) in first trimester and 25 (35.7%) at delivery. Nearly 80% of pregnant women in both first trimester and delivery answered that they were employed during pregnancy. More than a half of pregnant women 67 (56.3%) have been pregnant in first trimester and 46 (63.9%). A few of them (about 5%) have history of hypertension before the present pregnancy. Regarding smoking and drinking behaviors, all of the pregnant women in this study were non-smokers and no history of drinking as well. More than 50% of pregnant women in first trimester reported that they have exposed to secondhand smoke during this pregnancy. About 70% of them in first trimester and delivery have reported that their residence was proximity to the factories. But the residential proximity towards the agricultural farms and constructions site were less than 20% and no difference between periods.

Table 7 General characteristics differences between first trimester and delivery

General characteristics	Myanmar migrants		p-value
	1st trimester (n=119)	Delivery (n=72)	
Age (years)	28.05 ± 4.22	28.79 ± 4.09	0.271[a]
BMI in early pregnancy (kg/m^2)	23.64 ± 3.78	23.73 ± 3.93	0.704[a]
Monthly family income (THB)	15400.00 ± 5303.22	15534.72 ± 5181.20	0.825[a]
Duration of stay in the study area (years)	5.25 ± 2.81	5.82 ± 2.98	0.170[a]
Ethnicity			0.886[b]
Burmese	52 (43.7)	28 (37.8)	
Karen	26 (21.8)	18 (24.3)	
Mon	16 (13.4)	11 (14.9)	
Others	25 (21.1)	17 (23.0)	
Education			0.827[b]
Able to read and write	14 (11.8)	6 (8.3)	
Primary school	36 (30.2)	24 (33.4)	
Secondary school	44 (37.0)	25 (35.7)	
High school and above	25 (21.0)	17 (23.6)	
Occupation			0.855[b]
Employed	95 (79.8)	56 (77.8)	
Unemployed	24 (20.2)	16 (22.2)	
Have been pregnant			0.368[b]
Yes	67 (56.3)	46 (63.9)	
No	52 (43.7)	26 (36.1)	
Number of previous child			0.657[b]
≥ 1 child	63 (52.9)	31 (43.1)	
No child	56 (47.1)	41 (56.9)	

Table 7 Continued

General characteristics	Myanmar migrants		p-value
	1st trimester (n=119)	Delivery (n=72)	
History of hypertension			0.735[b]
Yes	5 (4.2)	4 (5.6)	
No	114 (95.8)	68 (94.4)	
Family history of hypertension			0.865[b]
Yes	29 (24.4)	19 (26.4)	
No	90 (75.6)	53 (73.6)	
History of secondhand smoke exposure			0.300[b]
Yes	65 (54.6)	33 (45.8)	
No	54 (45.5)	39 (54.2)	
Residential proximity to the factories			0.520[b]
Yes	84 (70.6)	47 (65.3)	
No	35 (29.4)	25 (34.7)	
Residential proximity to the agricultural farms			1.000[b]
Yes	14 (11.8)	8 (11.1)	
No	105 (88.2)	64 (88.9)	
Residential proximity to the construction sites			0.455[b]
Yes	21 (17.6)	16 (22.2)	
No	98 (82.4)	56 (77.8)	

kg = kilogram, m = meter, THB = Thai Baht

Data were presented as mean ± standard deviation (mean ± SD) and number (frequency) (n, %)

[a] = Independent t test, [b] = Chi-square for test of homogeneity

4.2 Maternal blood biomarkers

Concentrations of each heavy metals (Pb, Hg, Cd, As) and BDNF were demonstrated in descriptive values: mean (± standard deviation SD), median (Interquartile range IQR), minimum and maximum. Heavy metals (Pb, Hg, As, Cd) and BDNF concentrations were detected in (μg/L). The detection rates of all biomarkers were 100 %. The standard values of some heavy metals levels according to CDC were Pb <50 μg/L and Hg <10 μg/L. Table 8 represents the descriptive analysis of maternal blood biomarkers concentrations and their detection rates in first trimester. And table 9 represents the results of those biomarkers in third trimester.

Table 8 Blood biomarkers concentrations and detection limits in first trimester

n = 119	Concentration				Detection	Standard
	Mean ± SD	Median (IQR)	Range		limits	CDC
Pb	30.66 (± 14.90)	27.40 (13.80)	12.00-125.40	μg/L	12.00	< 50
Hg	7.04 (± 4.17)	6.20 (5.60)	1.00-21.10	μg/L	1.00	< 10
Cd	0.90 (± 0.48)	0.91 (0.85)	0.18-2.56	μg/L	0.18	
As	4.13 (± 0.84)	4.00 (1.10)	2.70-6.80	μg/L	2.70	
BDNF	57.89 (± 21.20)	64.60 (15.60)	4.90-85.10	μg/L	4.90	

Table 9 Blood biomarkers concentrations and detection limits in third trimester

n = 72	Concentration				Detection	Standard
	Mean ± SD	Median (IQR)	Range		limits	CDC
Pb	21.96 (± 9.82)	19.90 (11.40)	6.00-62.00	μg/L	6.00	< 50
Hg	5.42 (± 20.57)	2.60 (2.00)	1.20-177.20	μg/L	1.20	< 10
Cd	1.02 (± 0.36)	1.06 (0.46)	0.17-1.98	μg/L	0.17	
As	3.87 (± 1.59)	3.40 (1.40)	2.00-11.10	μg/L	2.00	
BDNF	25.86 (± 20.37)	18.27 (23.40)	0.30-71.60	μg/L	0.3	

4.3 Factors affecting maternal blood heavy metals levels

4.3.1 Association between general characteristics of pregnancy and Pb exposure in first trimester

The association between general characteristics and Pb exposure in first trimester was presented in table 10. There were no statistically significant associations between general characteristics including (socio-demographics, health histories, health behaviors and environmental factors) and Pb-exposed groups (high Pb-exposed group [n = 59] and low Pb-exposed group [n = 60]) in first trimester. The average age (± SD) was 27.68 ± 4.21 (years) in the high-exposed group and 28.42 ± 4.23 (years) in the low-exposed group. Regarding BMI in early pregnancy, the average (± SD) was 23.75 ± 3.83 (kg/m^2) in high-exposed group and 23.54 ± 3.77 (kg/m^2) in low-exposed group. The average monthly family income (± SD) of high-exposed group, 15100.00 ± 5371.36 (THB) was lower than those of low-exposed group with 15700.00 ± 5262.13 (THB). About 50% of pregnant women in both high and low Pb-exposed groups were Burmese.

Table 10 Association between general characteristics of pregnancy and Pb exposure in first trimester

General characteristics	Total (n= 119)	Pb exposure		p-value
		High (n=59)	Low (n=60)	
Age (years)	28.05 ± 4.22	27.68 ± 4.21	28.42 ± 4.23	0.342[a]
BMI (kg/m^2)	23.64 ± 3.78	23.75 ± 3.83	23.54 ± 3.77	0.765[a]
Monthly family income (THB)	15415.97 ± 5303.22	15100.00 ± 5371.36	15700.00 ± 5262.13	0.524[a]
Duration of stay in the study area (years)	5.25 ± 2.82	4.85 ± 2.59	5.65 ± 2.99	0.121[a]
Ethnicity				0.652[b]
Burmese	52 (43.7)	27 (51.9)	25 (48.1)	
Others	67 (56.3)	32 (47.8)	35 (52.2)	

Table 10 Continued

General characteristics	Total (n= 119)	Pb exposure		p-value
		High (n=59)	Low (n=60)	
Education				0.769[b]
≤ Primary school	50 (42.2)	24 (48.0)	26 (52.0)	
> Primary school	69 (58.0)	35 (50.7)	34 (49.3)	
Occupational status				0.963[b]
Employed	95 (79.8)	47 (49.5)	48 (50.5)	
Unemployed	24 (2.2)	12 (50.0)	12 (50.0)	
Have been pregnant				0.054[b]
Yes	67 (56.3)	28 (41.8)	39 (58.2)	
No	52 (43.7)	31 (59.6)	21 (40.4)	
Secondhand smoke exposure				0.412[b]
Yes	65 (54.6)	30 (46.2)	35 (53.8)	
No	54 (45.4)	29 (53.7)	25 (46.3)	
Seafood consumption				0.653[b]
> Once a week	20 (16.8)	9 (45.0)	11 (55.0)	
≤ Once a week	99 (83.2)	50 (50.5)	49 (49.5)	
Hair coloring				0.924[b]
Yes	57 (47.9)	28 (49.1)	29 (50.9)	
No	62 (52.1)	31 (50.0)	31 (50.0)	
Amalgam filling				0.563[b]
Yes	12 (10.1)	5 (41.7)	7 (58.3)	
No	107 (89.9)	54 (50.5)	53 (49.5)	

Table 10 continued

General characteristics	Total (n= 119)	Pb exposure		p-value
		High (n=59)	Low (n=60)	
Residential proximity to the factories				0.795[b]
Yes	84 (70.6)	41 (48.8)	43 (51.2)	
No	35 (29.4)	18 (51.4)	17 (48.6)	
Residential proximity to the agricultural farms				0.094[b]
Yes	14 (11.8)	4 (28.6)	10 (71.4)	
No	105 (88.2)	55 (52.4)	50 (47.6)	
Residential proximity to the construction sites				0.777[b]
Yes	21 (17.6)	11 (52.4)	10 (47.6)	
No	98 (82.4)	48 (49.0)	50 (51.0)	

kg = kilogram, m = meter, THB = Thai Baht

Data were presented as mean ± standard deviation (mean ± SD) and frequency (n, %)

[a] = Independent t test, [b] = Chi-square test, [c] = Fisher's exact test (n < 5)

4.3.2 Association between general characteristics of pregnancy and Hg exposure in first trimester

Table 11 represents the association between general characteristics and Hg exposure in first trimester as the followings. There was a statistically significant association between the history of amalgam filling treatment before pregnancy and Hg exposure levels in first trimester (p-value = 0.047). About 75% of high Hg-exposed group (n= 57) had the history of taking amalgam filling treatment and 55.1% of low Hg-exposed group (n= 62) had no history of taking amalgam filling treatment.

There were no significant associations between the other characteristics and Hg exposure in first trimester. The average age (± SD) was 27.95 ± 4.04 (years) in high Hg-exposed group and 28.15 ± 4.40 (years) in low Hg-exposed group. Regarding BMI in early pregnancy the average (± SD) was 23.76 ± 3.90 (kg/m^2) in high-exposed group

and 23.52 ± 3.70 (kg/m^2) in low-exposed group. The average monthly income of the low Hg-exposed group 15800.00 ± 5474.64 (THB) was higher than that of high Hg-exposed group, 15000.00 ± 5127.38 (THB). More than half of the low Hg-exposed group (55.1%) had the education level above primary school and about 52% of high Hg-exposed group had the education level of primary school and lower. Most of the pregnant women in high and/or low Hg-exposed groups have stayed in the study area for an average of about 5 years.

Table 11 Association between general characteristics of pregnancy and Hg exposure in first trimester

General characteristics	Total	Hg exposure		p-value
	(n= 119)	High (n=57)	Low (n=62)	
Age (years)	28.05 ± 4.22	27.95 ± 4.04	28.15 ± 4.40	0.800[a]
BMI (kg/m^2)	23.64 ± 3.78	23.76 ± 3.90	23.52 ± 3.70	0.733[a]
Monthly family income (THB)	15415.97 ± 5303.22	15000.00 ± 5127.38	15800.00 ± 5474.64	0.424[a]
Duration of stay in the study area (years)	5.25 ± 2.82	5.25 ± 2.63	5.26 ± 2.99	0.981[a]
Ethnicity				0.973[b]
Burmese	52 (43.7)	25 (48.1)	27 (51.9)	
Others	67 (56.3)	32 (47.8)	35 (52.2)	
Education				0.446[b]
≤ Primary school	50 (42.2)	26 (52.0)	24 (48.0)	
> Primary school	69 (58.0)	31 (44.9)	38 (55.1)	
Occupational status				0.494[b]
Employed	95 (79.8)	47 (49.5)	48 (50.5)	
Unemployed	24 (2.2)	10 (41.7)	14 (58.3)	
Have been pregnant				0.480[b]
Yes	67 (56.3)	34 (50.7)	33 (49.3)	
No	52 (43.7)	23 (44.2)	29 (55.8)	

Table 11 continued

General characteristics	Total (n= 119)	Hg exposure		p-value
		High (n=57)	Low (n=62)	
Secondhand smoke exposure				0.960[b]
Yes	65 (54.6)	31 (47.7)	34 (52.3)	
No	54 (45.4)	26 (48.1)	28 (51.9)	
Seafood consumption				0.093[b]
> Once a week	20 (16.8)	13 (65.0)	7 (35.0)	
≤ Once a week	99 (83.2)	44 (44.4)	55 (55.6)	
Hair coloring				0.632[b]
Yes	57 (47.9)	26 (45.6)	31 (54.4)	
No	62 (52.1)	31 (50.0)	31 (50.0)	
Amalgam filling				**0.047[b]***
Yes	**12 (10.1)**	**9 (75.0)**	**3 (25.0)**	
No	**107 (89.9)**	**48 (44.9)**	**59 (55.1)**	
Residential proximity to the factories				0.477[b]
Yes	84 (70.6)	42 (50.0)	42 (50.0)	
No	35 (29.4)	15 (42.9)	20 (57.1)	
Residential proximity to the agricultural farm				0.123[b]
Yes	14 (11.8)	4 (28.6)	10 (71.4)	
No	105 (88.2)	53 (50.5)	52 (49.5)	
Residential proximity to the construction sites				0.322[b]
Yes	21 (17.6)	8 (38.1)	13 (61.9)	
No	98 (82.4)	49 (50.0)	49 (50.0)	

kg = kilogram, m = meter, THB = Thai Baht

Data were presented as mean ± standard deviation (mean ± SD) and frequency (n, %)

[a] = Independent t test, [b] = Chi-square test, [c] = Fisher's exact test (n < 5), * = p-value < 0.05

4.3.3 Association between general characteristics of pregnancy and Cd exposure in first trimester

The association between general characteristics of pregnant Myanmar migrants including socio-demographics, health histories, health behaviors, environmental factors and Cd exposure in first trimester was presented in the table 12. There were no statistically significant associations between these factors. The average age (± SD) of high Cd-exposed group was 27.73 ± 4.55 (years) and that of low Cd-exposed group was 28.37 ± 3.87 (years). Regarding BMI in early pregnancy, the average (± SD) was 23.71 ± 3.96 (kg/m^2) in high exposed group and 23.56 ± 3.63 (kg/m^2) in low exposed group. The average monthly income (± SD) was higher in the low Cd- exposed group 16200.00 ± 5519.22 (THB) than in the high Cd-exposed group, 14600.00 ± 4977.93 (THB). The average duration of stay in the study area (± SD) was 5.54 ± 3.10 (years) in high Cd-exposed group and 4.97 ± 2.49 (years) in low Cd-exposed group. The history of secondhand smoke exposure was 52.3% in the high Cd-exposed group and 47.7% in the low Cd-exposed group. The residential proximity to the construction sites was 57.1% in the high Cd-exposed group and 42.9% in the low Cd-exposed group.

Table 12 Association between general characteristics of pregnancy and Cd exposure in first trimester

General characteristics	Total	Cd exposure		p-value
	(n= 119)	High (n=59)	Low (n=60)	
Age (years)	28.05 ± 4.22	27.73 ± 4.55	28.37 ± 3.87	0.412[a]
BMI (kg/m^2)	23.64 ± 3.78	23.71 ± 3.96	23.56 ± 3.63	0.834[a]
Monthly family income (THB)	15415.97 ± 5303.22	14600.00 ± 4977.93	16200.00 ± 5519.22	0.084[a]
Duration of stay in the study area (years)	5.25 ± 2.82	5.54 ± 3.10	4.97 ± 2.49	0.267[a]

Table 12 continued

General characteristics	Total (n= 119)	Cd exposure		p-value
		High (n=59)	Low (n=60)	
Ethnicity				0.773[b]
Burmese	52 (43.7)	25 (48.1)	27 (51.9)	
Others	67 (56.3)	34 (50.7)	33 (49.3)	
Education				0.233[b]
≤ Primary school	50 (42.2)	28 (56.0)	22 (44.0)	
> Primary school	69 (58.0)	31 (44.9)	38 (55.1)	
Occupational status				0.615[b]
Employed	95 (79.8)	46 (48.4)	49 (51.6)	
Unemployed	24 (2.2)	13 (54.2)	11 (45.8)	
Have been pregnant				0.936[b]
Yes	67 (56.3)	33 (49.3)	34 (50.7)	
No	52 (43.7)	26 (50.0)	26 (50.0)	
Secondhand smoke exposure				0.514[b]
Yes	65 (54.6)	34 (52.3)	31 (47.7)	
No	54 (45.4)	25 (46.3)	29 (53.7)	
Seafood consumption				0.153[b]
> Once a week	20 (16.8)	7 (35.0)	13 (65.0)	
≤ Once a week	99 (83.2)	52 (52.5)	47 (47.5)	
Hair coloring				0.082[b]
Yes	57 (47.9)	33 (57.9)	24 (42.1)	
No	62 (52.1)	26 (41.9)	36 (58.1)	
Amalgam filling				0.976[b]
Yes	12 (10.1)	6 (50.0)	6 (50.0)	
No	107 (89.9)	53 (49.5)	54 (50.5)	

Table 12 continued

General characteristics	Total (n= 119)	Cd exposure		p-value
		High (n=59)	Low (n=60)	
Residential proximity to the factories				0.507[b]
Yes	84 (70.6)	40 (47.6)	44 (52.4)	
No	35 (29.4)	19 (54.3)	16 (45.7)	
Residential proximity to the agricultural farm				0.269[b]
Yes	14 (11.8)	5 (35.7)	9 (64.3)	
No	105 (88.2)	54 (51.4)	51 (48.6)	
Residential proximity to the construction sites				0.445[b]
Yes	21 (17.6)	12 (57.1)	9 (42.9)	
No	98 (82.4)	47 (48.0)	51 (52.0)	

kg = kilogram, m = meter, THB = Thai Baht

Data were presented as mean ± standard deviation (mean ± SD) and frequency (n, %)

[a] = Independent t test, [b] = Chi-square test, [c] = Fisher's exact test (n < 5)

4.3.4 Association between general characteristics of pregnancy and As exposure in first trimester

Table 13 represents the association between general characteristics and As exposure in first trimester. There was a statistically significant negative association between the history of hair coloring and As exposure (p-value = 0.007). Pregnant women with more history of hair coloring had lower As exposure.

There was no statistical association between the other general characteristics such as socio-demographics and environmental factors and As exposure. The average age (± SD) was (28.25 ± 3.95) years in the high As-exposed group and (27.88 ± 4.45) years in the low As-exposed group. The average monthly income (± SD) of low As-exposed group (15900.00 ± 5925.12) THB was higher than that of high As-exposed group (14800.00 ± 4449.81) THB. And 57.1% of the high As-exposed group had the

residential proximity to the agricultural farms and 55.2% in the low As-exposed group. About 70 % of pregnant in low As-exposed group had a history of hair coloring and about 30 % in high As-exposed group had the history of hair coloring.

There were no significant associations between the other characteristics and As exposure in first trimester. The average age (± SD) was 28.25 ± 3.95 (years) in high As-exposed group and 27.88 ± 4.45 (years) in low As-exposed group. Regarding BMI in early pregnancy the average (± SD) was 23.65 ± 3.57 (kg/m^2) in high As-exposed group and 23.62 ± 3.98 (kg/m^2) in low As-exposed group. The average monthly income of the high As-exposed group, 14800.00 ± 4449.81 (THB) was lower than that of high As-exposed group, 15900.00 ± 5925.12 (THB). Most of the pregnant women in high and/or low Hg-exposed groups have stayed in the study area for an average of about 5 years. Regarding seafood consumption, 13 (65%) in high As-exposed group reported a history of seafood consumption (more than once a week) and 7 (35%) in low As-exposed group reported that history. About 60% of pregnant in high As-exposed group reported the history of residential proximity towards the agricultural farm and that history was reported in 40 % of low As-exposed group.

Table 13 Association between general characteristics of pregnancy and As exposure in first trimester

General characteristics	Total	As exposure		p-value
	(n= 119)	High (n=55)	Low (n=64)	
Age (years)	28.05 ± 4.22	28.25 ± 3.95	27.88 ± 4.45	0.627[a]
BMI (kg/m^2)	23.64 ± 3.78	23.65 ± 3.57	23.62 ± 3.98	0.961[a]
Monthly family income (THB)	15415.97 ± 5303.22	14800.00 ± 4449.81	15900.00 ± 5925.12	0.249[a]
Duration of stay in the study area (years)	5.25 ± 2.82	4.71 ± 2.52	5.72 ± 2.98	0.051[a]
Ethnicity				0.702[b]
Burmese	52 (43.7)	23 (44.2)	29 (55.8)	
Others	67 (56.3)	32 (47.8)	35 (52.2)	

Table 13 continued

General characteristics	Total (n= 119)	As exposure		p-value
		High (n=55)	Low (n=64)	
Education				0.968[b]
≤ Primary school	50 (42.2)	23 (46.0)	27 (54.0)	
> Primary school	69 (58.0)	32 (46.4)	37 (53.6)	
Occupational status				0.966[b]
Employed	95 (79.8)	44 (46.3)	51 (53.7)	
Unemployed	24 (2.2)	11 (45.8)	13 (54.2)	
Have been pregnant				0.702[b]
Yes	67 (56.3)	32 (47.8)	35 (52.2)	
No	52 (43.7)	23 (44.2)	29 (55.8)	
Secondhand smoke exposure				0.700[b]
Yes	65 (54.6)	29 (44.6)	36 (55.4)	
No	54 (45.4)	26 (48.1)	28 (51.9)	
Seafood consumption				0.065[b]
> Once a week	20 (16.8)	13 (65.0)	7 (35.0)	
≤ Once a week	99 (83.2)	42 (42.4)	57 (57.6)	
Hair coloring				**0.007[b]***
Yes	**57 (47.9)**	**19 (33.3)**	**38 (66.7)**	
No	**62 (52.1)**	**36 (58.1)**	**26 (41.9)**	
Amalgam filling				0.345[b]
Yes	12 (10.1)	4 (33.3)	8 (66.7)	
No	107 (89.9)	51 (47.7)	56 (52.3)	

Table 13 continued

General characteristics	Total (n= 119)	As exposure		p-value
		High (n=55)	Low (n=64)	
Residential proximity to the factories				0.635[b]
Yes	84 (70.6)	40 (47.6)	44 (52.4)	
No	35 (29.4)	15 (42.9)	20 (57.1)	
Residential proximity to the agricultural farm				0.383[b]
Yes	14 (11.8)	8 (57.1)	6 (42.9)	
No	105 (88.2)	47 (44.8)	58 (55.2)	
Residential proximity to the construction sites				0.734[b]
Yes	21 (17.6)	9 (42.9)	12 (57.1)	
No	98 (82.4)	46 (46.9)	52 (53.1)	

kg = kilogram, m = meter, THB = Thai Baht

Data were presented as mean ± standard deviation (mean ± SD) and frequency (n, %)

[a] = Independent t test, [b] = Chi-square test, [c] = Fisher's exact test (n < 5), * = p-value < 0.05

4.4 Factors affecting the pregnancy outcomes

4.4.1 Factor affecting preeclampsia

Flow of the participants related to preeclampsia outcomes assessment was shown in figure 13.

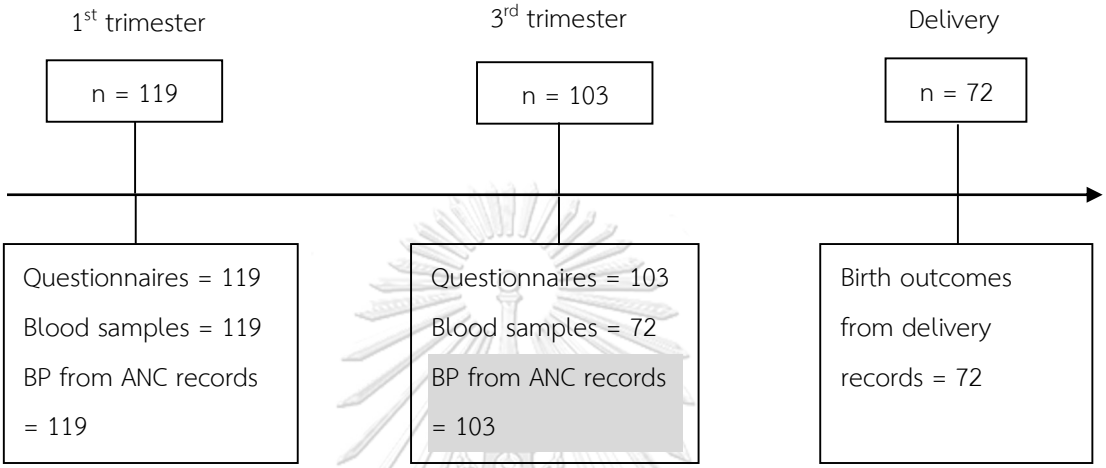


Figure 13 Flow of the participant related to preeclampsia

The systolic and diastolic BP of pregnant women were assessed in first trimester and third trimester. All of the participants in first trimester had BP within the normal values. In third trimester, 4 (3.47%) pregnant women had a high blood BP (systolic/diastolic) above the normal values (>140/90 mmHg) and they were diagnosed as preeclampsia.

The association between general characteristics and PE diagnosis in third trimester was examined. There was a significant association between BMI in early pregnancy and PE in third trimester (p-value= 0.005). The average BMI (± SD) of PE cases 28.87 ± 5.60 (kg/m^2) was significantly higher than that of non-PE cases whose BMI was 23.39 ± 3.70 (kg/m^2). There was also a significant association between the ethnic groups and PE cases (p-value= 0.023). There were 41 (39.8%) Burmese ethnic women in third trimester and all of PE cases were Burmese ethnicity.

There were no statistically significant associations between the other factors and preeclampsia in third trimester. The average age (± SD), 30.25 ± 4.11 (years) of PE cases was older than the average age, 28.16 ± 3.99 (years) of non-PE cases. The average monthly income (± SD) of PE cases, 14200.00 ± 5560.27 (THB) was less than

that the average income 15300.00 ± 5308.08 (THB) of non-PE cases. All of PE cases were Burmese ethnicity and they had an occupation in third trimester. Regarding history of hypertension, all of PE cases in third trimester reported no history of hypertension before the present pregnancy.

Table 14 Factors affecting preeclampsia in third trimester

Factors	Total (n=103)	PE (3rd trimester)		p-value
		Yes (n=4) (3.47%)	No (n=99) (86.09%)	
Age (years)	27.94 ± 4.14	30.25 ± 4.11	28.16 ± 3.99	0.308[a]
BMI in early pregnancy (kg/m^2)	**23.64 ± 3.83**	**28.87 ± 5.60**	**23.39 ± 3.70**	**0.005[a]***
Monthly family income (THB)	15308.70 ± 5316.55	14200.00 ± 5560.27	15300.00 ± 5308.08	0.694[a]
Duration of stay in the study area (years)	5.32 ± 2.80	5.25 ± 4.03	5.60 ± 2.80	0.812[a]
Ethnicity				**0.023[c]***
Burmese	**41 (39.8)**	**4 (9.8)**	**37 (90.2)**	
Others	**62 (60.2)**	**0**	**62 (100)**	
Education				1.000[c]
≤ Primary school	40 (38.8)	1 (2.5)	39 (97.5)	
> Primary school	63 (61.2)	3 (4.9)	60 (95.1)	
Occupational status				0.575[c]
Employed	81 (78.6)	4 (4.9)	77 (95.1)	
Unemployed	22 (21.4)	0	22 (100)	
Have been pregnant				0.634[c]
Yes	59 (57.3)	3 (5.1)	56 (94.9)	
No	44 (42.7)	1 (2.3)	43 (97.7)	

Table 14 continued

Factors	Total (n=103)	PE (3rd trimester)		p-value
		Yes (n=4) (3.47%)	No (n=99) (86.09%)	
Number of previous child				0.621[c]
≥ 1 child	55 (53.4)	3 (5.5)	52 (94.5)	
No child	48 (46.6)	1 (2.1)	47 (97.9)	
History of hypertension				1.000[c]
Yes	4 (3.9)	0	4 (100)	
No	99 (96.1)	4 (4.0)	95 (96.0)	
Family history of hypertension				1.000[c]
Yes	25 (24.3)	1 (4.0)	24 (96.0)	
No	78 (75.7)	3 (3.8)	75 (96.2)	
Secondhand smoke exposure				0.618[c]
Yes	51 (49.5)	1 (2.0)	50 (98.0)	
No	52 (50.5)	3 (5.8)	49 (94.2)	
Regular exercise				0.281[c]
Not daily	27 (26.2)	2 (7.4)	25 (92.6)	
Daily	76 (73.8)	2 (2.6)	74 (97.4)	
Seafood consumption				1.000[c]
≤ Once a week	83 (80.6)	4 (4.8)	79 (95.2)	
> Once a week	20 (19.4)	0	20 (100)	

kg = kilogram, m = meter, THB = Thai Baht

Data were presented as mean ± standard deviation (mean ± SD) and frequency (n, %)

[a] = Independent t test, [c] = Fisher's exact test (n < 5), * = p-value < 0.05

4.4.2 Factors affecting preterm birth among Myanmar migrants

Flow of the participants related to preterm birth outcomes was shown in the figure 14.

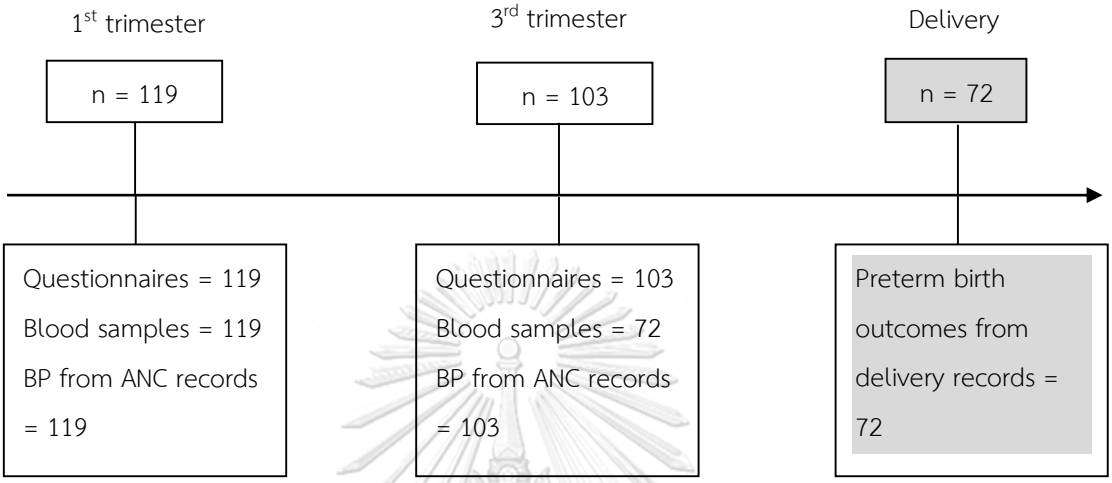


Figure 14 Flow of the participants related to preterm birth outcomes

According to table 15, there was a statistically significant association between BMI in early pregnancy and preterm birth (p-value = 0.002) and also between monthly family income and preterm birth (p-value = 0.011). The average BMI in early pregnancy (± SD) of preterm births was 27.50 ± 4.22 (kg/m^2) and that of normal full term births was 23.20 ± 3.62 (kg/m^2). The average monthly family income (± SD) of preterm births was 11400.00 ± 3004.62 (THB) and 16100.00 ± 5229.19 (THB) in normal full term births. However, there was no statistically significant associations between the other factors such as age, ethnicity or education and preterm births.

Table 15 Factors affecting preterm birth

Factors	Total (n=72)	Preterm		p-value
		Yes (n=9) (12.5%)	No (n=63) (87.5%)	
Age (years)	28.79 ± 4.09	28.22 ± 3.15	28.87 ± 4.22	0.658[a]
BMI in early pregnancy (kg/m^2)	**23.73 ± 3.93**	**27.50 ± 4.22**	**23.20 ± 3.62**	**0.002[a]***
Monthly family income (THB)	**15534.72 ± 5226.77**	**11400.00 ± 3004.62**	**16100.00 ± 5229.19**	**0.011[a]***
Duration of stay in the study area (years)	5.82 ± 2.98	6.33 ± 3.24	5.75 ± 2.96	0.584[a]
Ethnicity				0.297[c]
Burma	28 (38.9)	5 (17.9)	23 (81.1)	
Others	44 (61.1)	4 (9.1)	40 (90.9)	
Education				0.476[c]
≤ Primary school	30 (41.7)	5 (16.7)	25 (83.3)	
> Primary school	42 (58.3)	4 (9.5)	38 (90.5)	
Occupational status				1.000[c]
Employed	56 (77.8)	7 (12.5)	49 (87.5)	
Unemployed	16 (22.2)	2 (12.5)	14 (87.5)	
Have been pregnant				0.473[c]
Yes	46 (63.9)	7 (15.2)	39 (84.8)	
No	26 (36.1)	2 (7.7)	24 (92.3)	
Number of previous child				0.283[c]
≥ 1 child	41 (56.9)	7 (17.1)	34 (82.9)	
No child	31 (43.1)	2 (6.5)	29 (93.5)	
Secondhand smoke exposure				1.000[c]
Yes	33 (45.8)	4 (12.1)	29 (87.9)	
No	39 (54.2)	5 (12.8)	34 (87.2)	

Table 15 continued

kg = kilogram, m = meter, THB = Thai Baht

Data were presented as mean ± standard deviation (mean ± SD) and frequency (n, %)

[a] = Independent t test, [c] = Fisher's exact test (n < 5), * = p-value < 0.05

4.4.3 Factors affecting LBW newborns among Myanmar migrants

Flow of the participants related to LBW outcomes was shown in the figure 15.

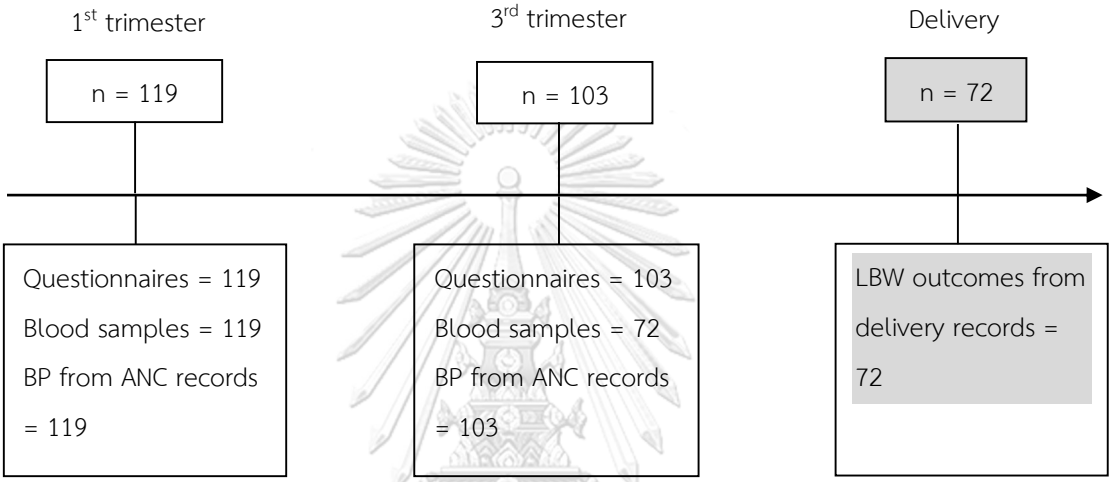


Figure 15 Flow of the participants related to LBW outcomes

Factors affecting LBW newborns among Myanmar migrants was mentioned in table 16 as follows. According to the table, there were 3 cases of LBW newborns among a total of 72 pregnant women. The statistically significant associations of LBW newborns were found for BMI in early pregnancy (p-value = 0,014) and monthly family income (p-value = 0.046). The average BMI in early pregnancy (± SD), 29.17 ± 5.75 (kg/m^2) was significantly higher in LBW newborns than that of normal birth weight newborns 23.50 ± 3.72 (kg/m^2). The average monthly income (± SD) of LBW newborns, 9666.67 ± 577.35 (THB) was significantly lower than that of normal birth weight newborns, 15800.00 ± 5189.36 (THB). The other factors of pregnancy such as age, ethnicity, education and occupation were not significantly associated with LBW newborns. Among the 3 LBW cases, 2 cases were Burmese ethnicity and another case was Mon ethnicity. All cases of mothers of LBW newborns had a history of occupation during the current pregnancy. Majority worked in the industrial sectors.

Table 16 Factors affecting LBW newborns

Factors	Total (n=72)	LBW		p-value
		Yes (n=3) (4.17%)	No (n=69) (95.83%)	
Age (years)	28.79 ± 4.09	28.00 ± 2.00	28.83 ± 4.16	0.735[a]
BMI in early pregnancy (kg/m^2)	**23.73 ± 3.93**	**29.17 ± 5.75**	**23.50 ± 3.72**	**0.014[a]***
Monthly family income (THB)	**15534.72 ± 5226.77**	**9666.67 ± 577.35**	**15800.00 ± 5189.36**	**0.046[a]***
Duration of stay in the study area (years)	5.82 ± 2.98	4.00 ± 1.73	5.90 ± 3.01	0.284[a]
Ethnicity				0.556[c]
Burmese	28 (38.9)	2 (7.1)	26 (92.9)	
Others	44 (61.1)	1 (2.3)	43 (97.7)	
Education				1.000[c]
≤ Primary school	30 (41.7)	1 (3.3)	29 (96.7)	
> Primary school	42 (58.3)	2 (4.8)	40 (95.2)	
Occupational status				1.000[c]
Employed	56 (77.8)	3 (5.4)	53 (94.6)	
Unemployed	16 (22.2)	0	16 (100.0)	
Have been pregnant				0.473[c]
Yes	46 (63.9)	2 (4.3)	44 (95.7)	
No	26 (36.1)	1 (3.8)	25 (96.2)	
Number of previous child				0.283[c]
≥ 1 child	41 (56.9)	2 (4.9)	39 (95.1)	
No child	31 (43.1)	1 (3.2)	30 (96.8)	
History of hypertension				1.000[c]
Yes	4 (5.6)	0	4 (100.0)	
No	68 (94.4)	3 (4.4)	65 (96.6)	

Table 16 continued

Factors	Total (n=72)	LBW		p-value
		Yes (n=3) (4.17%)	No (n=69) (95.83%)	
Secondhand smoke exposure				0.245[c]
Yes	33 (45.8)	0	33 (100.0)	
No	39 (54.2)	3 (7.7)	36 (92.3)	

kg = kilogram, m = meter, THB = Thai Baht

Data were presented as mean ± standard deviation (mean ± SD) and frequency (n, %)

[a] = Independent t test, [c] = Fisher's exact test (n < 5), * = p-value < 0.05

4.5 Effect of maternal blood heavy metals levels on BDNF

4.5.1 Effect of maternal blood heavy metals on BDNF in first trimester

There were a total of 119 pregnant completed blood samples collection in first trimester. Among them, 11 pregnant women have a very high (or) low extreme values of BDNF concentrations. Therefore, those 11 outliers were excluded and sub-sample analysis (n= 108) was done to find the association between blood heavy metals levels and BDNF concentrations. Flow of the participants related to BDNF assessment in first trimester was shown in the figure 18.

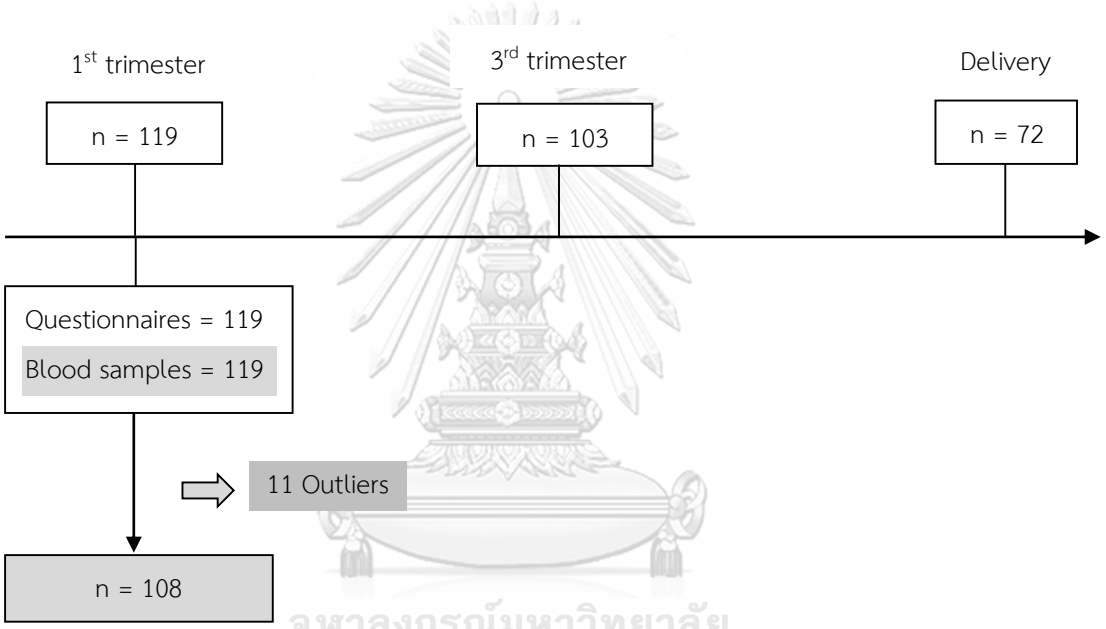


Figure 16 Flow of the participants related to BDNF levels in first trimester

Table 17 shows the binary logistic regression models examining the associations between blood heavy metal levels and plasma BDNF levels in first trimester. Test of normality was performed for BDNF concentrations and it was found that there was a non-normal distribution. Thus, the analyses were performed by categorizing each heavy metal (Pb, Hg, Cd, As) into 2 groups and BDNF into 2 groups: high exposed groups (≥ median), low exposed groups (< median). The multivariate model was adjusted for potential confounding factors, including age (years), BMI (kg/m^2), secondhand smoke exposure (yes or no) and history of regular aerobic exercise (yes or no). A statistically significant association was found between blood As

levels and plasma BDNF levels in the simple bivariate model (OR = 2.483, 95% CI: 1.142, 5.397, p-value = 0.022). Having a high blood AS level increased the odds of having low BDNF levels by 2.603 fold after adjusting for potential confounding factors (aOR = 2.603, 95% CI: 1.178, 5.751, p-value = 0.018). There were no significant associations between plasma BDNF levels and Pb, Hg, or Cd in either regression model.

Table 17 Binary logistic regressions for blood heavy metals (independent) and BDNF (dependent) in first trimester

Heavy metals (n= 108)	BDNF (High [ref.], Low)					
	High n (%)	Low n (%)	OR	95% CI	aOR	95% CI
Pb						
Low	28 (51.9)	26 (48.1)	1	Reference	1	Reference
High	26 (48.1)	28 (51.9)	1.160	0.545, 2.467	1.230	0.569, 2.660
Hg						
Low	26 (46.4)	30 (53.6)	1	Reference	1	Reference
High	28 (53.8)	24 (46.2)	0.743	0.348, 1.584	0.707	0.324, 1.541
Cd						
Low	25 (46.3)	29 (53.7)	1	Reference	1	Reference
High	29 (53.7)	54 (50.0)	0.743	0.349, 1.583	0.705	0.324, 1.531
As						
Low	**35 (60.3)**	**23 (39.7)**	**1**	**Reference**	**1**	**Reference**
High	**19 (38.0)**	**31 (62.0)**	**2.483***	**1.142, 5.397**	**2.603***	**1.178, 5.751**

Low exposed groups (< median), High exposed groups (≥ median)

Adjusted for Age (years), BMI (kg/m^2), Secondhand smoke exposure (Yes/ No), Regular exercise (Yes/ No)

OR = Crude Odd Ratio

aOR = Adjusted Odd Ratio

* p-value < 0.05

4.5.2 Effect of maternal blood heavy metals on BDNF in third trimester

There were a total of 72 pregnant completed blood samples collection in third trimester. Among them, 1 pregnant women has a very high (or) low extreme value of BDNF concentration. Therefore, that 1 outlier was excluded and sub-sample analysis (n= 71) was done to examine the association between heavy metals levels and BDNF concentrations. Flow of the participants related to BDNF assessment in first trimester was shown the figure 17.

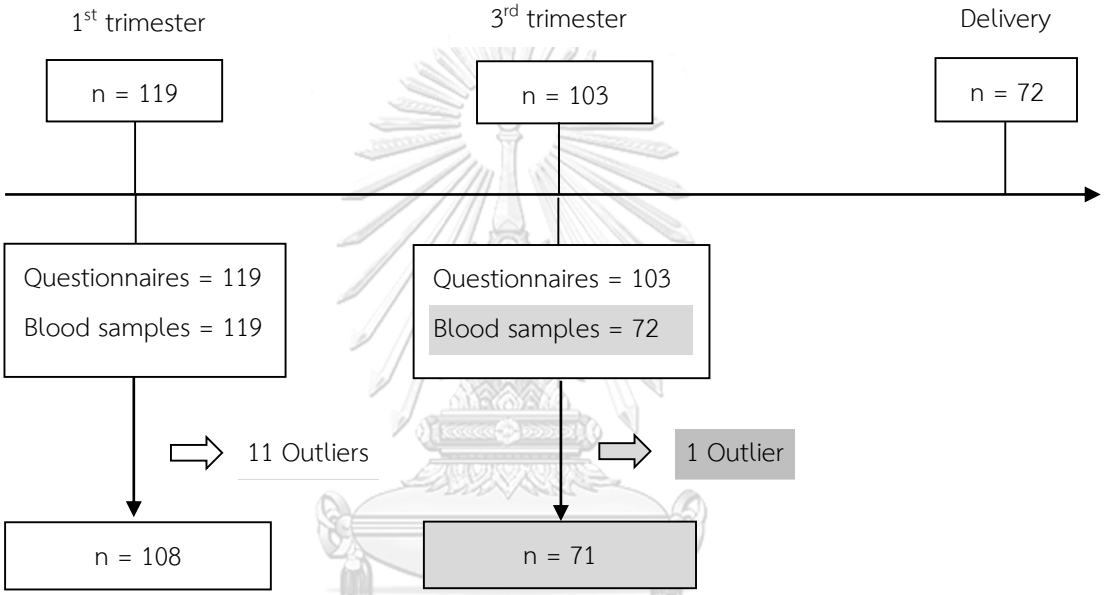


Figure 17 Flow of the participants related to BDNF levels in third trimester

Table 18 shows the binary logistic regression models examining the associations between blood heavy metal levels and plasma BDNF levels in third trimester. Test of normality was performed for third trimester-BDNF concentrations and it was found that there was a non-normal distribution. Thus, the analyses were performed by categorizing each heavy metal into 2 groups and BDNF into 2 groups: high exposed groups (≥ median), low exposed groups (< median). The multivariate model was adjusted for potential confounding factors, including age (years), BMI (kg/m^2), secondhand smoke exposure (yes or no) and history of regular exercise (yes or no). There were no significant associations between plasma BDNF levels and Pb, Hg, Cd or As in either regression model.

Table 18 Binary logistic regressions for blood heavy metals (independent) and BDNF (dependent) in third trimester

Heavy metals (n= 71)	BDNF (High [ref.], Low)					
	High n (%)	Low n (%)	OR	95% CI	aOR	95% CI
Pb						
Low	17 (48.6)	18 (51.4)	1	Reference	1	Reference
High	17 (50.0)	17 (50.0)	0.944	0.367, 2.428	0.892	0.330, 2.409
Hg						
Low	19 (51.4)	18 (48.6)	1	Reference	1	Reference
High	15 (46.9)	17 (53.1)	1.196	0.464, 3.085	1.176	0.439, 3.153
Cd						
Low	18 (51.4)	17 (48.6)	1	Reference	1	Reference
High	16 (47.1)	18 (52.9)	1.191	0.463, 3.064	1.088	0.406, 2.910
As						
Low	17 (47.2)	19 (52.8)	1	Reference	1	Reference
High	17 (51.5)	16 (48.5)	0.842	0.327, 2.168	0.779	0.290, 2.087

Low exposed groups (< median), High exposed groups (≥ median)

Adjusted for Age (years), BMI (kg/m^2), Secondhand smoke exposure (Yes/ No), Regular aerobic exercise (Yes/ No)

OR = Crude Odd Ratio

aOR = Adjusted Odd Ratio

4.6 Effect of maternal blood heavy metals on pregnancy outcomes

4.6.1 Association between maternal blood heavy metals in first trimester and blood pressures in third trimester

Flow of the participants related to pregnancy outcomes including BP levels in third trimester was shown the figure 18.

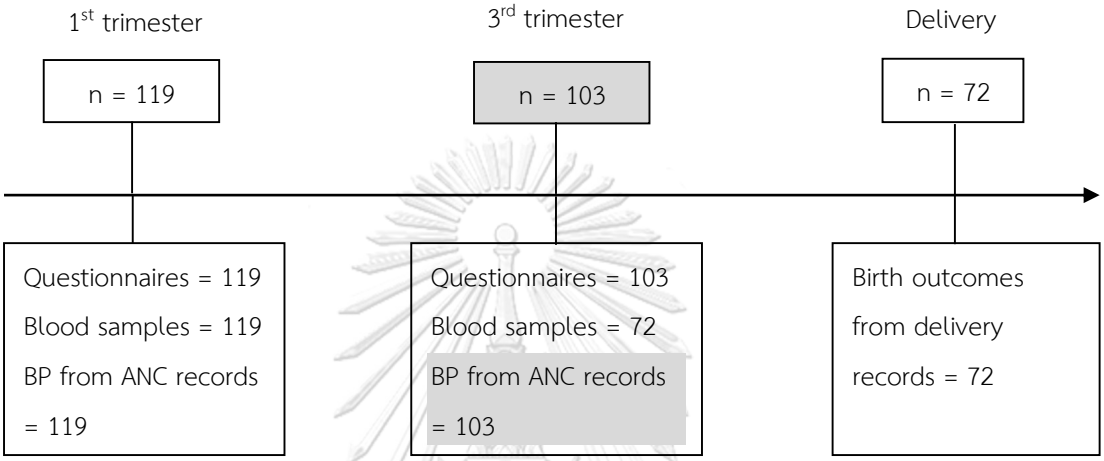


Figure 18 Flow of the participants related to BP assessment in third trimester

Assessment of BP was done in first and third trimesters. Diagnosis of PE was done in third trimester SBP/DBP >140/90 (mmHg). Table 19 shows the linear regression models examining the associations between blood heavy metal concentrations in first trimester and SBP (mmHg) in third trimester. Test of normality was performed and it was found that there was a normal distribution. Thus, the linear regression analyses was performed for continuous variables. The potential confounders including age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB) were adjusted in the models. There were no significant associations between SBP (mmHg) in third trimester and first trimester Pb, Hg, Cd or As in either regression models.

Table 19 Linear regressions for blood heavy metals in first trimester (independent) and SBP in third trimester (dependent)

Heavy metals (n = 103)	SBP in 3rd trimester (mmHg)					
	Unadjusted			Adjusted		
	β	p-value	95% CI	β	p-value	95% CI
Pb	1.126	0.451	-1.838, 4.090	0.962	0.488	-1.792, 3.717
Hg	0.776	0.936	-6.680, 8.232	2.079	0.555	-4.915, 9.073
Cd	4.829	0.181	-2.293, 11.950	3.953	0.243	-2.745, 10.652
As	-16.549	0.374	-53.415, 20.317	-8.843	0.613	-43.575, 25.889

Adjusted for age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB)

Table 20 shows the linear regression models examining the associations between blood heavy metal concentrations in first trimester and DBP (mmHg) in third trimester. The potential confounders including age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB) were adjusted in the models. There were no significant associations between DBP (mmHg) in third trimester and first trimester-Pb, Hg, Cd or As of in either regression models.

Table 20 Linear regressions for blood heavy metals in first trimester (independent) and DBP in third trimester (dependent)

Heavy metals (n= 103)	DBP in 3rd trimester (mmHg)					
	Unadjusted			Adjusted		
	β	p-value	95% CI	β	p-value	95% CI
Pb	2.181	0.097	-0.407, 4.769	2.095	0.098	-0.397, 4.586
Hg	2.381	0.474	-4.210, 8.971	3.396	0.293	-3.003, 9.795
Cd	1.453	0.652	-4.936, 7.841	0.832	0.791	-5.392, 7.055
As	-9.545	0.564	-42.348, 23.258	-4.094	0.799	-36.098, 27.910

Adjusted for age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB)

4.6.2 Association between maternal blood heavy metals in third trimester and blood pressures in third trimester

Flow of the participants related to pregnancy outcomes including BP levels in third trimester was shown the figure 19.

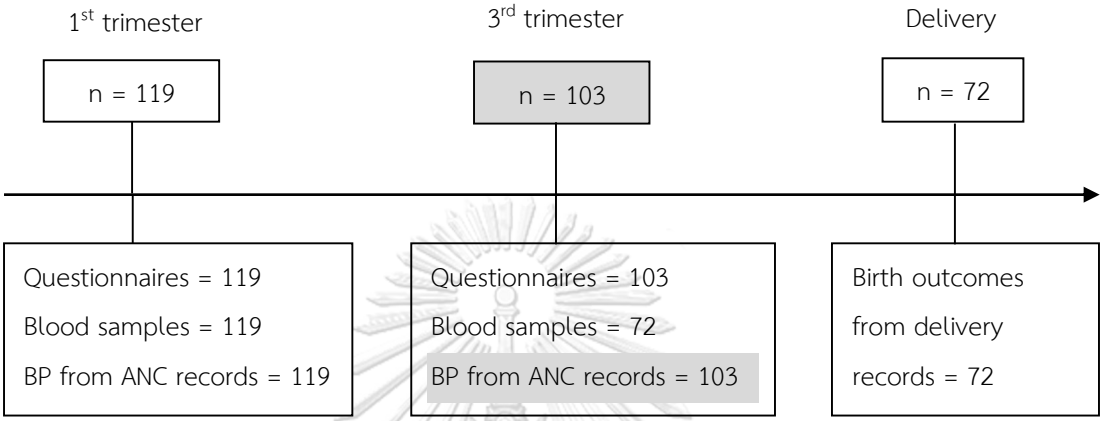


Figure 19 Flow of the participants related to BP assessment in third trimester

Table 21 shows the linear regression models examining the associations between blood heavy metal concentrations in third trimester and SBP (mmHg) in third trimester. The potential confounders including age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB) were adjusted in the models. There were no significant associations between SBP (mmHg) in third trimester and Pb, Hg, Cd or As of in either regression models.

Table 21 Linear regressions for blood heavy metals in third trimester (independent) and SBP in third trimester (dependent)

Heavy metals (n= 72)	SBP in 3rd trimester (mmHg)					
	Unadjusted			Adjusted		
	β	p-value	95% CI	β	p-value	95% CI
Pb	1.564	0.337	-1.662, 4.790	1.523	0.321	-1.521, 4.568
Hg	-0.512	0.511	-2.057, 1.033	-0.349	0.637	-1.821, 1.122
Cd	-4.582	0.290	-13.153, 3.989	-1.849	0.658	-10.151, 6.454
As	-13.869	0.165	-33.590, 5.852	-10.377	0.266	-28.837, 8.084

Adjusted for age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB)

Table 22 shows the linear regression models examining the associations between blood heavy metal concentrations in third trimester and DBP (mmHg) in third trimester. The potential confounders including age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB) were adjusted in the models. In adjusted models, there was a significant association between DBP (mmHg) in third trimester and blood Pb concentrations in third trimester. About 2.766 (mmHg) DBP in third trimester will be higher in every one unit increase of blood Pb concentrations in third trimester. There were no significant associations between DBP (mmHg) in third trimester and Pb, Hg, Cd or As of in either regression models.

Table 22 Linear regressions for blood heavy metals in third trimester (independent) and DBP in third trimester (dependent)

Heavy metals (n= 72)	DBP in 3rd trimester (mmHg)					
	Unadjusted			Adjusted		
	β	p-value	95% CI	β	p-value	95% CI
Pb	**2.742**	**0.055**	**-0.063, 5.547**	**2.766**	**0.048***	**0.026, 5.506**
Hg	0.001	0.999	-1.373, 1.376	0.118	0.863	-1.238, 1.474
Cd	-6.661	0.081	-14.157, 0.836	-5.040	0.187	-12.591, 2.511
As	-11.758	0.185	-29.269, 5.753	-9.355	0.276	-26.347, 7.637

Adjusted for age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB)

* = p-value < 0.05

4.6.3 Association between blood heavy metals in first and third trimester and gestational age at delivery

Flow of the participants related to birth outcomes at delivery was shown in the following figure 20.

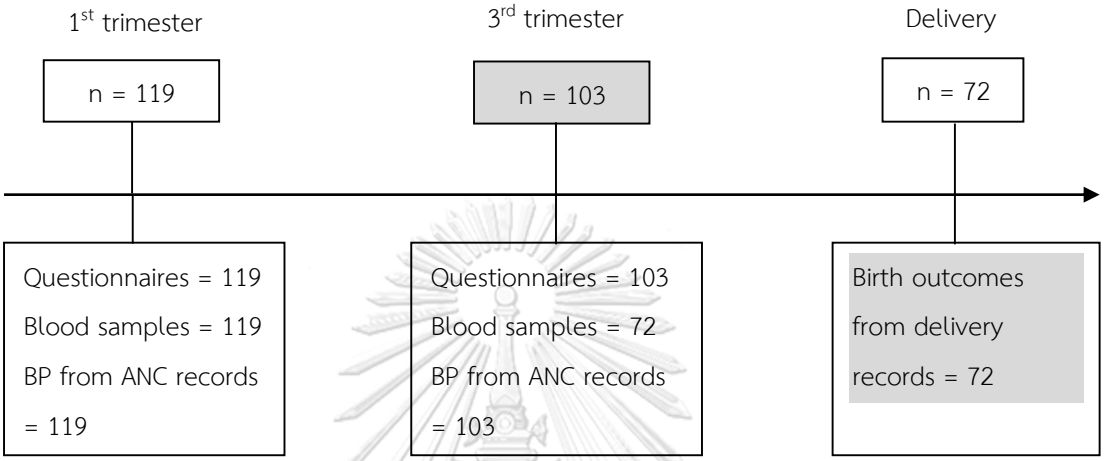


Figure 20 Flow of the participants related to birth outcomes at delivery

Birth outcomes of gestational age (weeks) at delivery were assessed from delivery records of the hospital. Table 23 shows the linear regression models examining the associations between blood heavy metal concentrations in first trimester and gestational age at delivery. The potential confounders including age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB) were adjusted in the models. In adjusted models, there was a positively significant association between gestational age (weeks) at delivery and blood As concentrations in first trimester. There were no significant associations between gestational age at delivery and first trimester-Pb, Hg or Cd in either regression models.

Table 23 Linear regressions for blood heavy metals in first trimester (independent) and gestational age at delivery (dependent)

Heavy metals (n= 72)	Gestational age (weeks)					
	Unadjusted			Adjusted		
	β	p-value	95% CI	β	p-value	95% CI
Pb	-0.051	0.731	-0.345, 0.243	-0.008	0.957	-0.287, 0.272
Hg	0.121	0.744	-0.616, 0.858	0.139	0.697	-0.569, 0.849
Cd	-0.423	0.236	-1.130, 0.283	-0.243	0.480	-0.924, 0.439
As	**4.606**	**0.011***	**1.107, 8.105**	**4.167**	**0.016***	**0.801, 7.534**

Adjusted for age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB)

Table 24 shows the linear regression models examining the associations between blood heavy metal concentrations in third trimester and gestational age at delivery. The potential confounders including age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB) were adjusted in the models. There were no significant associations between gestational age at delivery and third trimester-Pb, Hg, Cd or As in either regression models.

Table 24 Linear regressions for blood heavy metals in third trimester (independent) and gestational age at delivery (dependent)

Heavy metals (n= 72)	Gestational age (weeks)					
	Unadjusted			Adjusted		
	β	p-value	95% CI	β	p-value	95% CI
Pb	0.114	0.482	-0.207, 0.434	0.116	0.455	-0.192, 0.425
Hg	-0.055	0.476	-0.208, 0.098	-0.108	0.144	-0.255, 0.038
Cd	0.473	0.270	-0.374, 1.320	0.303	0.473	-0.534, 1.140
As	1.369	0.166	-0.582, 3.320	1.082	0.251	-0.783, 2.946

Adjusted for age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB)

4.6.4 Association between blood heavy metals in first and third trimester and birth weight of newborn at delivery

Birth outcomes on the weight (kg) of newborn at delivery were assessed from delivery records of the hospital. Table 25 shows the linear regression models examining the associations between blood heavy metal concentrations in first trimester and birth weight of newborn (kg) at delivery. The potential confounders including age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB) were adjusted in the models. There were no significant associations between birth weight of newborn (kg) at delivery and first trimester-Pb, Hg, Cd or As in either regression models.

Table 25 Linear regressions for blood heavy metals in first trimester (independent) and birth weight of newborn at delivery (dependent)

Heavy metals (n= 72)	Birth weight (kg)					
	Unadjusted			Adjusted		
	β	p-value	95% CI	β	p-value	95% CI
Pb	-0.002	0.971	-0.096, 0.092	-0.002	0.960	-0.098, 0.093
Hg	-0.063	0.597	-0.298, 0.173	-0.035	0.776	-0.276, 0.207
Cd	-0.031	0.789	-0.259, 0.197	-0.038	0.748	-0.270, 0.195
As	0.454	0.441	-0.714, 1.622	0.598	0.319	-0.591, 1.787

Adjusted for age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB)

Table 26 shows the linear regression models examining the associations between blood heavy metal concentrations in third trimester and birth weight (kg) of newborn at delivery. The potential confounders including age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB) were adjusted in the models. There were no significant associations between birth weight of newborn at delivery and third trimester-Pb, Hg, Cd or As in either regression models.

Table 26 Linear regressions for blood heavy metals in third trimester (independent) and birth weight of newborn at delivery (dependent)

Heavy metals (n= 72)	Birth weight (kg)					
	Unadjusted			Adjusted		
	β	p-value	95% CI	β	p-value	95% CI
Pb	0.027	0.607	-0.076, 0.129	0.033	0.538	-0.073, 0.138
Hg	0.003	0.916	-0.046, 0.052	0.004	0.868	-0.046, 0.055
Cd	0.020	0.884	-0.253, 0.293	0.073	0.613	-0.213, 0.358
As	-0.221	0.488	-0.851, 0.410	-0.177	0.584	-0.817, 0.464

Adjusted for age (years), BMI in early pregnancy (kg/m^2), monthly family income (THB)

CHAPTER V

DISCUSSIONS

5.1 General characteristics of pregnant Myanmar migrants in Thailand

In this study, there were a total of 119 participants recruited in the first trimester and 72 participants in the third trimester. The general characteristics of those participants in the first trimester and third trimester were found as no significant differences. It was found that most of the characteristics of Myanmar migrants in this study were similar to the previous findings. The average age was 28 years old and it was within the less risky range of maternal age to carry the pregnancy (Gossett, Nayak, Bhatt, & Bailey, 2013). Regarding the ethnicity in this cohort, it was found that most of Myanmar migrants visited to the ANC clinic were Burmese, Karen, Mon and Dewi. Among them, about 50% pregnant women were Burmese. It is consistent to the previous report which has mentioned that the most common ethnic groups of Myanmar migrants in Thailand were Burmese (44.1%) (Chantavanich & Vungsiriphisal, 2012). About one-third of participants have reported that they had finished the secondary school leveled education in Myanmar. More than 80% of them have occupation during their first ANC visit and even in the third trimester visit. Among those who have reported as working in pregnancy, over 90% were general workers from the industrial sectors and others were from the agriculture and domestic works. It was found that the average duration of stay in the study area was 5 years. Most of them have reported that they worked in the same factory (or) industry throughout their stays in the study area. This finding may be supportive for their potential to continuous exposure towards environmental heavy metals. It was noted that an average BMI in early pregnancy was 23.64 ± 3.78 (kg/m^2) in first trimester (n= 119) and 23.73 ± 3.93 (kg/m^2) at delivery (n= 72). According to the Asian BMI cut-offs, underweight is (BMI<18.5 kg/m^2), overweight is (23.0–27.4 kg/m^2), and obesity is (≥27.5 kg/m^2). The additional trigger points of Asian population BMI for public health action were identified as 23 kg/m^2 or higher, representing increased risk (WHO Expert Consultation, 2014). Therefore, pregnant women in this study can be assumed as at risk of overweight implications.

More than half of pregnant women reported that they have been pregnant (i.e., parity 1) and the majority were second pregnancy. Regarding health history and health behaviors, a few of them (about 5%) have a history of hypertension before pregnancy. The potential exposure towards heavy metals was assessed in terms of residential proximity towards the risky places such as factories, agricultural farms and construction sites. About 70% of participants have stayed near to the factories. Because maternal residential proximity to the industrial complexes have been studied in several population, it can be assumed that pregnant women in this study were at risk of exposure to heavy metals pollution. Previous studies also found that residential proximity to the industries was associated with increased risk of adverse pregnancy outcomes (Sarov et al., 2008) and LBW (Bhopal, Tate, Foy, Moffatt, & Phillimore, 1999).

5.2 Maternal blood biomarkers

For biomarker assessment, blood heavy metal concentrations were measured by using ICP-MS and plasma BDNF by ELISA kits. Both the first and third trimester BDNF concentrations in our study were much lower than those found in a previous study on Peruvian pregnant women (N. Yang et al., 2017). Although previous studies have examined broader populations of pregnant women, only Myanmar migrants with similar characteristics were focused in this study. Therefore, the difference BDNF levels could be due to genetic, racial, and/or physical lifestyle variations. Thus, more studies focusing on the other races and lifestyles and providing detailed comparisons among individuals of differing racial backgrounds and lifestyles are needed.

Maternal blood heavy metals (Pb, Hg, Cd, As) concentrations were examined two times (first and third trimester). In comparing to the previous findings, the median concentrations of Pb and Hg were lower than the CDC standard levels. But Pb concentrations in a few of them were higher than the CDC references (NIOSH., 2015). The median levels Cd were above the standard levels for the US general population (CDC., 2012) (ATSDR., 2012). The median As concentration was higher than that found in Canadian women (S. E. Adrienne et al., 2016) but lower than that found in Iranian women (Mohsen, Kazuhito, Takehisa, Atsuko, & Katsumi, 2015). Previous studies were not specific about the characteristics of the participants. In this study, it was focused on the migrant population, and the unique socio-demographic characteristics and health behaviors may have contributed to some different levels of heavy metal concentrations in the early stages of their pregnancies.

5.3 Factors affecting maternal blood heavy metals levels

The associations between general characteristic factors and heavy metals exposure were examined in this study. Having a history of taking Hg-containing amalgam filling treatment was significantly associated with Hg exposure. This significant association can be discussed according to the previous knowledge and findings. The WHO has recommended the dental amalgam fillings as the major sources of Hg exposure in the general population. Moreover, many studies have examined the association between the amalgam filling and high Hg exposure. One of these studies has assessed the exposed Hg levels in the scalp hair and saliva of Iranian women with amalgam fillings. They demonstrated that the amalgam filling could be the determinant of Hg exposure and amalgam can cause the increased absorption of Hg (Fakour, Esmaili-Sari, & Zayeri, 2010). Most of previous studies used saliva and/or scalp hairs biomarkers and found the significant associations with high Hg-exposed level for amalgam filling. In this study, whole blood Hg biomarker was used for Hg exposure and the association between blood Hg levels and the history of amalgam filling treatment was found among migrants population.

It was also found that having a history of hair coloring within three months before the first ANC visit was negatively associated with As exposure. Most of pregnant women who had a history of hair coloring were found in the low As exposure group. But, there were no associations between hair coloring and Pb and Cd. There are limited findings between hair coloring and As exposure in the previous studies. Nowadays, the use of hair dyes has been increased particularly in Asian countries. The effect of hair coloring and uses of hair dyes on high levels of metals ions has been demonstrated. They have assessed the hair levels of Pb, Cd and other trace elements among women with history of hair dyes (Ozbek & Akman, 2016), but lack of findings related to As.

5.4 Factors affecting pregnancy outcomes

In this study, the important pregnancy outcomes including SBP and DBP, gestational age and birth weight at delivery, diagnosis of PE, preterm delivery and LBW were studied. It was found that BMI in early pregnancy was significantly associated with PE in third trimester. The average early pregnancy BMI of all PE cases was about 29 kg/m^2 which can be identified as overweight. Maternal pre-pregnancy overweight or obesity was regarded as one of the strongest potentially modifiable risk factors for PE (Bodnar, Catov, Klebanoff, Ness, & Roberts, 2007). The incidence of high BMI in early pregnancy has consequently increased in some low and middle-income countries. And the role of early pregnancy BMI becomes an important concern for maternal and child health implications (Villamor et al., 2006). Previous studies in rural India and Pakistan have demonstrated that BMI in early pregnancy was related to increased risk of hypertensive diseases in pregnancy, preeclampsia and eclampsia. They have concluded that overweight or high BMI pregnant women had a significant risk of increased perinatal mortality rate (Short et al., 2018). Many studies have reported that obesity was associated with inflammation and oxidative stress which were proposed to participate in the pathophysiology of preeclampsia (Roberts & Gammill, 2005) (Bodnar, Ness, Markovic, & Roberts, 2005). Although the underlying mechanisms of the relationship between BMI and PE are still limited, the findings in this study may support the existing knowledge.

This study found that Burmese ethnicity was significantly associated with PE diagnosis in third trimester. About a half of pregnant Myanmar migrants have reported their ethnicity as Burmese and all of diagnosed PE cases in third trimester were Burmese women. This finding may be explained by reviewing previous findings about the relationship between the Myanmar migrants' utilization of Thai health services and the ethnicity. They have mentioned about the link between the more health beliefs in spirits and herbal medicine and the less utilization of health services. They found that those kinds of believes were higher among Karen than Burmese (Isarabhakdi, 2004). Burmese women may have less herbal concerns about their high blood pressure and food consumption. Therefore, it can be assumed that Burmese ethnicity and PE in the third trimester were significantly associated in this

study. Moreover, previous studies in the UK and Uganda have examined the significant relationship between black ethnicity and PE (Webster et al., 2018) (Madar-Shapiro et al., 2018). They stated that genetic variations for the placentation was related to the higher risk of PE in the blacks (Nakimuli et al., 2014). Others factors such as social and cultural differences and medical influences might affect our findings. However, there were no other significant factors related to the diagnosis of PE in third trimester.

Regarding birth outcomes, the early pregnancy BMI (kg/m^2) and monthly family income (THB) had statistically significant associations with both preterm birth and LBW. It was found that most of preterm birth and LBW cases have higher BMI in early pregnancy and less monthly family income than normal cases. But no association was found between other socio-economic factors. These findings are comparable to previous studies and existing knowledge. For example, a study in China has showed that obese and overweight Chinese women diagnosed in early pregnancy had higher risk of preterm delivery (T. Wang, Zhang, Lu, Xi, & Li, 2011). A study in Russia has also found a significant association between maternal early pregnancy BMI and risk of preterm birth (Sharashova, Anda, & Grjibovski, 2014). A previous Chilean study has demonstrated that there was a statistically significant association between maternal BMI in early pregnancy and birth weight of the newborn (Caradeux et al., 2016). It is well known that socio-economic factors including income, economy and educational level of mothers are associated with adverse pregnancy outcomes. The higher income was associated with improved birth outcomes (Burris & Hacker, 2017). A study in the southern Brazil has demonstrated that economic inequalities resulting from income were related with the risk of preterm birth (Sadovsky et al., 2018). A study in the US has also pointed out the role of maternal or family income in the risk of adverse birth outcomes. They found a significant relationship between poor income and preterm birth, small for gestational age and LBW (Parker, Schoendorf, & Kiely, 1994).

5.5 Effect of maternal blood heavy metal level on BDNF

The associations between maternal blood heavy metals levels and plasma BDNF levels in first and third trimester of pregnancy were examined in this study. A statistically significant association was found between blood As levels and plasma BDNF levels during first trimester of pregnancy. Pregnant women with a high blood As levels had a 2.6-fold increased risk of low plasma BDNF levels in comparison with the low blood As group. The present findings are consistent with those of previous in vitro and in vivo studies although the existing human studies are limited. Prior studies have found that As can significantly reduce the expression of BDNF. Researchers have tested low BDNF expression in the carbonic anhydrase 1 (CA1) and dentate gyrus areas of the dorsal hippocampus by administering tap water containing As to mice (Sun, Wang, Yu, Yu, & Xiao, 2015). Another study proved that As can reduce mitochondria membrane potential (MMP) and decrease BDNF gene expression in As-treated human neuroblastoma SH-SY_5Y cells (Chou, Lin, Kong, Chen, & Hwang, 2013). As induces hippocampal neuronal apoptosis via upregulated bone morphogenic protein 2 (BMP2) and Smad-dependent attenuation of the BDNF TrkB pathway, resulting in cognitive impairments (Rukmani et al., 2017). Sub-chronic As exposure in a mouse model of chemically-induced depression has also been found to enhance depression-related behaviors via the cerebral prefrontal cortex's BDNF-TrkB signaling pathway (Chang et al., 2015). Taken together, the above findings confirm that As and BDNF are significantly associated with each other via neurotoxicity and cognitive impairment mechanisms.

Regarding the role of As for this study, it can be discussed according to the significant factors of As in the previous findings. As and its compounds have been used for many purposes in different settings, such as industrial (e.g., alloy manufacturing, pigment manufacturing, electronics, and leather preservatives) and agricultural (e.g., pesticides, herbicides, and insecticides) (IARC., 2012). Consumption of contaminated drinking water and food are the main routes of As exposure in humans. Dermal exposure to As is also common. However, specific sources and routes of exposure was not specified in this study. Previous studies have demonstrated that As induces multiple disease pathways, and chronic exposure to

As has diverse effects on the central nervous system (Rodriguez, Jimenez-Capdeville, & Giordano, 2003). The neurological effects of As are most commonly found in the hippocampus region of the brain, which plays a major role in carrying environmental signals (Sweatt, 2004). Via toxicological activity, As exposure first produces functional alterations in the brain. Second, it alters molecules in the hippocampus, where it affects BDNF and results in cognitive function changes (Sun et al., 2015). Even low exposure to As can induce cognitive dysfunction (Naujokas et al., 2013). One study demonstrated that As has a direct effect on oxidative stress and on imbalances of defensive anti-oxidative mechanisms and neurotransmitter metabolism in the hippocampus (Xi et al., 2010). In addition, perinatal As exposure can result in developmental neurotoxicity, with abrupt changes in the reactive oxygen species (ROS), oxidative stress, mitochondrial functions, and apoptosis in the developing brain (Chandravanshi et al., 2018).

The present findings may be considered as an important concern for the relationship between As exposure and depression in pregnancy. Studies have found that chronic low-level As exposure has a positive association with the prevalence of depression and neurobehavioral symptoms among Indian women of child-bearing age. A recent cohort study also found an association between low-level As exposure in pregnancy and postpartum depression symptoms among Chilean women without any history of depression. The researchers measured As concentrations in urine samples and used the standard Edinburgh Postpartum Depression Scale to estimate depressive symptoms (Valdés, Hanchey, Muñoz, Baumert, & Iglesias, 2017). These accumulated findings suggested that As exposure in pregnancy plays an important role in increasing the burden of depression in women. Researchers have also assessed As exposure levels by analyzing contaminated groundwater samples and assessed depressive symptoms using a subjective symptoms questionnaire (Mukherjee, Bindhani, Saha, Sinha, & Ray, 2014). In this study, As exposure was measured in whole blood and a statistically significant association was found with BDNF level in first trimester. Therefore, the results of this study appear to support the existing body of research. However, there were no significant association between

them in third trimester pregnancy. The depressive symptoms was not assessed in this study and such an assessment should be considered in future studies.

In this study of migrant pregnant women, no significant association was found between Pb, Hg, or Cd and BDNF during the first and third trimester. Therefore, these findings on Pb, Hg, and Cd were inconsistent with those of previous experiments. Evidence of the effects of other heavy metals (Pb, Hg, Cd) on BDNF has also been found in previous studies. For example, Pb exposure in rats causes persistent alteration of BDNF expression, leading to long-term potentiation dysfunction and impaired neuronal plasticity (Guilarte, Mcglothan, & Nihei, 2000). Cd can compel downregulation of BDNF in the mechanism of neuronal cell death (Durczok et al., 2005). In addition to causing individual effects, heavy metals can also cause neurotoxicity in the hippocampus in a mixed-mode fashion. This mixture exhibits common effects on BDNF, which intensifies the resulting cognitive dysfunction. In the hippocampus, there are dynamic interactions between heavy metals and neurochemicals (e.g., N-methyl-D-aspartate [NMDA], acetylcholine esterase [AchE], and calcium ions [Ca]). These interactions can cause poor neuronal cell integrity via downregulation of BDNF and other antioxidants (e.g., catalase and superoxide dismutase [SOD]). This is followed by an imbalance between the defensive elements and reactive oxygen species (ROS), which is known as oxidative stress. Oxidative stress leads to neuronal cell death and ultimately cognitive dysfunction (Hashimoto, Shimizu, & Iyo, 2004) (Gavazzo et al., 2008) (Ceccatelli et al., 2010) (Karri et al., 2016) (Stackelberg et al., 2013). In addition, a very recent study found that Pb exposure was negatively associated with serum BDNF concentration among preschool Chinese children. Although the researchers also assessed other metals, including Hg, they found no associations between these other metals and BDNF (Zhou et al., 2019). The inconsistent findings in this study may be explained in such that this is the first human study to examine the association between heavy metals and BDNF in early pregnancy. Further studies using larger sample sizes should be conducted.

5.6 Effect of maternal blood heavy metal level on pregnancy outcomes

Pregnancy outcomes including preeclampsia, preterm birth and low birth weight of newborns were assessed in this study. The association between blood heavy metals in first and third trimester and pregnancy outcomes was examined. A statistically significant association was found between blood Pb concentrations in third trimester and DBP in third trimester. These findings are consistent to those of previous studies although the existing knowledge on the effect of prenatal Pb exposure on BP of migrant workers are still limited. A prior study in the US has examined a significant association between low-leveled Pb exposure and the elevated BP in late pregnancy. They measured umbilical cord Pb levels and assessed SBP and DBP during admission and delivery. They compared BP measurements between those in the highest and lowest quartiles of Pb levels. And they found that a 6.87-mmHg (1.51–12.21 mmHg) of admission SBP and a 4.40-mmHg (0.21–8.59 mmHg) of admission DBP were significantly increased after confounders adjustment (Wells et al., 2011). The present study assessed the maternal blood Pb concentrations and BP in first and third trimester. Moreover, it has been demonstrated that Pb exposure had a significant effect on BP of female Pb-exposed workers. They have discussed that Pb may induce changes in lipoprotein metabolism which may be an important role in the mechanism of increased BP among female workers (Nomiyama et al., 2002). A study in Pb-polluted region of China has found that blood Pb levels were significantly associated with increased SBP and DBP among the adult-aged (20-44 years old) population, most apparently in women (Lu et al., 2015). A positive association between blood Pb level and high BP (SBP, DBP) and high morbidity of hypertension has also been found among highly Pb-exposed occupational Chinese population (Han et al., 2018). A previous animal study have also examined the association between BP exposure and BP in rats. They included control and experiment groups where the treatment was given with 100 ppm of Pb in the drinking water. They found that BP of the Pb-treated rats was significantly elevated from the first week of Pb exposure and remained the same level over a month (Fioresi et al., 2014). But there was no significant association between Pb concentration and SBP in either first or third trimester.

Role of Pb on BP for this study can be discussed according to the significant factors of Pb in prior researches. It is well-known that Pb exposure can induce the multi-organ effect in the human body. Many studies have discussed on the mechanisms of underlying effect of Pb on BP but it has not been elucidated. Previous researches have demonstrated that Pb affects directly on the excitability and contractility of the heart, alters the compliance of vascular smooth muscle tissue and causes a direct effect on the parts of CNS which are important for the regulation of BP (Nash et al., 2003) (Kopp, Barron, & Tow, 1988). A prior study has mentioned that Pb has an effect on angiotensin II-induced renal vasoconstriction which may precede the development of high BP and hypertension (Robles et al., 2007). Another study has described that hypertension in Pb-exposed cases may be induced by decreased NO levels and subsequent vasoconstriction rather than decreased renal blood flow (Dursun, Arifoglu, Süer, & Keskinol, 2005). Some researchers have indicated that BP changes by Pb was not related to the alteration of kidney functions (Lu et al., 2015). Therefore, the present findings may support the existing knowledge, however, further researches will be needed to elucidate the mechanism of Pb effect on the BP or incidence of hypertension.

Regarding the gestational age, it was assessed from the delivery records and the association with heavy metals exposure in first and third trimesters was also examined. A positively significant association was found between blood As concentrations in first trimester and gestational age of newborn at delivery. But these findings are inconsistent to the previous researches because they have mentioned the negatively significant association between these factors. A study in Bangladesh have examined the effect of prenatal heavy metals exposure on the gestational length among a high risk population living near the mining sites. They collected maternal and umbilical cord blood samples at delivery to examine the levels of heavy metals exposure. They found that increased maternal blood As concentration was significantly associated with decreased gestational length (Claus et al., 2016). A strong negative causal relationship between prenatal As exposure and gestational age has also been reported in a prospective cohort. They performed analyses of gestational age in continuous variables and suggested that their results might be

useful to use in the clinical definition of preterm birth, i.e., ≤ 37 weeks gestation (Kile et al., 2016). They assessed As exposure from personal drinking water at enrollment and toenails samples in postpartum. This study assessed As exposure in maternal whole blood during first and third trimester. Therefore, different population and different exposure levels may impact the inconsistent findings with previous studies.

In this study, there were no significant associations between Pb, Hg or Cd and birth outcomes although previous epidemiological studies have found the significant associations between Pb, Hg or Cd and birth outcomes. A study in Mexico has examined the relationship of maternal plasma Pb levels in each trimester and the gestational length. They found that the length of gestation was adversely impacted by prenatal Pb exposure mainly in first trimester of pregnancy. But they estimated the length of gestation by the date of recalled last menstrual period (LMP) which might be weakness (Cantonwine et al., 2010). In this study, the gestational age of the newborn was estimated using both date of LMP and ultrasound. Significant associations between prenatal Pb exposure and preterm birth have been examined in many populations, e.g., Chinese population (Li et al., 2017) and Massachusetts population (Perkins et al., 2014). A study in Shoshone country of Idaho has found that maternal exposure to airborne Pb emissions was significantly associated with LBW or birth weight (Berkowitz, Price-Green, Bove, & Kaye, 2006). Effect of prenatal Hg exposure on the gestational age has also been reported in a Philippine study. They assessed the levels of Hg exposure in maternal blood, breast milk, umbilical cord blood, infant's hair and meconium. And they found a significant relationship between cord blood Hg levels and gestational age (Ramirez, Cruz, Pagulayan, Ostrea, & Dalisay, 2000). A cohort study in China has found that each in-unit increase in urinary Cd concentration (μg/g creatinine) was significantly associated with decreased gestational age and increased likelihood of preterm birth. They estimated the gestational age using both the woman's LMP and ultrasound findings (J. Yang et al., 2016). A study in Japan has reported that the gestational age was significantly correlated with maternal urinary Cd concentrations (Nishijo et al., 2002). A positive association between maternal blood Cd levels and risk of preterm birth has been shown on Japanese population (Tsuji et al., 2018). In addition, it was also found that

elevated placental Cd levels were significantly related with a reduced birth weight and LBW newborns (Freire et al., 2019).

Despite many inconsistent findings, this study was consistent to some existing studies which have found no significant association between these factors. A recent study in Turkey has reported that there were no significant associations between Pb, Hg, Cd concentrations in maternal blood, urine or amniotic fluid and the incidence of preterm birth (Yıldırım et al., 2019). A retrospective cohort in the US has found that there were no statistically significant differences in gestational age or birth weight between occupationally Pb-exposed and control groups (Lin, Hwang, Marshall, & Marion, 1998). There were some studies which have reported no significant associations between maternal Hg exposure and adverse birth outcomes. For example, a Chinese birth cohort did not find the significant associations between maternal exposure to Hg and birth weight and other anthropometric measurements (Ding et al., 2013). A study in UK has found that moderate blood Hg levels in pregnancy were not associated with birth weight or on the odds of preterm birth or LBW (C.M. Taylor, J. Golding, & A.M. Emond, 2016). A prospective study in the US has also observed no association between prenatal Hg exposure and either preterm birth or LBW (Bashore et al., 2014). Researchers examined whether the treatment of Hg containing dental fillings in pregnancy increased the risk of LBW. They found no significant associations between these factors (Hujoel et al., 2005).

CHAPTER VI

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

To identify the association between maternal blood heavy metals level and BDNF among Myanmar migrants, concentrations of blood heavy metals (Pb, Hg, Cd, As) and plasma BDNF were collected two times across the pregnancy and measured using standard tools. Binary logistic regressions were used and potential confounding variables such as age, BMI in early pregnancy, history of secondhand smoke exposure and regular exercise were adjusted. About 62% of women in high As-exposed group had low BDNF levels and only 37.9% of women in low As-exposed group had low BDNF levels. The results indicate that plasma BDNF was associated with whole blood As levels during early pregnancy among Myanmar migrants in Thailand. Pregnant women in high As-exposed group were 2.603 risk of low BDNF level than those in low exposed group during first trimester. But no association was found between Pb, Hg, or Cd and plasma BDNF in this population.

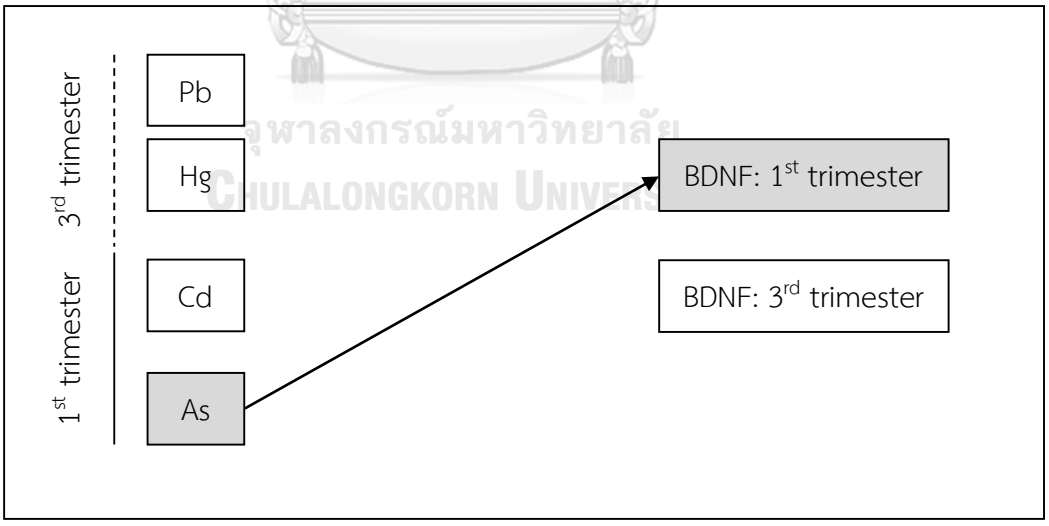


Figure 21 Association between maternal blood heavy metal level and BDNF

To identify the associations between maternal blood heavy metals level and pregnancy outcomes among Myanmar migrants, blood heavy metals concentrations were measured two times across the pregnancy using standard measurement tools. Pregnancy outcomes were reviewed from the clinical records of the hospital. Linear regression models were used by adjusting potential confounding factors such as age, BMI in early pregnancy and monthly family income. The results indicate that DBP (mmHg) in third trimester was higher in every unit of increased third trimester blood Pb concentrations. Moreover, the present findings demonstrate that gestational age (weeks) was associated with first trimester As levels. But no association was found between Hg, or Cd and pregnancy outcomes in this population.

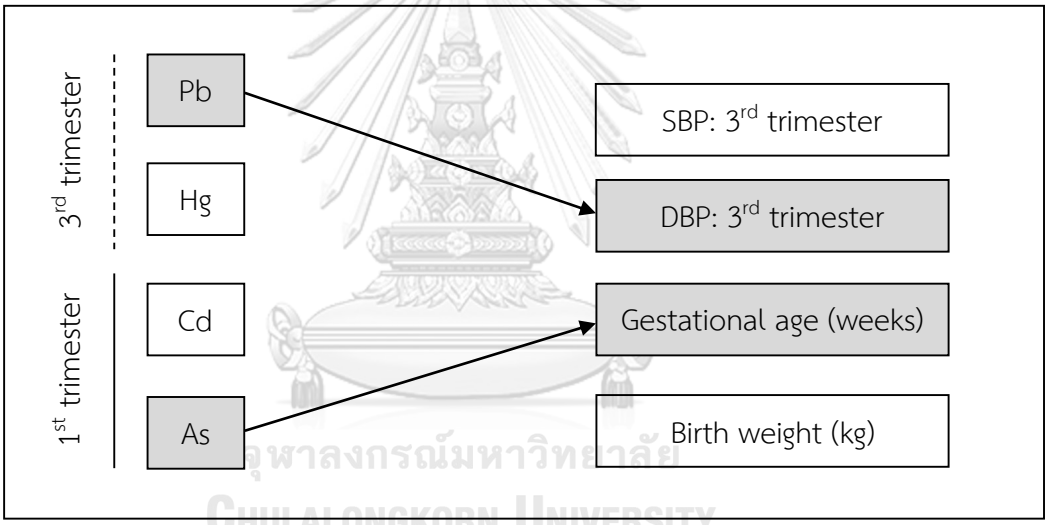


Figure 22 Association between maternal blood heavy metal level and pregnancy outcomes

To find the factors related to exposed heavy metals levels among Myanmar migrants, the associations between general characteristics of pregnant Myanmar migrants and each heavy metals were examined. History of taking amalgam filling treatment was associated with higher blood Hg levels in early pregnancy. About 75% of pregnant having history of taking amalgam filling treatment had high Hg-exposed levels and only 44.9% of women without any filling treatment had low Hg-exposed levels. In addition, history of hair coloring or hair dyes was inversely associated with lower blood As levels in early pregnancy. Only 33.3% of pregnant women with a

history of hair coloring (or) hair dyes during the present pregnancy had high blood As levels and 66.7% of them had low blood As levels in first trimester.

To find the risk factors affecting pregnancy outcomes among Myanmar migrants, it was examined the associations between general characteristics of pregnancy and the interested pregnancy outcomes including SBP/DBP for preeclampsia, gestational age at birth for preterm birth and birth weight of newborn at delivery. There were 4 cases of preeclampsia: SBP/DBP> 140/90 (mmHg), 9 cases of preterm birth: gestational age <37 weeks at delivery and 3 cases of LBW: birth weight of newborn <2500g (or) 2.5kg. This study demonstrates that preeclampsia in third trimester was significantly associated with high BMI in early pregnancy and Burmese ethnicity. The average early pregnancy BMI of preeclampsia pregnant women: 28.87 ± 5.60 (kg/m^2) was significantly higher than that of pregnant women with no preeclampsia: 23.39 ± 3.70 (kg/m^2). All of pregnant women with preeclampsia are Burmese.

The results present that both preterm birth and low birth weight were significantly associated with high BMI in early pregnancy and low monthly family income. The average early pregnancy BMI of women given preterm birth: 27.50 ± 4.22 (kg/m^2) was significantly higher than that of women given term birth: 23.20 ± 3.62 (kg/m^2). Also the average early pregnancy BMI of low birth weight cases: 29.17 ± 5.75 (kg/m^2) was significantly higher than that of normal birth weight cases: 23.50 ± 3.72 (kg/m^2). Regarding monthly family income, the average income of preterm birth cases: 11400.00 ± 3004.62 (THB) was significantly lower than that of term birth cases: 16100.00 ± 5229.19 (THB). Also the average income of low birth weight cases: 9666.67 ± 577.35 (THB) was significantly lower than that of normal birth weight cases: 15800.00 ± 5189.36. The findings conclude that Burmese ethnic, pregnant Myanmar migrants with poor socio-economic status had more risk of adverse pregnancy outcomes.

To assess maternal blood heavy metals and BDNF concentrations among Myanmar migrants, whole blood heavy metals concentration (Pb, Hg, Cd, As) were measured two times: first and third trimester and plasma BDNF concentrations two times: first and third trimester. Standard measurement tools were used for laboratory analysis and all concentrations have been detectable. The concentrations were mentioned in mean (± Standard deviation [SD]), and median (Interquartile Range [IQR]) as follows.

1) Pb (μg/L)

   30.66 (± 14.90), 27.40 (13.80) in first trimester

   21.96 (± 9.82), 19.90 (11.40) in third trimester

2) Hg (μg/L)

   7.04 (± 4.17), 0.62 (0.56) in first trimester

   5.42 (± 20.57), 2.60 (2.00) in third trimester

3) Cd (μg/L)

   0.90 (± 0.48), 0.91 (0.85) in first trimester

   1.02 (± 0.36), 1.06 (0.46) in third trimester

4) As (μg/L)

   4.13 (± 0.84), 4.00 (1.10) in first trimester

   3.87 (± 1.59), 3.40 (1.40) in third trimester

5) BDNF (μg/L)

   57.89 (± 21.20), 64.60 (15.60) in first trimester

   25.86 (± 20.37), 18.27 (23.40) in third trimester

6.2 Benefits and strength

1) This is the first Myanmar migrant birth cohort measuring exposed heavy metals levels and pregnancy outcomes.

2) This is the first study measuring BDNF concentrations among migrant population. The findings will be introduced to the role of BDNF in pregnancy mental health among Myanmar migrants.

3) This is the first study on the association between heavy metals and BDNF across the pregnancy among migrant population.

4) A total of four outcomes including BDNF, preeclampsia, preterm birth and low birth weight could be studied.

5) The significant association between maternal blood As levels and plasma BDNF during early pregnancy was first demonstrated. The association might be supportive for the environmental and occupational preventive measures on As exposure during pregnancy.

6) The association between blood Pb concentration and systolic BP might be supportive for the environmental and occupational preventive measures on Pb exposure during pregnancy.

6.3 Limitations

There are some limitations of this study that might have affected the results.

1) The small sample size of Myanmar migrants with similar socio-demographic characteristics limits the generalizability of the study results to other populations.
2) Total loss to follow up rate of this study is 39.49% which might affect the findings.
3) Our study did not consider the genetic variations within the participant population that could affect metal absorption and distribution.
4) The sources of heavy metal exposure were also unspecified in our study, which should be considered in the future.
5) We used a self-report questionnaire to measure the health related behaviors which is another weakness of our study.
6) We measured BDNF using ELISA kits that can detect both mature BDNF and its precursor, proBDNF, under specificity of antibody. Thus, we were not able to differentiate between these 2 BDNF expressions in this study. Concerning the differential diagnostic properties of BDNF expression, the authors of a previous study have suggested that mature BDNF is associated with depressive disorder, and proBDNF is associated with bipolar disorder (Hashimoto, 2015) (Yoshida et al., 2012). In future studies, it would be better to use advanced ELSIA kits that can differentiate between mature BDNF and proBDNF.

6.4 Recommendations

1) Future large-scale birth cohorts are recommended to confirm our findings.
2) Further researches will be needed to study the concentrations of BDNF during the postpartum and among the offspring to estimate the effects of maternal risks on the fetus.
3) Prenatal As exposure should be concerned for decreased BDNF levels and pregnancy mental health consequences throughout the pregnancy.
4) Prenatal Pb exposure should be also concerned for high BP in third trimester, preeclampsia and other consequences.
5) The sources of As and Pb exposures and their routes of contamination should be evaluated in the future studies.
6) Health education for the awareness on the prevention of As and Pb exposures should be introduced to the migrants and local residents.
7) The health authority and local government should concern for policy implementation of Pb and As exposure among Myanmar migrants as well as general population living proximity to the industrial plant. Public health interventions to address both exposure conditions and associated risk factors should be promoted to improve the health of the Myanmar migrants.

REFERENCES

Abalos, E., Cuesta, C., Carroli, G., Qureshi, Z., Widmer, M., Vogel, J. P., & Souza, J. P. (2014). Preeclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *International Journal of Obstetrics & Gynaecology, 121*, 14-24.

Acheson A, Concover JC, Fandl JP, DeChiara TM, Russell M, Thadani A, . . . Lindsay RM. (1995). A BDNF autocrine loop in adult sensory neurones prevents cell death. *Nature, 374*(6521), 450-453.

Adrienne, S., & Anne, G. (2010). *Guidelines for the identification and management of lead exposure in pregnant and lactating women*. Atlanta, GA: U.S. Department of Health and Human Services.

Adrienne, S. E., Tye, E. A., Mandy, F., Chun, L. L., Karelyn, D., Ciprian, M. C., . . . William, D. F. (2016). Arsenic levels among pregnant women and newborns in Canada: Results from the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort. *Environmental Research, 153*, 8-16.

Ahamed, M., Mehrotra, P. K., Kumar, P., & Siddiqui, M. K. (2009). Placental lead-induced oxidative stress and preterm delivery. *Environental Toxicology Pharmacology, 27*, 70-74.

Al-Saleh, I., Shinwari, N., Mashhour, A., Mohamed Gel, D., & Rabah, A. (2011). Heavy metals (lead, cadmium and mercury) in maternal, cord blood and placenta of healthy women. *International Journal of Hygiene and Environmental Health, 214*(2), 79-101.

American College of Obstetricians and Gynecologists. (2013). Task Force on Hypertension in Pregnancy. *Obstetrics and Gynecology, 122*(5), 1122-1131.

Andrews, K. W., Savitz, D. A., & Hertz-Picciotto, I. (1994). Prenatal lead exposure in relation to gestational age and birth weight: A review of epidemiologic studies. *American Journal Industrial Medicine, 26*(1), 13-32.

Angell, N. F., & Lavery, J. P. (1982). The relationship of blood lead levels to obstetric

outcome. *American Journal Obstetrics and Gynecology, 142*(1), 40-46.

Anisur, R., Marie, V., Allan, H. S., Barbro, N., Mohammed, Y., Shams, E. A., . . . Eva-Charlotte, E. (2009). Arsenic exposure during pregnancy and size at birth: A prospective cohort study in Bangladesh. *American Journal of Epidemiology, 169*(3), 304-312.

ATSDR. (2012). *Toxic guide for Cadmium*. Retrieved from https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=48&tid=15

Bailey, K., & Fry, R. C. (2014). Long-term health consequences of prenatal arsenic exposure: links to the genome and the epigenome. *Reviews on Environmental Health, 29* (1-2), 9-12.

Bangkok: Pollution Control Department. (2015). *Thailand State of Pollution Report*. Retrieved from http://infofile.pcd.go.th/mgt/PollutionReport2015_en.pdf

Bashore, C. J., Geer, L. A., He, X., Puett, R., Parsons, P. J., Palmer, C. D., & Sapkota, A. (2014). Maternal mercury exposure, season of conception and adverse birth outcomes in an urban immigrant community in Brooklyn, New York, U.S.A. *International Journal of Environmental Research on Public Health, 11*(8), 8414–8442.

Bathina, S., & Das, U. N. (2015). Brain-derived neurotrophic factor and its clinical implications. *Archives of Medical Science, 11*(6), 1164–1178.

Bayat, F., Akbari, S. A., Dabirioskoei, A., Nasiri, M., & Mellati, A. (2016). The realtionship between blood lead level and preeclampsia. *Electronic Physician, 8*(12), 3450-3455.

Berkowitz, Z., Price-Green, P., Bove, F., & Kaye, W. E. (2006). Lead exposure and birth outcomes in five communities in Shoshone County, Idaho. *International Journal of Hygiene and Environmental Health, 209*(2), 123-132.

Bernad, R. (2000). *Fundamentals of biostatistics* (5th ed.): Cengage Learning.

Bhopal, R. S., Tate, J. A., Foy, C., Moffatt, S., & Phillimore, P. R. (1999). Residential proximity to industry and adverse birth outcomes. *Lancet, 354*(9182), 920-921.

Binder, D. K., & Scharfman, H. E. (2004). Brain-derived neutrophic factor. *Growth factors, 22*, 123-131.

Blencowe, H., Cousens, S., Chou, D., Oestergaard, M., Say, L., Moller, A. B., . . . Lawn, J.

(2013). Born too soon: the global epidemiology of 15 million preterm births. *Reproductive Health, 10*

Bodnar, L. M., Catov, J. M., Klebanoff, M. A., Ness, R. B., & Roberts, J. M. (2007). Prepregnancy Body Mass Index and the Occurrence of Severe Hypertensive Disorders of Pregnancy. *Epidemiology, 18*(2), 234-239.

Bodnar, L. M., Ness, R. B., Markovic, N., & Roberts, J. M. (2005). The Risk of Preeclampsia Rises with Increasing Prepregnancy Body Mass Index. *Annals of Epidemiology, 15*(7), 475-482.

Boerleider, R. Z., Roeleveld, N., & Scheepers Paul, T. J. (2017). Human biological monitoring of mercury for exposure assessment. *AIMS Environmental Sciences, 4*(2), 251-276.

Bose-O'Reilly, S., McCarty, K. M., Steckling, N., & Lettmeier, B. (2010). Mercury exposure and children's health. *Current Problems in Pediatric and Adolescent Health Care, 40*(8), 186-215.

Bradl, H. (2002). *Heavy metals in the environment: Origin, interaction and remediation* (Vol. 6): London: Academic Press.

Burris, H. H., & Hacker, M. R. (2017). Birth outcome racial disparities: A result of intersecting social and environmental factors. *Seminars in Perinatology, 41*(6), 360-366.

Cantonwine, D., Hu, H., Sánchez, B. N., Lamadrid-Figueroa, H., Smith, D., Ettinger, A. S., . . . Téllez-Rojo, M. M. (2010). Critical windows of fetal lead exposure: adverse impacts on length of gestation and risk of premature delivery. *Journal of Occupational and Environmental Medicine, 52*(11), 1106-1111.

Caradeux, J., Serra, R., Palmeiro, Y., Correa, P. J., Valenzuela, I., Olguin, J., . . . Illanes, S. (2016). Correlation between Maternal Characteristics during Early Pregnancy, Fetal Growth Rate and Newborn Weight in Healthy Pregnancies. *Journal of Occupational and Environmental Medicine, 81*(3), 202-206.

Carmen, D., & Carla, A. (2003). *Global burden of hypertensive disorders of pregnancy in the year 2000*. Geneva: Evidence and Information for Policy, World Health Organization.

CDC. (2010). *Guidelines for the identification and management of lead exposure in*

pregnant and lactating women. . Atlanta (GA): Centers for Disease Control and Prevention,.

CDC. (2012). *Fourth national report on human exposure to environmental chemicals*. Retrieved from https://www.cdc.gov/exposurereport/index.html

Ceccatelli, S., Daré, E., & Moors, M. (2010). Methylmercury induced neurotoxicity andapoptosis. *Chemico-Biological Interactions, 188*(2), 301-308.

Chaiyaraa, R., Ngoendeeb, M., & Kruatrachue, M. (2013). Accumulation of Cd, Cu, Pb, and Zn in water, sediments, and mangrove crabs (Sesarma mederi) in the upper Gulf of Thailand. *Sciences Asia, 39*, 376-383.

Chandravanshi, L. P., Gupta, R., & Shukla, R. K. (2018). Developmental Neurotoxicity of Arsenic: Involvement of Oxidative Stress and Mitochondrial Functions. *Biological Trace Element Research, 186*(1), 185-198.

Chang, C. Y., Guo, H. R., Tsai, W. C., Yang, K. L., Lin, L. C., Cheng, T. J., & Chuu, J. J. (2015). Subchronic Arsenic Exposure Induces Anxiety-Like Behaviors in Normal Mice and Enhances Depression-Like Behaviors in the Chemically Induced Mouse Model of Depression. *Biomed Research International*, 159015.

Chantavanich S, & Vunsiriphisal P. (2012). *Myanmar migrants to Thailand: economic analysis and implications to Myanmar development*. Retrieved from Bangkok Research Center, Bangkok, Thailand:

Chantavanich, S., & Vungsiriphisal, P. (2012). *Myanmar Migrants to Thailand: Economic Analysis and Implications to Myanmar Developmet*. Retrieved from Bangkok, Thailand:

Chen B, Dowlatshahi D, MacQueen GM, Wang JF, & Young LT. (2001). Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol Psychiatry, 50*, 260-265.

Cho, G. J., Kim, L. Y., Min, K. J., Sung, Y. N., Hong, S. C., Oh, M. J., . . . Kim, H. J. (2015). Prior cesarean section is associated with increased preeclampsia risk in a subsequent pregnancy. *BMC Pregnancy Childbirth, 15*(1), 24.

Chou, C. T., Lin, W. F., Kong, Z. L., Chen, S. Y., & Hwang, D. F. (2013). Taurine prevented cell cycle arrest and restored neurotrophic gene expression in arsenite-treated SH-SY5Y cells. *Amino Acids, 45*, 811-819.

Christian, L. M., Mitchell, A. M., Gillespie, S. L., & Palettas, M. (2016). Serum brain-derived neurotrophic factor (BDNF) across pregnancy and postpartum: Associations with race, depressive symptoms, and low birth weight. *Psychoneuroendocrinology, 74*, 69–76.

Chuang, H. Y., Schwartz, J., Gonzales-Cossio, T., Lugo, M. C., Palazuelos, E., Aro, A., & Hernandez-Avila, M. (2001). Interrelations of lead levels in bone, venous blood, and umbilical cord blood with exogenous lead exposure through maternal plasma lead in peripartum women. *Environmental Health Perspectives, 109*(5), 527-532.

Chunhabundit, R. (2016). Cadmium exposure and potential health risk from foods in contaminated area, Thailand. *Toxicological Research, 32*(1), 65-72.

Clarkson, T. W. (1987). Metal toxicity in the central nervous system. *Environmental Health Perspectives, 75*(15), 59-64.

Claus, H. B., Ettinger, A. S., Hopkins, M. R., Jim, R., Amarasiriwardena, C., Christiani, D. C., & Wright, R. O. (2016). Prenatal arsenic exposure and birth outcomes among a population residing near a mining-related superfund site. *Environmental Health Perspectives, 124*(8), 1308-1315.

Coonrod, D. V., Hickok, D. E., Zhu, K., Easterling, T. R., & Daling, J. R. (1995). Risk factors for preeclampsia in twin pregnancies: A population-based cohort study *Obstetrics and Gynecology, 85*(5), 649-660.

da Fonseca, C. R. B., Strufaldi, M. W. L., de Carvalho, L. R., & Puccini, R. F. (2012). Risk factors for low birth weight in Botucatu city, SP state, Brazil: A study conducted in the public health system from 2004 to 2008. *BMC Research Notes, 5*(1), 60.

Deborah, R., Juan, M., Mary, D., Samuel, P., & Neill, E. (2012). Brain-derived neurotrophic factor is altered in human pregnancy. *Clinical Neuropsychiatry, 9*(6), 207-211.

Ding, G., Cui, C., Chen, L., Gao, Y., Zhou, Y., Shi, R., & Tian, Y. (2013). Prenatal low-level mercury exposure and neonatal anthropometry in rural northern China. *Chemosphere, 92*(9), 1085-1089.

Disha., Sharma, S., Goyal, M., Kumar, P. K., Ghosh, R., & Sharma, P. (2019). Association of raised blood lead levels in pregnant women with preeclampsia: a study at tertiary centre. *Taiwan Journal of Obstetrics and Gynecology, 58*(1), 60-63.

Duley, L. (2003). Pre-eclampsia and the hypertensive disorders of pregnancy. *British Medical Bulletin, 67*, 167-176.

Duman, R. S. (2002). Pathophysiology of depression: the concept of synaptic plasticity. *European Psychiatry*, 306-310.

Duman, R. S., Malberg, J., Nakagawa, S., & D'Sa, C. (2000). Neuronal plasticity and survival in mood disorders. *Biological Psychiatry, 48*, 732-739.

Durczok, A., Szkilnik, R., Nowak, P., Labus Dabrowska, J., Bortel, A., Zagził, T., . . . Brus, R. (2005). The effects of zinc on the central dopaminergic system of ratsprenatally exposed to cadmium. *Polish Journal of Environmental Studies, 14*(5), 569-576.

Dursun, N., Arifoglu, C., Süer, C., & Keskinol, L. (2005). Blood pressure relationship to nitric oxide, lipid peroxidation, renal function, and renal blood flow in rats exposed to low lead levels. *Biological Trace Element Research, 104*(2), 141-149.

Endling, A. E., Nanavati, T., Johnson, J. M., & Tuohy, V. K. (2004). Human and murine lymphocyte neutrophin expression is confined to B cells. *Journal of Neuroscience Research, 77*, 709-717.

Euan, M., Pukchanok, P., & Premjai, V. (2015). *Assessing potential changes in the migration patterns of Myanmar migrants and the impacts on Thailand: supplementry report*: International Organization for Migration, Country Mission Thailand.

Fakour, H., Esmaili-Sari, A., & Zayeri, F. (2010). Scalp hair and saliva as biomarkers in determination of mercury levels in Iranian women: amalgam as a determinant of exposure. *Journal of Hazardous Materials, 177*(1-3), 109-113.

Falcon, M., Vinas, P., & Luna, A. (2003). Placental lead and outcome of pregnancy. *Toxicology, 185*(1-2), 59-66.

Farzan, S. F., Chen, Y., Wu, F., Jiang, J., Liu, M., Baker, E., & Karagas, M. R. (2015). Blood pressure changes in relation to arsenic exposure in a U.S. pregnancy cohort. *Environmental Health Perspectives, 123*(10), 999-1066.

Fergusson, J. E. (1990). *The heavy elements: chemistry, environmental impact and health effects*: Oxford: Pergamon Press.

Fewtrell, L., Kaufmann, R., & Pruss-Ustun, A. (2003). *Lead: Assessing the environmental burden of disease at national and local levels*: World Health Organization,

Geneva.

Fiore, G., & Capasso, A. (2008). Effects of vitamin E and C on placental oxidative stress: An in vitro evidence for the potential therapeutic or prophylactic treatment of preeclampsia. *Journal of Medical Chemistry, 4*(6), 526-530.

Fioresi, M., Simões, M. R., Furieri, L. B., Broseghini-Filho, G. B., Vescovi, M. V., Stefanon, I., & Vassallo, D. V. (2014). Chronic lead exposure increases blood pressure and myocardial contractility in rats. *PLOS ONE, 9*(5), e96900.

Fleiss, J. L., Levin, B., & Paik, M. C. (2003). *Statistical methods for rates and proportions* (3rd ed.): John Wiley & Sons

Fowler, B., Ishnishi, N., Tsuchiya, K., & Vahter, M. (1979). *Arsenic*. New york: Elsevier North-Holland Biomedical Press.

Freire, C., Amaya, E., Gil, F., Murcia, M., LLop, S., Casas, M., . . . Fernández, M. F. (2019). Placental metal concentrations and birth outcomes: The Environment and Childhood (INMA) project. *International Journal of Hygiene and Environmental Health, 222*(3), 468-478.

Frerking, M., Malenka, R. C., & Nicoll, R. A. (1998). Brain-derived neurotrophic factor (BDNF) modulates inhibitory, but not excitatory, transmission in the CA1 region of the hippocampus. *Journal of Neurophysiology, 80*(6), 3383-3386.

Fung, J., Gelaye, B., Zhong, Q., Rondon, M. B., Sanchez, S. E., Barrios, Y., . . . Williams, M. A. (2015). Association of decreased serum brain-derived neurotrophic factor (BDNF) concentrations in early pregnancy with antepartum depression. *BMC Psychiatry, 15*(1), 43.

Gabriela, B., & Tongiorgi, E. (2009). BDNF splice variants from the second promoter cluster support cell survival of differentiated neuroblastoma upon cytotoxic stress. *Journal of Cell Science, 122*, 36-43.

Gao, X., Wang, J., Yao, H., Cai, Y., & Cheng, R. (2016). Serum BDNF concentration after delivery is associated with development of postpartum depression: A 3-month follow up study. *Journal of Affective Disorders, 200*, 25-30.

Gavazzo, P., Zanardi, I., Baranowska-Bosiacka, I., & Marchetti, C. (2008). Moleculardeterminants of Pb+2interaction with NMDA receptor channels. *Neurochemistry International, 52*(1-2), 329-337.

Gazal, M., Motta, L. S., Wiener, C. D., Fernandes, J. C., Quevedo, L. A., Jansen, K., . . . Oses, J. P. (2012). Brain-derived neurotrophic factor in postpartum depressive mothers. *Neurochemical Research, 37*(3), 583-587.

Gebremedhin, M., Ambaw, F., Admassu, E., & Berhane, H. (2015). Maternal associated factors of low birth weight: a hospital based cross-sectional mixed study in Tigray, Northern Ethiopia. *BMC Pregnancy and Childbirth, 15*(1), 222.

Gilbert-Diamond, D., Emond, J. A., Baker, E. R., Korrick, S. A., & Karagas, M. R. (2016). Relation between in utero arsenic exposure and birth outcomes in a cohort of mothers and their newborns from New Hampshire. *Environmental Health Perspectives, 124*(8), 1299-1307.

Glenn, M. J., Gibson, E. M., Kirby, E. D., Mellott, T. J., Blusztajn, J. K., & Williams, C. L. (2007). Prenatal choline availability modulates hippocampal neurogenesis and neurogenic responses to enriching experiences in adult female rats. *European Journal of Neuroscience, 25*, 2473-2482.

Gossett, D. R., Nayak, S., Bhatt, S., & Bailey, S. C. (2013). What do healthy women know about the consequences of delayed childbearing? *Journal of Health Communication, 18*(1), 118-128.

Guilarte, R., Mcglothan, J. L., & Nihei, M. K. (2000). Hippocampal expression of N-methyl-D-asparate receptor (NMDAR1) submit splice variant mRNA is altered by developmental exposure to Pb. *Molecular Brain Research, 76*(2), 299-305.

Gundacker, C., & Hengstschläger, M. (2012). The role of the placenta in fetal exposure to heavy metals. *Wiener Medizinische Wochenschrift, 162*(9), 201-206.

Hack, M., Flannery, D. J., Schluchter, M., Cartar, L., Borawski, E., & Klein, N. (2002). Outcomes in young adulthood for very low birth weight infants. *New England Journal of Medicine, 346*(3), 149-157.

Hameed, E., Sherif, L. S., Samie, O., Ahmed, H. H., Ahmed, A., Atta, H., & Fahmy, R. F. (2018). Mercury materno-fetal burden and its nutritional impact. *Open Access Macedonian Journal of Medical Sciences, 6*(9), 1652-1658.

Han, L., Wang, X., Han, R., Xu, M., Zhao, Y., Gao, Q., . . . Zhang, H. (2018). Association between blood lead level and blood pressure: An occupational population-based study in Jiangsu province, China. *PLOS ONE, 13*(7), e0200289.

Harada, M. (1964). Neuropsychiatric disturbances due to organic mercury poisoning during the perinatal period. *Psychiatria et neurologia paediatrica japonica, 66*, 429-468.

Hashimoto, K. (2015). Brain-derived neurotrophic factor (BDNF) and its precursor proBDNF as diagnostic biomarkers for major depressive disorder and bipolar disorder. *European Archives of Psychiatry and Clinical Neuroscience, 265*(1), 83-84. doi:10.1007/s00406-014-0557-x

Hashimoto, K., Shimizu, E., & Iyo, M. (2004). Critical role of brain-derived neurotrophic factor in mood disorders. *Brain Research Reviews, 45*(2), 104-114.

Hayes, J. D., & McLellan, L. I. (1999). Glutathione and glutathionedependent enzymes represent a co-ordinately regulated defence against oxidative stress. *Free Radical Research, 31*(4), 273-300.

He, Z. L., Yang, X. E., & Stoffella, P. J. (2005). Trace elements in agroecosystems and impacts on the environment. *Journal of Trace Elements in Medicine and Biology, 19*(2-3), 125-140.

Hernández-Díaz, S., Toh, S., & Cnattingius, S. (2009). Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. *British Medical Journal, 338*, b2255.

Huang, E. J., & Reichardt, L. F. (2001). Neutrophins: Roles in neuronal development and function. *Annual Review of Neuroscience, 24*, 667-736.

Hujoel, P. P., Lydon-Rochelle, M., Bollen, A. M., Woods, J. S., Geurtsen, W., & del Aguila, M. A. (2005). Mercury exposure from dental filling placement during pregnancy and low birth weight risk. *American Journal of Epidemiology, 161*(8), 734-740.

Hungspreugs, M., Utoomprurkporn, W., Dharmvanijj, S., & Sompongchaiyakul, P. (1989). The present status of the aquatic environment of Thailand. *Marine Pollution Bulletin, 20*(7), 327-332.

Hursh, J. B., Clarkson, T. W., Miles, E. F., & Goldsmith, L. A. (1989). Percutaneous absorption of mercury vapor by man. *Archives of Environmental Health, 44*(2), 120 -127.

Hussaini, S. K., Holley, P., & Ritenour, D. (2011). Reducing low birth weight infancy: assessing the effectiveness of the health state program in Arizona. *Maternal and*

Child Health Journal, 15(2), 225-233.

Huyck, K. L., Kile, M. L., Mahiuddin, G., Quamruzzaman, Q., Rahman, M., Breton, C. V., . . . Christiani, D. C. (2007). Maternal arsenic exposure associated with low birth weight in Bangladesh. *Journal of Occupational and Environmental Medicine, 49*(10), 1097-1104.

IARC. (2012). *Arsenic, Metals, Fibres and Dusts.* Retrieved from https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100C.pdf

Igberase, G., & Ebeigbe, P. (2006). Eclampsia: ten-years of experience in a rural tertiary hospital in the Niger delta, Nigeria. *Journal of Obstetrics and Gynaecology, 26*(5), 414-417.

Ikeh-Tawari, E. P., Anetor, J. I., & Charles-Davies, M. A. (2013). Cadmium level in pregnancy, influence on neonatal birth weight and possible amelioration by some essential elements. *Toxicological International, 20*(1), 108-112.

ILO. (2017). Labor migration. Retrieved from https://www.ilo.org/global/topics/labour-migration/lang--en/index.htm.

Institute for health Metrics and Evaluation. (2017). *GDB compare*. University of Washington.

International Organization for Migration. (2011). *Thailand Migration Report 2011*.

IPCS. (1991). *Inorganic mercury*. Geneva: World Health Organization.

IPCS. (1995). *Inorganic lead*. Geneva: World Health Organization.

Isarabhakdi, P. (2004). Meeting at the Crossroads: Myanmar Migrants and Their Use of Thai Health Care Services. *Asia Pacific Migration Journal, 13*(107-126).

Iyengar, G. V., & Rapp, A. (2001). Human placenta as a 'dual' biomarker for monitoring fetal and maternal environment with special reference to potentially toxic trace elements. Part 3: Toxic trace elements in placenta and placenta as a biomarker for these elements. *Science of the Total Environment, 280*(1-3), 221-238.

Jan, A. T., Azam, M., Siddiqui, K., Ali, A., Choi, I., & Haq, Q. M. (2015). Heavy metals and human health: Mechanistic insight into toxicity and counter defense system of antioxidants. *International Journal of Molecular Sciences, 16*(12), 29592-29630.

Jana, T. (2017). *Mercury in fish from industrial sites in Thailand*.

Järup, L., & Akesson, A. (2009). Current status of cadmium as an environmental health

problem. *Toxicology and Applied Pharmacology, 238*(3), 201-208.

John, B., & Gary, R. (2001). *Clinical environmental health and toxic exposures* (2 ed.). Philadelphia, US: Lippincott Williams and Wilkins.

Joseph, L., & Robert, J. (2014). *Current occupational and environmenatal medicine* (5 ed.). US: McGraw - Hill Companies.

Karege, F., Perret, G., Bondolfi, G., Schwald, M., Bertschy, G., & Aubry, J. M. (2002). Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Research, 109*(2), 143-148.

Karri, V., Schuhmacher, M., & Kumar, V. (2016). Heavy metals (Pb, Cd, As and MeHg) as risk factors for cognitive dysfunction: A general review of metal mixture mechanism in brain. *Environmental Toxicology and Pharmacology, 48*, 203-213.

Kawamura, K., Kawamura, N., Fukuda, J., Kumagai, J., Hsueh, A. J., & Tanaka, T. (2007). Regulation of preimplanatation embryo development by brain-derived neurotrophic factor *Developmental Biology, 311*(1), 147-158.

Kawamura, K., Kawamura, N., Sato, W., Fukuda, J., Kumagai, J., & Tanaka, T. (2009). Brain-derived neurotrophic factor promotes implantation and subsequent placental development by stimulating trophoblast cell growth and survival. *Endocrinology, 150*(8), 3774-3782.

Kile, M. L., Cardenas, A., Rodrigues, E., Mazumdar, M., Dobson, C., Golam, M., . . . Christiani, D. C. (2016). Estimating Effects of Arsenic Exposure During Pregnancy on Perinatal Outcomes in a Bangladeshi Cohort. *Epidemiology, 27*(2), 173-181.

Kim, E. H., Kim, I. K., Kwon, J. Y., Kim, S. W., & Park, Y. W. (2006). The effect of fish consumption on blood mercury levels of pregnant women. *Yonsei Medical Journal, 47*(5), 623-633.

Kobayashi, S., Kishi, R., Saijo, Y., Ito, Y., Oba, K., Araki, A., . . . Nitta, H. (2019). Association of blood mercury levels during pregnancy with infant birth size by blood selenium levels in the Japan Environment and Children's Study: A prospective birth cohort. *Ennvironmental International, 125*, 418-429.

Kopp, S. J., Barron, J. T., & Tow, J. P. (1988). Cardiovascular actions of lead and relationship to hypertension: a review. *Environmental Health Perspectives, 78*, 91-99.

Lamminpää, R., Vehviläinen-Julkunen, K., Gissler, M., & Heinonen, S. (2012). Preeclampsia complicated by advanced maternal age: A registry-based study on primiparous women in Finland 1997–2008. *BMC Pregnancy and Childbirth, 12*, 47.

Li, J., Wang, H., Hao, J. H., Chen, Y. H., Liu, L., Yu, Z., . . . Xu, D. X. (2017). Maternal serum lead level during pregnancy is positively correlated with risk of preterm birth in a Chinese population. *Environmental Pollution, 227*, 484-489.

Liac, J., Wang, H., Hao, J. H., Chen, Y. H., Liu, L., Yu, Z., . . . Xu, D. X. (2017). Maternal serum lead level during pregnancy is positively correlated with risk of preterm birth in a Chinese population. *Environmental Pollution, 227*, 484-489.

Liao, K. W., Chang, C. H., Tsai, M. S., Chien, L. C., Chung, M. Y., Mao, I. F., . . . Chen, M. L. (2018). Associations between urinary total arsenic levels, fetal development, and neonatal birth outcomes: A cohort study in Taiwan. *Science of the Total Environment, 612*, 1373-1379.

Licinio, J., & Wong, M. L. (2002). Brain-derived neurotrophic factor (BDNF) in stress and affective disorders. *Molecular Psychiatry, 7*(6), 519.

Lin, S., Hwang, S. A., Marshall, E. G., & Marion, D. (1998). Does paternal occupational lead exposure increase the risks of low birth weight or prematurity? *American Journal of Epidemiology, 148*(2), 73-81.

Liu, H., Lu, S., Zhang, B., Xia, W., Liu, W., Peng, Y., . . . Li, Y. (2018). Maternal arsenic exposure and birth outcomes: A birth cohort study in Wuhan, China. *Environmental Pollution, 236*, 817-823.

Liu, L., Oza, S., Hogan, D., Chu, Y., Perin, J., Zhu, J., . . . Black, R. E. (2016). Global, regional and national causes of under-5 mortality in 2000-15: An updated systematic analysis with implications for the Sustainable Development Goals. *Lancet, 388*(10063), 3027-3035.

Lormphongs, S., Miyashita, K., Morioka, I., Chaikittiporn, C., Miyai, N., & Yamamoto, H. (2003). Lead exposure and blood lead level of workers in a battery manufacturing plant in Thailand. *Industrial Health, 41*(4), 348-353.

Lu, Y., Liu, X., Deng, Q., Duan, Y., Dai, H., Li, Y., . . . Yuan, H. (2015). Continuous Lead Exposure Increases Blood Pressure but Does Not Alter Kidney Function in Adults

20-44 Years of Age in a Lead-Polluted Region of China. *Kidney and Blood Pressure Research, 40*, 207-214.

Lugo, G., Cassady, G., & Palmisano, P. (1969). Acute maternal arsenic intoxication with neonatal death. *American Journal of Diseases of Children, 117*(3), 328-330.

Luo, Y., McCullough, L. E., Tzeng, J. Y., Darrah, T., Vengosh, A., Maguire, R. L., & Hoyo, C. (2017). Maternal blood cadmium, lead and arsenic levels, nutrient combinations and offspring birthweight. *BMC Public Health, 17*, 354.

Madar-Shapiro, L., Karady, I., Trahtenherts, A., Syngelaki, A., Akolekar, R., Poon, L., . . . Meiri, H. (2018). Predicting the Risk to Develop Preeclampsia in the First Trimester Combining Promoter Variant -98A/C of LGALS13 (Placental Protein 13), Black Ethnicity, Previous Preeclampsia, Obesity, and Maternal Age. *Fetal Diagnosis and Therapy, 43*(4), 250-265.

Maekawa, R., Ito, R., Iwasaki, Y., Saito, K., Akutsu, K., Takatori, S., . . . Sugino, N. (2017). Evidence of exposure to chemicals and heavy metals during pregnancy in Japanese women. *Reproductive Medicine and Biology, 16*(4), 337-348.

Mario, M., Ferran, B., Ashley, M., CarmenIñiguez., Damaskini, V., Mikel, B., . . . Sabrina, L. (2016). Prenatal mercury exposure and birth outcomes. *Environmental Research, 151*, 11-20.

Mayeur, S., Silhol, M., Moitrot, E., Barbaux, S., Breton, C., Gabory, A., . . . Lesage, J. (2010). Placental BDNF/TrkB signaling system is modulated by fetal growth disturbances in rat and human. *Placenta, 31*(9), 785-791.

McMichael, A. J., Vimpani, G. V., Robertson, E. F., Baghurst, P. A., & Clark, P. D. (1986). The Port Pirie cohort study: maternal blood lead and pregnancy outcome. *Journal of Epidemiology and Community Health, 40*(1), 18-25.

Miyake, Y., Tanaka, K., & Arakawa, M. (2013). Active and passive maternal smoking during pregnancy and birth outcomes: the Kyushu Okinawa maternal and child health study. *BMC Pregnancy and Childbirth, 13*(1), 157.

Mohsen, V., Kazuhito, Y., Takehisa, M., Atsuko, S., & Katsumi, O. (2015). The Relation of Maternal Blood Arsenic to Anemia During Pregnancy. *Women and Health, 55*, 42-57.

Morton, L. (2006). *Environmental toxicants* (2 ed.). New Jersey, US: John Wiley and

sons.

Muhihi, A., Sudfeld, C. R., Smith, E. R., Noor, R. A., Mshamu, S., Briegleb, C., . . . Chan, G. J. (2016). Risk factors for small-for-gestational-age and preterm births among 19,269 Tanzanian newborns. *BMC Pregnancy and Childbirth, 16*, 110.

Mukherjee, B., Bindhani, B., Saha, H., Sinha, D., & Ray, M. R. (2014). Platelet hyperactivity, neurobehavioral symptoms and depression among Indian women chronically exposed to low level of arsenic. *Neurotoxicology, 45*, 159-167. doi:10.1016/j.neuro.2014.10.011

Nakahashi, T., Fujimura, H., Altar, C. A., Li, J., Kambayashi, J., Tandon, N. N., & Sun, B. (2000). Vascular endothelial cells synthesize and secrete brain-derived neurotrophic factor. *FEBS Letters, 470*(2), 113-117.

Nakimuli, A., Chazara, O., Byamugisha, J., Elliott, A. M., Kaleebu, P., Mirembe, F., & Moffett, A. (2014). Pregnancy, parturition and preeclampsia in women of African ancestry. *American Journal of Obstetrics and Gynecology, 210*, 510-520.

Nash, D., Magder, L., Lustberg, M., Sherwin, R. W., Rubin, R. J., Kaufmann, R. B., & Silbergeld, E. K. (2003). Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. *JAMA, 289*(12), 1523-1532.

National Academy of Sciences. (1977). *Medical and biologic effects of environmental pollutants, arsenic*. Washington National Research Council, National Academy of Sciences.

Naujokas, M. F., Acheson, B., Ahsan, H., Aposhian, H. V., Graziano, J., Thompson, C., & Suk, W. A. (2013). The broad scope of health effects from chronic arsenic exposure: update on a worldwide public health problem. *Environmental Health Perspectives, 121*(3), 295-302.

Ngamjarus, C., & Chongsuvivatwong, V. (2014). *n4Studies: Sample size and power calculations for iOS.*

NIOSH. (2015). *Adult Blood Lead Epidemiology and Surveillance (ABLES)*. Retrieved from Atlanta https://www.cdc.gov/niosh/topics/ables/description.html

Nishijo, M., Nakagawa, H., Honda, R., Tanebe, K., Saito, S., Teranishi, H., & Tawara, K. (2002). Effects of maternal exposure to cadmium on pregnancy outcome and breast milk. *Occupational and Environmental Medicine, 59*, 394-397.

Nomiyama, K., Nomiyama, H., Liu, S. J., Tao, Y. X., Nomiyama, T., & Omae, K. (2002). Lead induced increase of blood pressure in female lead workers. *Occupational and Environmental Medicine, 59*, 734-739.

Nriagu, J. O. (1989). A global assessment of natural sources of atmospheric trace metals. *Nature, 338*, 47-49.

Obadia, P. M., Kayembe-Kitenge, T., Haufroid, V., Banza, C., Nkulu, L., & Nemery, B. (2018). Preeclampsia and blood lead (and other metals) in Lubumbashi, DR Congo. *Environmental Research, 167*, 468-471.

Ozbek, N., & Akman, S. (2016). Determination of lead, cadmium and nickel in hennas and other hair dyes sold in Turkey. *Regulatory Toxicology and Pharmacology, 79*, 49-53.

Pan, W., Banks, W. A., Fasold, M. B., Bluth, J., & Kastin, A. J. (1998). Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology, 37*(12), 1553-1561.

Parker, J. D., Schoendorf, K. C., & Kiely, J. L. (1994). Associations between measures of socioeconomic status and low birth weight, small for gestational age, and premature delivery in the United States. *Annals of Epidemiology, 4*(4), 271-278.

Perkins, M., Wright, R. O., Amarasiriwardena, C. J., Jayawardene, I., Rifas-Shiman, S. L., & Oken, E. (2014). Very low maternal lead level in pregnancy and birth outcomes in an eastern Massachusetts population. *Annals of Epidemiology, 24*(12), 915-919.

Philip N, & Louise K. (1917). *Obstetrics by Ten Teacher* (20 ed.): CRC Press.

Polprasert, C. (1982). Heavy metal pollution in the Chao Phraya River Estuary, Thailand. *Water Research, 16*(6), 775-784.

Pruunsild, P., Kazantseva, A., Aid, T., Palm, K., & Timmusk, T. (2007). Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. *Genomics, 90*(3), 397-406.

Rabinowitz, M. B., Wetherill, G. W., & Kopple, J. D. (1976). Kinetics analysis of lead metabolism in healthy humans. *Journal of Clinical Investigation, 58*(2), 260-270.

Radka, S. F., Holst, P. A., Fritsche, M., & Altar, C. A. (1996). Presence of brain-derived neurotrophic factor in brain and human and rat but not mouse serum detected

by a sensitive and specific immunoassay. *Brain Research Reviews, 709*(1), 122-130.

Rahman, M. L., Valeri, L., Kile, M. L., Mazumdar, M., Mostofa, G., Qamruzzaman, Q., & Christiani, D. C. (2017). Investigating causal relation between prenatal arsenic exposure and birthweight: Are smaller infants more susceptible? *Environmental International, 108*, 32-40.

Ramirez, G. B., Cruz, M. C., Pagulayan, O., Ostrea, E., & Dalisay, C. (2000). The Tagum Study I: Analysis and Clinical Correlates of Mercury in Maternal and Cord Blood, Breast Milk, Meconium, and Infants' Hair. *Paediatrics, 106*(4), 774-781.

Rehman, K., Fatima, F., Waheed, I., & Akash, M. S. H. (2017). Prevalence of exposure of heavy metals and their impact on health consequences. *Journal of Cellular Biochemistry, 119*(1), 157-184.

Renzetti, S., Just, A. C., Burris, H. H., Oken, E., Amarasiriwardena, C., Svensson, K., . . . Téllez-Rojo, M. M. (2017). The association of lead exposure during pregnancy and childhood anthropometry in the Mexican PROGRESS cohort. *Environmental Research, 152*, 226-232.

Reus, I. S., Bando, I., Andrés, D., & Cascales, M. (2003). Relationship between expression of HSP70 and metallothionein and oxidative stress during mercury chloride induced acute liver injury in rats. *Journal of Biochemical and Molecular Toxicology, 17*(3), 161-168.

Richard, J., Avory, A., & Michele, C. (2015). *Fanaroff and Martin's Neonatal Perinatal Medicine: Diseases of the fetus and infant* (10 ed.).

Roberts, J. M., & Gammill, H. S. (2005). Preeclampsia: Recent insights. *Hypertension, 46*, 1243-1249.

Robles, H. V., Romo, E., Sanchez-Mendoza, A., Rios, A., Soto, V., Avila-Casado, M. C., . . . Escalante, B. (2007). Lead exposure effect on angiotensin II renal vasoconstriction. *Human and Experimental Toxicology, 26*(6), 499-507.

Rodriguez, V. M., Jimenez-Capdeville, M. E., & Giordano, M. (2003). The effects of arsenic exposure on the nervous system. *Toxicology Letters, 145*, 1-18.

Rukmani, P., Vipin, R., Juhi, M., Kapil, M., Somendu, K., & Sanghamitra, B. (2017). Arsenic Induces Hippocampal Neuronal Apoptosis and Cognitive Impairemnents via an

Up-Regulated BMP2/Smad-Dependent reduced BDNF/ TrkB Signaling in Rats. *Toxicological sciences, 159*(1), 137-158.

Sadovsky, A. D., Matijasevich, A., Santos, I. S., Barros, F. C., Miranda, A. E., & Silveira, M. F. (2018). Socioeconomic inequality in preterm birth in four Brazilian birth cohort studies. *Journal de Pediatria, 94*(1), 15-22.

Sarov, B., Bentov, Y., Kordysh, E., Karakis, I., Bolotin, A., Hershkovitz, R., & Belmaker, I. (2008). Perinatal mortality and residential proximity to an industrial park. *Archives of Environmental and Occupational Health, 63*(1), 17-25.

Schwartz, M. O., Rajan, S. S., Askury, A. K., Putthapiban, P., & Djaswadi, S. (1995). The Southern Asian tin belt. *Earth-Science Reviews, 38*(2-4), 95-293.

Shallari, S., Schwartz, C., Hasko, A., & Morel, J. L. (1998). Heavy metals in soils and plants of serpentine and industrial sites of Albania. *Science of the Total Environment, 209*(2-3), 133-142.

Shao, Y., Qiu, J., Huang, H., Mao, B., Dai, W., He, X., . . . Zhang, Y. (2017). Pre-pregnancy BMI, gestational weight gain and risk of preeclampsia: a birth cohort study in Lanzhou, China. *BMC Pregnancy and Childbirth, 17*, 400.

Sharashova, E. E., Anda, E. E., & Grjibovski, A. M. (2014). Early pregnancy body mass index and spontaneous preterm birth in Northwest Russia: a registry-based study. *BMC Pregnancy and Childbirth, 14*(303).

Short, V. L., Geller, S. E., Moore, J. L., McClure, E. M., Goudar, S. S., Dhaded, S. M., & Derman, R. J. (2018). The Relationship between Body Mass Index in Pregnancy and Adverse Maternal, Perinatal, and Neonatal Outcomes in Rural India and Pakistan. *American Journal of Perinatology, 35*(9), 844-851.

Stackelberg, K. V., Elizabeth, G., Tian, C., & Birgit, C. H. (2013). *Mixtures, metals, genesand pathways: A systematic review methods for research synthesis*.

Sun, B. F., Wang, Q. Q., Yu, Z. J., Yu, Y., & Xiao, C. L. (2015). Exercise Prevents Memory Impairment Induced by Arsenic Exposure in Mice: Implication of Hippocampal BDNF and CREB. *PLOS ONE, 10*(9), e0137810. doi:https://doi.org/10.1371/journal.pone.0137810

Suvapepun, S. (1991). Long term ecological changes in the Gulf of Thailand. *Marine Pollution Bulletin, 23*, 213-217.

Sweatt, J. D. (2004). Hippocampal function in cognition. *Psychopharmacology (Berl), 174*(1), 99-110.

Tabacova, S., Little, R. E., Balabaeva, L., Pavlova, S., & Petrov, I. (1994). Complications of pregnancy in relation to maternal lipid peroxides, glutathione, and exposure to metals. *Reproductive Toxicology, 8*(3), 217-224.

Tamura, S., Nagasawa, A., Masuda, Y., Tsunematsu, T., Hayasaka, K., Matsuno, K., . . . Moriyama, T. (2012). BDNF, produced by a TPO-stimulated megakaryocytic cell line,regulates autocrine proliferation. *Biochemical and Biophysical Research Communications, 427*(3), 542-546.

Tang, M., Xu, C., Lin, N., Liu, K., Zhang, Y., Yu, X., & Liu, W. (2016). Lead, mercury, and cadmium in umbilical cord serum and birth outcomes in Chinese fish consumers. *Chemosphere, 148*, 270-275.

Taylor, C. M., Golding, J., & Emond, A. M. (2014). Adverse effects of maternal lead levels on birth outcomes in the ALSPAC study: A prospective birth cohort study. *BJOG, 122*(3), 322-328.

Taylor, C. M., Golding, J., & Emond, A. M. (2016). Blood mercury levels and fish consumption in pregnancy: Risks and benefits for birth outcomes in a prospective observational birth cohort. *International Journal of Hygiene and Environmental Health, 219*(6), 513-520.

Taylor, C. M., Golding, J., & Emond, A. M. (2016). Moderate prenatal cadmium exposure and adverse birth outcomes: a role for sex-specific differences? *Paediatric and Perinatal Epidemiology, 30*(6), 603-611.

Tchounwou, P. B., Yedjou, C. G., Patlolla, A. K., & Sutton, D. J. (2012). Heavy metal toxicity and the environment. *Experientia supplementum, 101*, 133-164.

Tessema, G. A., Tekeste, A., & Ayele, T. A. (2015). Preeclampsia and associated factors among pregnant women attending antenatal care in Dessie referral hospital, Northeast Ethiopia: A hospital-based study. *BMC Pregnancy and Childbirth, 15*, 73.

Thein, T. T., Myint, T., Lwin, S., Oo, W. M., Kyaw, A. K., Myint, M. K., & Thant, K. Z. (2012). Promoting antenatal care services for early detection of pre-eclampsia. *WHO South East Asia Journal of Public Health, 1*(3), 290-298.

Thomas, K., & Davies, A. (2005). Neurotrophins: A ticket to ride for BDNF. *Current Biology, 15*(7), 262-264.

Thomas, W., Lars, F., Gunnar, F., & Rolly, R. (1988). *Biological Monitoring of toxic metals*. New York and London: Plenum.

Travaglia, A., & La Mendola, D. (2017). Zinc interactions with brain neutrophic factor and related peptide fragments. *Vitamins and Hormones, 104*, 29-56.

Tsuji, M., Shibata, E., Morokuma, S., Tanaka, R., Senju, A., Araki, S., . . . Kawamoto, T. (2018). The association between whole blood concentrations of heavy metals in pregnant women and premature births: The Japan Environment and Children's Study (JECS). *Environmental Research, 166*, 562-569.

UNICEF. (2014). *UNICEF Data: Monitoring the Situation of Children and Women*. Retrieved from https://data.unicef.org/

Uzan, J., Carbonnel, M., Piconne, O., Asmar, R., & Ayoubi, J. (2011). Pre-eclampsia: pathophysiology, diagnosis, and management. *Vascular Health and Risk Management, 7*, 467-474.

Valdés, M., Hanchey, A., Muñoz, M. P., Baumert, B., & Iglesias, V. (2017). Low-level arsenic exposure during pregnancy and its association with postpartum depression: A cohort study of women from Arica, Chile. *Revue d'épidémiologie et de santé publique, 65*(6), 427-435. doi:10.1016/j.respe.2017.05.010

Vigeh, M., Nishioka, E., Ohtani, K., Omori, Y., Matsukawa, T., Koda, S., & Yokoyama, K. (2018). Prenatal mercury exposure and birth weight. *Reproductive Toxicology, 76*, 78-83.

Vigeh, M., Yokoyama, K., Ramezanzadeh, F., Dahaghin, M., Sakai, T., Morita, Y., . . . Kobayashi, Y. (2006). Lead and other trace metals in preeclampsia: A case–control study in Tehran, Iran. *Environmental Research, 100*(2), 268-275.

Villamor, E., Msamanga, G., Urassa, W., Petraro, P., Spiegelman, D., Hunter, D. J., & Fawzi, W. W. (2006). Trends in obesity, underweight, and wasting among women attending prenatal clinics in urban Tanzania, 1995-2004. *American Journal of Clinical Nutrition, 83*(6), 1387-1394.

Wagura, P., Wasunna, A., Laving, A., Wamalwa, D., & Ng'ang'a, P. (2018). Prevalence and factors associated with preterm birth at kenyatta national hospital. *BMC*

Pregnancy and Childbirth, 18(1), 107.

Wai, K. M., Mar, O., Satoko, K., Mitsutoshi, U., & Chiho, W. (2017). Prenatal heavy metal exposure and adveres birth outcomes in Myanmar: A birth cohort study. *International Journal of Environmental Research and Public Health, 14*(11), pii: E1339.

Wang, F., Fan, F., Wang, L., Ye, W., Zhang, Q., & Xie, S. (2018). Maternal cadmium levels during pregnancy and the relationship with preeclampsia and fetal biometric parameters. *Biological Trace Element Research, 186*(2), 322-329.

Wang, H., Li, J., Zhang, X., Zhu, P., Hao, J. H., Tao, F. B., & Xu, D. X. (2018). Maternal serum arsenic level during pregnancy is positively associated with adverse pregnant outcomes in a Chinese population. *Toxicology and Applied Pharmacology, 356*, 114-119.

Wang, H., Liu, L., Hu, Y. F., Hao, J. H., Chen, Y. H., Su, P. Y., . . . Xu, D. X. (2016). Association of maternal serum cadmium level during pregnancy with risk of preterm birth in a Chinese population. *Environmental Pollution, 216*, 851-857.

Wang, T., Zhang, J., Lu, X., Xi, W., & Li, Z. (2011). Maternal early pregnancy body mass index and risk of preterm birth. *Archives of Gynecology and Obstetrics, 284*(4), 813-819.

Ward, C., Lewis, S., & Coleman, T. (2007). Prevalence of maternal smoking and environmental tobacco smoke exposure during pregnancy and impact on birth weight: retrospective study using Millennium Cohort. *BMC Public Health, 7*, 81.

Weast, R. (1974). *Handbook of chemistry and physics* (55 ed.). Cleveland, Ohio: CRC Press.

Webster, L. M., Gill, C., Seed, P. T., Bramham, K., Wiesender, C., Nelson-Piercy, C., . . . Chappell, L. C. (2018). Chronic hypertension in pregnancy: impact of ethnicity and superimposed preeclampsia on placental, endothelial, and renal biomarkers. *American Journal of Physiology, 315*(1), R36-R47.

Wells, E. M., Navas-Acien, A., Herbstman, J. B., Apelberg, B. J., Silbergeld, E. K., Caldwell, K. L., . . . Goldman, L. R. (2011). Low-Level Lead Exposure and Elevations in Blood Pressure during Pregnancy. *Environmental Health Perspectives, 119*(5), 664-669.

WHO Expert Consultation. (2014). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet, 363*(9403), 157-163.

WHO. (1976). *Environmental Health Criteria 1: Mercury*. Geneva: World Health Organization.

WHO. (2004). *Coverage of Maternity Care: A Listing of Available Information*. Geneva, Switzerland: World Health Organization.

WHO. (2005). *World Health Report 2005: Make every mother and child healthy*. Retrieved from https://www.who.int/whr/2005/en/

WHO. (2009). *Global health risks: Mortality and burden of disease attributable to selected major risks*. Geneva,: World Health Organization.

WHO. (2010). *WHO human health risk assessment tooklist: chemical hazards*. Geneva: World Health Organization.

WHO. (2017). *Ten chemicals of major public health concern*. Geneva: World Health Organization.

Xi, S., Guo, L., Qi, R., Sun, W., Jin, Y., & Sun, G. (2010). Prenatal and early life arsenic exposure induced oxidative damage and altered activities and mRNA expressions of neurotransmitter metabolic enzymes in offspring rat brain. *Journal of Biochemical and Molecular Toxicology, 24*(6), 368-378.

Xie, X., Ding, G., Cui, C., Chen, L., Gao, Y., Zhou, Y., . . . Tian, Y. (2013). The effects of low-level prenatal lead exposure on birth outcomes. *Environmental Pollution, 175*, 30-34.

Yang, C. Y., Chang, C. C., Tsai, S. S., Chuang, H. Y., Ho, C. K., & Wu, T. N. (2003). Arsenic in drinking water and adverse pregnancy outcome in an arseniasis-endemic area in northeastern Taiwan. *Environmental Research, 91*(1), 29-34.

Yang, J., Huo, W., Zhang, B., Zheng, T., Li, Y., Pan, X., . . . Xu, S. (2016). Maternal urinary cadmium concentrations in relation to preterm birth in the Healthy Baby Cohort Study in China. *Environmental International, 94*, 300-306.

Yang, K., Julan, L., Rubio, F., Sharma, A., & Guan, H. (2006). Cadmium reduces 11β-hydroxysteroid dehydrogenase type 2 activity and expression in human

placental trophoblast cells. *American Journal of Physiology-Endocrinology and Metabolism, 290*(1), E135-E142.

Yang, N., Levey, E., Gelaye, B., Zhong, Q. Y., Rondon, M. B., Sanchez, S. E., & Williams, M. A. (2017). Correlates of early pregnancy serum brain-derived neurotrophic factor in a Peruvian population. *Archives of Womens and Mental Health, 20*(6), 777-785.

Yıldırım, E., Derici, M. K., Demir, E., Apaydın, H., Koçak, O., Kan, O., & Görkemet, U. (2019). Is the Concentration of Cadmium, Lead, Mercury, and Selenium Related to Preterm Birth? *Biological Trace Element Research*, 1-7.

Yokel, R. A. (2006). Blood brain barrier flux of aluminium, managese, iron and other metals suspected to contribute to metal induced neurodegeneration. *Journal of Alzheimers Disease, 10*(2-3), 223-253.

Yoshida, T., Ishikawa, M., Niitsu, T., Nakazato, M., Watanabe, H., Shiraishi, T., . . . Hashimoto, K. (2012). Decreased serum levels of mature brain-derived neurotrophic factor (BDNF), but not its precursor proBDNF, in patients with major depressive disorder. *PLOS ONE, 7*(8), e42676. doi:10.1371/journal.pone.0042676

Young, J. L., Cai, L., & States, J. C. (2018). Impact of prenatal arsenic exposure on chronic adult diseases. *Systems Biology in Reproductive Medicine, 64*(6), 469-483.

Zhou, C. C., Gao, Z. Y., He, Y. Q., Wu, M. Q., Chen, F., Wang, J., . . . Yan, C. H. (2019). Effects of lead, mercury, aluminium and manganese co-exposure on the serum BDNF concentration of pre-school children in Taizhou, China. *Chemosphere, 217*, 158-165. doi:10.1016/j.chemosphere.2018.11.028

APPENDICES

Appendix A: Certificate of ethical approval by Chulalongkorn University

AF 02-12

The Research Ethics Review Committee for Research Involving Human Research Participants, Health Sciences Group, Chulalongkorn University

Jamjuree 1 Building, 2nd Floor, Phyathai Rd., Patumwan district, Bangkok 10330, Thailand, Tel/Fax: 0-2218-3202 E-mail: eccu@chula.ac.th

COA No. 251/2018

Certificate of Approval

Study Title No. 149.1/61 : EFFECT OF MATERNAL BLOOD HEAVEY METALS LEVEL ON BRAIN-DERIVED NEUROTROPHIC FACTOR AND PREGNANCY OUTCOMES AMONG MYANMAR MIGRANTS IN SAMUT SAKHON PROVINCE, THAILAND

Principal Investigator : MR. YE HTET ZAW

Place of Proposed Study/Institution : College of Public Health Sciences, Chulalongkorn University

The Research Ethics Review Committee for Research Involving Human Research Participants, Health Sciences Group, Chulalongkorn University, Thailand, has approved constituted in accordance with the International Conference on Harmonization – Good Clinical Practice (ICH-GCP).

Signature: ..... Signature: .....

(Associate Professor Prida Tasanapradit, M.D.) (Assistant Professor Nuntaree Chaichanawongsaroj, Ph.D.)

Chairman Secretary

Date of Approval : 27 October 2018 Approval Expire date : 26 October 2019

The approval documents including

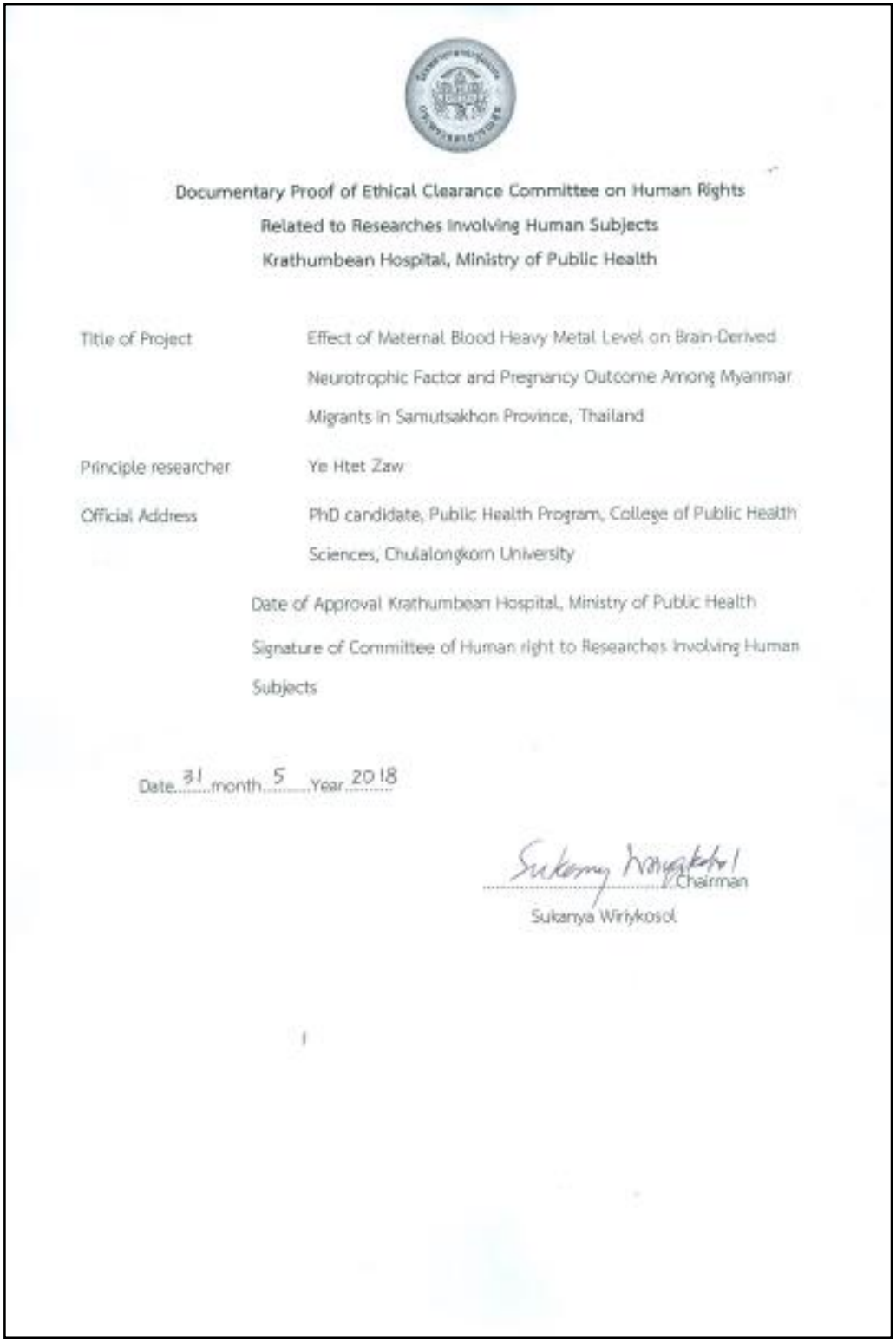
1) Research proposal
2) Patient/Participant Information Sheet and Informed Consent Form
3) Researcher
4) Questionnaire

Protocol No. 149.1/61
Date of Approval 27 OCT 2018
Approval Expire Date 26 OCT 2019

The approved investigator must comply with the following conditions:

1. *The research/project activities must end on the approval expired date of the Research Ethics Review Committee for Research Involving Human Research Participants, Health Sciences Group, Chulalongkorn University (RECCU). In case the research/project is unable to complete within that date, the project extension can be applied one month prior to the RECCU approval expired date.*
2. *Strictly conduct the research/project activities as written in the proposal.*
3. *Using only the documents that bearing the RECCU's seal of approval with the subjects/volunteers (including subject information sheet, consent form, invitation letter for project/research participation (if available).*
4. *Report to the RECCU for any serious adverse events within 5 working days*
5. *Report to the RECCU for any change of the research/project activities prior to conduct the activities.*
6. *Final report (AF 03-12) and abstract is required for a one year (or less) research/project and report within 30 days after the completion of the research/project. For thesis, abstract is required and report within 30 days after the completion of the research/project.*
7. *Annual progress report is needed for a two- year (or more) research/project and submit the progress report before the expire date of certificate. After the completion of the research/project processes as No. 6.*

Appendix B: Proof of ethical clearance by Krathum Baen Hospital (English)



Documentary Proof of Ethical Clearance Committee on Human Rights
Related to Researches Involving Human Subjects
Krathumbean Hospital, Ministry of Public Health

Title of Project	Effect of Maternal Blood Heavy Metal Level on Brain-Derived Neurotrophic Factor and Pregnancy Outcome Among Myanmar Migrants in Samutsakhon Province, Thailand
Principle researcher	Ye Htet Zaw
Official Address	PhD candidate, Public Health Program, College of Public Health Sciences, Chulalongkorn University

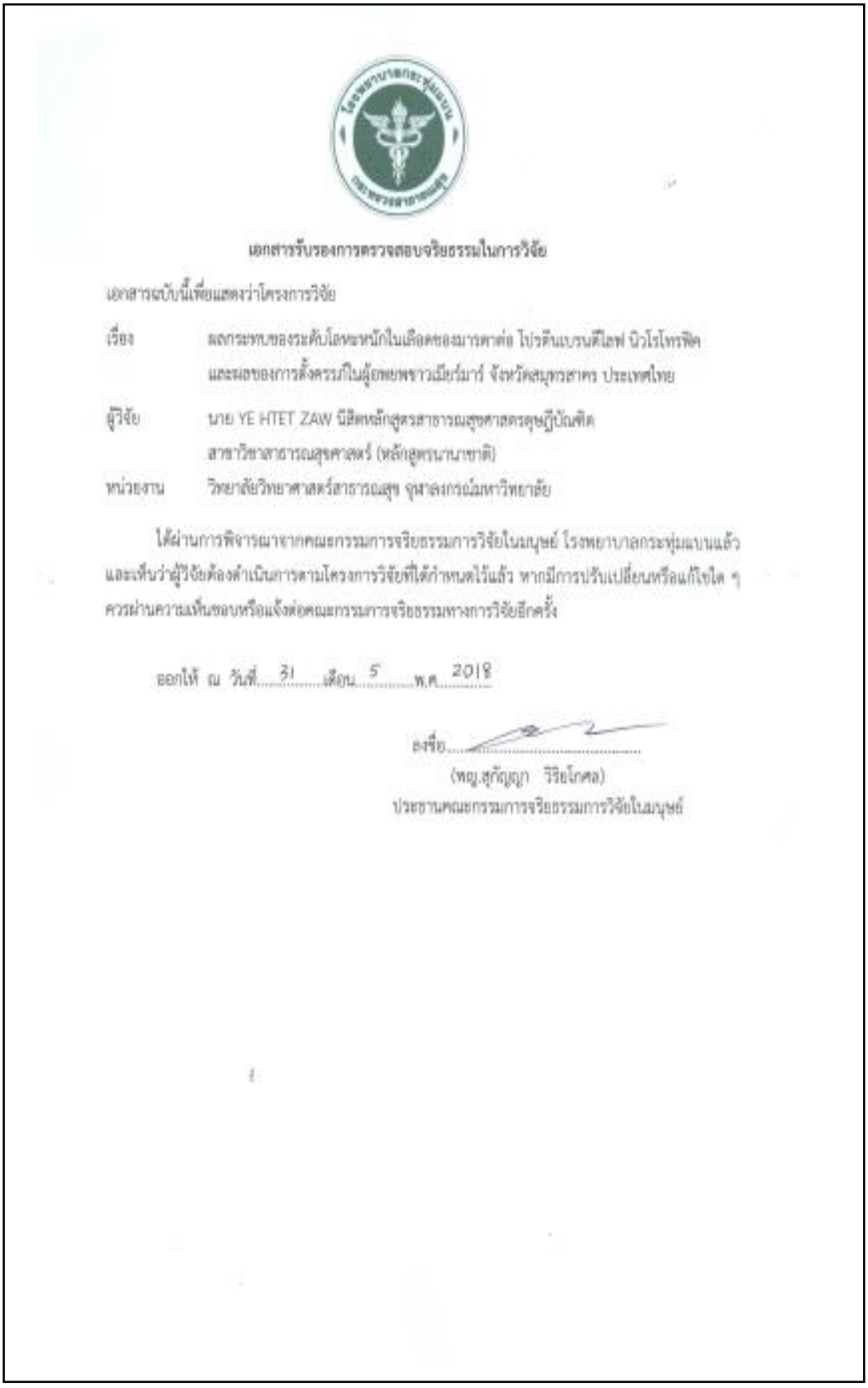
Date of Approval Krathumbean Hospital, Ministry of Public Health

Signature of Committee of Human right to Researches Involving Human Subjects

Date 31 month 5 Year 2018

Chairman
Sukanya Wiriykosol

Appendix C: Proof of ethical clearance by Krathum Baen Hospital (Thai)



เอกสารรับรองการตรวจสอบจริยธรรมในการวิจัย

เอกสารฉบับนี้เพื่อแสดงว่าโครงการวิจัย

เรื่อง ผลกระทบของระดับโลหะหนักในเลือดของมารดาต่อ โปรตีนแบรนดีไลฟ์ นิวโรโทรฟิค และผลของการตั้งครรภ์ในผู้อพยพชาวเมียร์มาร์ จังหวัดสมุทรสาคร ประเทศไทย

ผู้วิจัย นาย YE HTET ZAW นิสิตหลักสูตรสาธารณสุขศาสตรดุษฎีบัณฑิต สาขาวิชาสาธารณสุขศาสตร์ (หลักสูตรนานาชาติ)

หน่วยงาน วิทยาลัยวิทยาศาสตร์สาธารณสุข จุฬาลงกรณ์มหาวิทยาลัย

ได้ผ่านการพิจารณาจากคณะกรรมการจริยธรรมการวิจัยในมนุษย์ โรงพยาบาลกระทุ่มแบนแล้ว และเห็นว่าผู้วิจัยต้องดำเนินการตามโครงการวิจัยที่ได้กำหนดไว้แล้ว หากมีการปรับเปลี่ยนหรือแก้ไขใด ๆ ควรผ่านความเห็นชอบหรือแจ้งต่อคณะกรรมการจริยธรรมทางการวิจัยอีกครั้ง

ออกให้ ณ วันที่ 31 เดือน 5 พ.ศ. 2018

ลงชื่อ.....

(พญ.สุกัญญา วิริยโกศล)

ประธานคณะกรรมการจริยธรรมการวิจัยในมนุษย์

Appendix D: Test Validity of the Questionnaires

- Title of the research

  Effect of maternal blood heavy metal level on Brain-derived neurotrophic factor (BDNF) and pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand

- Researcher

  Ye Htet Zaw, MBBS, MMed Sc (Environmental Health)

  Doctorate student, Public Health Program, College of Public Health Sciences, Chulalongkorn University

- Objectives

  General: to identify the association between maternal blood heavy metal level and maternal serum BDNF level and pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand

  Specific: 1) to describe the risk factors affecting pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand 2) to assess maternal blood heavy metals and maternal serum BDNF among Myanmar migrants in Samut Sakhon Province, Thailand

- Questionnaires consisted of three parts:

  1) Baseline self-administered questionnaires (socio demographic characteristics, health history and health behaviors, environmental factors related to heavy metals exposure)

  2) Second trimester-self-administered questionnaires (health behavioral changes, occupational changes, residence changes)

  3) Third trimester-self-administered questionnaires (health behavioral changes, occupational changes, residence changes)

- The Item-Objective Congruence Index (IOC) was analyzed for questionnaires' content validity testing by the following experts:

  1) Expert of Obstetrics and Gynecology:

  Dr. May Thu Htun, MBBS, MMed Sc

  Senior Assistant Surgeon, Obstetrics and Gynecology Specialist

  Organization: Central Women Hospital, Yangon, Myanmar

  Email: drmaythutun.mc@gmail.com

  2) Expert of Heavy Metals:

  Dr. Pokkate Wongsasuluk, Ph.D

  Organization: College of Public Health Sciences, Chulalongkorn University

  Email: pokkate.w@chula.ac.th

  (3) Expert of Public Health:

  Dr. Wandee Sirichokchatchawan, Ph.D

  Organization: College of Public Health Sciences, Chulalongkorn University

  Email: wandee.s@chula.ac.th

- The IOC of the questionnaires was 0.84
- According to three experts, the content validity of the questionnaires used in this study is approved for measuring

Appendix E: Questionnaires (English)

Self-reported questionnaire for first trimester (baseline)

This research is about "Effect of maternal blood heavy metal level on brain-derived neurotrophic factor and pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand". For this part of interview you are asked to answer the following questions on the interview from yourself. Please answer the questions by placing an "X" mark over the box next to the response that you have chosen. The questions in this part of interview contain those dealing with your socio-demographics, health history, health behaviors and environmental factors that are possible to expose heavy metals. As with any part of interview, you are free to choose not to participate, or if you choose to participate you can skip any question that you do not wish to answer. Your responses are confidential as neither your name, address nor any other identifier will be attached to any of your responses.

Socio-demographics

1) How old are you? ---------- (years)

2) What is your ethnicity?

☐ 1. Burmese

☐ 2. Karen

☐ 3. Mon

☐ Others (Please specify) ----------

3) What is your marital status?

☐ 1. Married: official married

☐ 2. Single

☐ 3. Separated/ Divorced

☐ 4. Stay together without married (not married but living together with partner)

☐ 5. Windowed

4) What is your highest education?

☐ 1. Can read and write

☐ 2. Primary school

☐ 3. Secondary school

☐ 4. High school and above

6) Do you have any current occupation?

☐ 1. Yes

☐ 2. No

If 'Yes", which one of the following sectors you work related to?

☐ 1. Industry

☐ 2. Construction

☐ 3. Domestic work

☐ 4. Fishery and fishery products factory

☐ 5. Agriculture

☐ 6. Others (Please specify) ----------

7) What is your average monthly family income ----------(THB/month)

8) How long did you stay in Samut Sakhon? ----------(years)

Health history and health behaviors

9) Have you ever been pregnant?

☐ 1. Yes

☐ 2. No

10) How many child (ren) have you given birth to? ----------

11) Have you ever suffer any gynecological problems such as abnormal menstruations, mass in the uterus or ovary?

☐ 1. Yes

☐ 2. No

If "Yes", please specify when----------what ----------?

12) Do you have past history of hypertension?

☐ 1. Yes

☐ 2. No

13) Do you have family history of hypertension?

☐ 1. Yes

☐ 2. No

14) Do you have family history of depression?

☐ 1. Yes

☐ 2. No

15) Have you ever smoke?

☐ 1. Current

☐ 2. Not current

☐ 3. Never

16) Did you contact secondhand smoke exposure during the present pregnancy?

☐ 1. Yes

☐ 2. No

17) Have you ever drink?

☐ 1. Current

☐ 2. Not current

☐ 3. Never

18) Have you ever go to apply coloring your hair during this pregnancy (or) 3 months before?

☐ 1. Yes

☐ 2. No

19) Have you ever receive amalgam filling treatment during this pregnancy (or) 3 months before?

☐ 1. Yes

☐ 2. No

20) Have you ever take walking exercise (at least 20 minutes per day) during the present pregnancy?

☐ 1. Yes

☐ 2. No

If "Yes", how often do you go to do?

☐ 1. Daily

☐ 2. Not daily

21) How many frequency do you have seafood during the present pregnancy?

☐ 1. Less than once a week

☐ 2. Once a week

☐ 3. 2-3 times per week

☐ 4. >3 times per week

Environmental factors

22) Is your house/ room located within 1 km to the factory?

☐ 1. Yes

☐ 2. No

If "Yes", please choose the type of factory (ies). (You can chose more than one answer)

☐ 1. Alloy production factory

☐ 2. Battery manufacturing factory

☐ 3. Ceramic manufacturing factory

☐ 4. Electronics manufacturing factory

☐ 5. Glass manufacturing factory

☐ 6. Insecticides/ pesticides manufacturing factory

☐ 7. Metal pipe production factory

☐ 8. Paints production factory

☐ 9. Paper manufacturing factory

☐ 10. Pigments manufacturing factory

☐ 11. Plastics manufacturing factory

☐ 12. Textile printing factory

☐ 13. Others (Please specify) ----------

23) Is your house/ room located within 1 km to the followings? (You can choose more than one answer)

☐ 1. Construction site

☐ 2. Farm using insecticides/ pesticides

☐ 3. Solid waste combustion site

Self-reported questionnaire for second trimester

For this part of interview you are asked to answer the following questions on the interview from yourself. Please answer the questions by placing an "X" mark over the box next to the response that you have chosen. The questions in this part of interview contain those dealing with your health behavioral changes, occupation and residential changes. As with any part of interview, you are free to choose not to participate, or if you choose to participate you can skip any question that you do not wish to answer. Your responses are confidential as neither your name, address nor any other identifier will be attached to any of your responses.

1) Have you ever go to take walking exercise (at least 20 minutes per day) during this trimester?

☐ 1. Yes

☐ 2. No

If "Yes", how often do you go to do that?

☐ 1. Daily

☐ 2. Not daily

2) How many frequency do you have seafood during this trimester?

☐ 1. Less than once a week

☐ 2. Once a week

☐ 3. 2-3 times per week

☐ 4. >3 times per week

3) Do you still have occupation in this trimester?

☐ 1. Yes

☐ 2. No

If "Yes", did you change to another occupational sector?

☐ 1. Yes

☐ 2. No

If "Yes", which one of the following sectors you current occupation is related to?

- ☐ 1. Industry
- ☐ 2. Construction
- ☐ 3. Domestic work
- ☐ 4. Fishery and fishery product factory
- ☐ 5. Agriculture
- ☐ 6. Others (Please specify) ----------

4) Have you move your house/ room during this trimester?

- ☐ 1. Yes
- ☐ 2. No

If "Yes", is your house/ room located within 1 km to the followings? (You can choose more than one answer)

- ☐ 1. Alloy production factory
- ☐ 2. Battery manufacturing factory
- ☐ 3. Ceramic manufacturing factory
- ☐ 4. Electronics manufacturing factory
- ☐ 5. Glass manufacturing factory
- ☐ 6. Insecticides/ pesticides manufacturing factory
- ☐ 7. Metal pipe production factory
- ☐ 8. Paints production factory
- ☐ 9. Paper manufacturing factory
- ☐ 10. Pigments manufacturing factory
- ☐ 11. Plastics manufacturing factory
- ☐ 12. Textile printing factory
- ☐ 13. Construction site
- ☐ 14. Farm using insecticides/ pesticides
- ☐ 15. Solid waste combustion sites

Self-reported questionnaire for third trimester

For this part of interview you are asked to answer the following questions on the interview from yourself. Please answer the questions by placing an "X" mark over the box next to the response that you have chosen. The questions in this part of interview contain those dealing with your health related behavioral changes, occupation and residential changes. As with any part of interview, you are free to choose not to participate, or if you choose to participate you can skip any question that you do not wish to answer. Your responses are confidential as neither your name, address nor any other identifier will be attached to any of your responses.

1) Have you ever go to take walking exercise (at least 20 minutes per day) during this trimester?

☐ 1. Yes

☐ 2. No

If "Yes", how often do you go to do that?

☐ 1. Daily

☐ 2. Not daily

2) How many frequency do you have seafood during this trimester?

☐ 1. Less than once a week

☐ 2. Once a week

☐ 3. 2-3 times per week

☐ 4. >3 times per week

3) Do you still have occupation in this trimester?

☐ 1. Yes

☐ 2. No

If "Yes", did you change to another occupational sector?

☐ 1. Yes

☐ 2. No

If "Yes", which one of the following sectors you current occupation is related to?

- ☐ 1. Industry
- ☐ 2. Construction
- ☐ 3. Domestic work
- ☐ 4. Fishery and fishery product factory
- ☐ 5. Agriculture
- ☐ 6. Others (Please specify) ----------

4) Have you move your house/ room during this trimester?

- ☐ 1. Yes
- ☐ 2. No

If "Yes", is your house/ room located within 1 km to the followings? (You can choose more than one answer)

- ☐ 1. Alloy production factory
- ☐ 2. Battery manufacturing factory
- ☐ 3. Ceramic manufacturing factory
- ☐ 4. Electronics manufacturing factory
- ☐ 5. Glass manufacturing factory
- ☐ 6. Insecticides/ pesticides manufacturing factory
- ☐ 7. Metal pipe production factory
- ☐ 8. Paints production factory
- ☐ 9. Paper manufacturing factory
- ☐ 10. Pigments manufacturing factory
- ☐ 11. Plastics manufacturing factory
- ☐ 12. Textile printing factory
- ☐ 13. Construction site
- ☐ 14. Farm using insecticides/ pesticides
- ☐ 15. Solid waste combustion sites

Appendix F: Participant Information Sheet (English)

Title of research project Effect of maternal blood heavy metal level on Brain-derived Neurotrophic Factor and pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand

Principle researcher's name Ye Htet Zaw Position PhD student, Public Health Program, College of Public Health Sciences, Chulalongkorn University

Office address College of Public Health Sciences, Chulalongkorn University

Home address (Current address in Thailand) CUihouse 268 Soi Chulalongkorn 9, Charasmuang road, Wangmai, Pathumwan, Bangkok 10330, Thailand

Cell phone 0924747033 E-mail: yehtet.roman@gmail.com

1) You are being invited to take part in a research project. Before you decide to participate it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and do not hesitate to ask if anything is unclear or if you would like more information.
2) This research project involves the study of association between maternal blood heavy metals level and Brain-derived neurotrophic factor (BDNF) and pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand. In this study, heavy metal means lead, mercury, cadmium and arsenic. The general objective is to identify the effect of maternal blood heavy metal level on BDNF and pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand.
3) Details of participant
   - ❖ Characteristics including inclusion and exclusion criteria.

   Participants will be registered Myanmar migrants with pregnancy

   Inclusion criteria

   1) Those who visited ANC clinic of the hospital within first trimester gestation
   2) Those who stayed in the study area at least three months before
   3) Those who aged between 18 to 35 years

4) Those who planned to deliver the baby at the study hospital

5) Those who could read, write and communicate in Myanmar language

6) Those who were willing to participate

Exclusion criteria

1) Those who is multiparous with more than five parity

2) Those who has less than one year inter-pregnancy interval

3) Those who is confirmed as multiple pregnancy by ultrasound

4) Those who has past history of PE, preterm birth, LBW and depression

❖ This study needs totally 124 participants.

4. Procedure upon participants

❖ Research procedure will be provided by the principle researcher. Self-reported questionnaires will be collected by the trained research assistant. Blood collection will be provided by the trained nurse. Blood analysis will be provided by the laboratory technician.

❖ The duration of the study: the participants will participate in the study until delivery of baby.

❖ The operation programs: it will be operated a total 4 times.

(1) First trimester (baseline)

(1.1) Principle researcher will select the participants by screening list. Participants' information sheet will be provided and informed consent will be asked to all selected participants. It will take about 15 minutes to complete self-reported questionnaires.

(1.2) the nurse will collect one teaspoonful whole blood of the participants by single-used needle and syringe into two sterile tubes. (Blood samples will be destroyed after the end of research)

(2) Second trimester

(2.1) During second trimester ANC visit, the research assistant will identify the participants and distribute the questionnaires. It will take about 5 minutes to complete questionnaires.

(3) Third trimester

(3.1) During third trimester ANC visit, the research assistant will identify the participants and distribute the questionnaires. It will take about 5 minutes to complete questionnaires.

(3.2) The nurse will collect one teaspoonful whole blood of the participants by single-used needle and syringe into two sterile tubes. (Blood samples will be destroyed after the end of research)

(4) Delivery

The nurse of the delivery room will collect the information on birth outcomes from the post-delivery note of the participants.

5. Process of providing information which also be stated in the proposal.

5.1 The principle researcher will provide information to potential participants through meeting and coordinate with the management team of the hospital.

5.2 All potential participants can read, write and communicate in Myanmar language.

5.3 If the process of screening potential participant found a person not meet the inclusion criteria and in need of help/ advice or any problems in any period of pregnancy, the principle researcher will give health education on pregnancy care and refer to the related specialist doctor in the Krathum Baen hospital for check-up and further advanced treatment as soon as possible.

6. In screening process: to approach potential participant, the antenatal care clinic of the Krathum Baen Hospital provide routine antenatal care services to Myanmar migrants. All pregnant women come to the clinic have to do registration both at the first visit and every visit. This study will use the information from the antenatal care clinic registration at the beginning of the screening process with the permission to access and participant's consent.

7. Use of clinical record

This study will involve clinical records (1. antenatal care card to get information of routine ultrasound (abdomen and pelvis) findings, systolic and diastolic blood pressure, 2. post-delivery records to get information of birth outcomes). Permission to access the clinical records will be asked from the hospital. Patient's consent to access the clinical records will be obtained.

8. Risk management

If the participants have miscarriage or any other obstetric problems during the study period, they will be referred to the specialist and excluded from the study.

9. Your participation in this study is completely voluntary and there is no compensation for participation. However, the researcher will give snacks and drinks to you as appreciation for your participation. You will be received health education about exposure to heavy metals by the researcher after the study.

10. The results of the study will be very beneficial to improve environmental health, pregnancy health, and migrant health.

11. Participation to the study is voluntary and participants has the right to deny and/ or withdraw from the study at any time, no need to give any reason, and there will be no bad impact upon that participant.

12. If you have any question or would like to obtain more information, the principle researcher can be reached at all time. If the researcher has new information regarding benefit or risk/harm, participants will be informed as soon as possible. This practice will provide an opportunity for participants to decide whether to stay/ not stay with the project.

Principle researcher's name: Ye Htet Zaw

Position: A doctorate degree student, Public Health Program, College of Public Health Sciences, Chulalongkorn University, Mobile: +66 924747033 E-mail: yehtet.roman@gmail.com

13. Information directly related to you will be kept in confidential. Results of the study will be reported as total picture. Any information which could be able to identify you will not appear in the report.

14. There will be no compensation for participation.

15. If researcher does not perform upon participants as indicated in the information, the participants can report the incident to the Research Ethics Review Committee for Research Involving Human Research Participants, Health Sciences Group, Chulalongkorn University (RECCU). Chamchuri 1 Bldg., 2nd Fl., 254 Phyathai Rd., Patumwan district, Bangkok 10330, Thailand, Tel./Fax. 0-2218-3202 E-mail: eccu@chula.ac.th.

Appendix G: Informed Consent Form (English)

Address ----------

Date----------

Code number of participant ----------

I who have signed here below agree to participate in this research project Title "Effects of maternal blood heavy metal level on Brain-derived neurotrophic factor and pregnancy outcomes among Myanmar migrants in Samut Sakhon Province, Thailand"

Principle researcher's name Ye Htet Zaw

Contact address CUihouse, 268, Soi Chulalongkorn 9, Charasmaung Road, Pathumwan, Wangmai, Bangkok 10330, Thailand

Telephone + 66 92474 7033

I have (read or been informed) about rationale and objective(s) of the project, what I will be engaged with in details, risk/harm and benefit of this project. The researcher has explained to me and I clearly understand with satisfaction.

I willingly agree to participate in this project and consent the researcher to response to questionnaires three times during each antenatal care visit, to give blood samples two times (one teaspoonful of blood during first visit and one teaspoonful of blood during third visit). After the project, personal data of blood samples will be destroyed.

I have the right to withdraw from this research project at any time as I wish with no need to give any reason. This withdrawal will not have any negative impact upon me.

Researcher has guaranteed that procedure(s) acted upon me would be exactly the same as indicated in the information. Any of my personal information will be kept confidential. Results of the study will be reported as total picture. Any of personal information which could be able to identify me will not appear in the report.

If I am not treated as indicated in the information sheet, I can report to the Research Ethics Review Committee for Research Involving Human Research Participants, Health Sciences Group, Chulalongkorn University (RECCU). Chamchuri 1 Bldg., 2nd Fl., 254 Phyathai Rd., Patumwan district, Bangkok 10330, Thailand, Tel./Fax. 0-2218-3202 E-mail: eccu@chula.ac.th.

I also have received a copy of information sheet and informed consent form

Sign----------

(----------)

Researcher

Sign----------

(----------)

Participant

Sign----------

(----------)

Witness

Appendix H: Questionnaires (Myanmar)

ကိုယ်တိုင်ဖတ်ပြီးဖြေရသော အခြေခံပထမမေးခွန်းလွှာ

ဤသုတေသနသည် ထိုင်းနိုင်ငံ၊ စမွတ်ဆခွန်ခရိုင်ရှိ ရွှေ့ပြောင်းနေထိုင်သူ မြန်မာနိုင်ငံသားများ၌ ကိုယ်ဝန်ဆောင်မိခင်သွေးအတွင်း သတ္တုလေးပါဝင်မှုပမာဏ၏ အာရုံကြောဖွံ့ဖြိုးရေးအထောက်အပံ့ပေးပရိုတင်းနှင့် ကိုယ်ဝန်ဆောင်ကျန်းမာရေးရလဒ်များ အပေါ် သက်ရောက်မှုကို လေ့လာသောသုတေသနဖြစ်ပါသည်။ မေးခွန်းများကိုကိုယ်တိုင် ဖတ်ပြီးဖြေဆိုပေးဖို့ သင့်အားဖိတ်ခေါ်ပါတယ်။ သင်ရွေးချယ်သည့် အဖြေမှန်ဘေးရှိ အကွက်ထဲတွင် ကြက်ခြေခတ်သင်္ကေတထည့်ခြင်းဖြင့် မှန်ကန်သည့်အဖြေများကို ရွေးချယ်ဖြေဆိုပါ။ ပါဝင်မည့်မေးခွန်းများမှာ သင်၏လူမှုရေးရာအခြေခံအချက်များ၊ ကျန်းမာရေးရာဇဝင်များ၊ ကျန်းမာရေးနှင့်သက်ဆိုင်သောအမူအကျင့်များ၊ ပတ်ဝန်းကျင်နှင့်သက်ဆိုင်သော အကြောင်းအရာများ ဖြစ်သည်။ မေးခွန်းများကိုဖြေဆိုရာတွင် ဆက်လက်ဖြေဆိုလိုစိတ်မရှိတော့ပါက လွတ်လပ်စွာငြင်းပယ်ခွင့်ရှိပါသည် (သို့မဟုတ်) သင်မဖြေဆိုလိုသော မေးခွန်းများကို ကျော်လိုကကျော်သွားနိုင်သည်။ သင့်အဖြေများကို စနစ်တကျလုံခြုံစွာ ထိန်းသိမ်းပေးသွားမည်ဖြစ်ပြီး သင်ဟုသိစေနိုင်မည့် အမည်၊ နေရပ်လိပ်စာ၊ အခြားမည်သည့်အရာမှလည်း ဖော်ပြသွားမှာမဟုတ်ပါ။

လူမှုရေးရာအခြေခံအချက်များ

(၁) သင့်အသက် (ပြည့်ပြီး) ဘယ်လောက်ရှိပြီလဲ။ ---------- (နှစ်)

(၂) သင်ဘာလူမျိုးလဲ။

☐ ၁။ ဗမာ

☐ ၂။ ကရင်

☐ ၃။ မွန်

☐ ၄။ အခြား (ကျေးဇူးပြုပြီးဖော်ပြပါ) ----------

(၃) သင့်အိမ်ထောင်ရေးအခြေအနေက ဘယ်လိုလဲ။

☐ ၁။ တရားဝင်လက်ထပ်ထား

☐ ၂။ အိမ်ထောင်မရှိ

☐ ၃။ အိမ်ထောင်ကွဲ၊ တခုလပ်

☐ ၄။ လက်မထပ်ဘဲအတူနေ

☐ ၅။ မုဆိုးမ၊ ယောကျ်ားဆုံးပါး

(၄) သင်နောက်ဆုံး သင်ယူတတ်မြောက်ထားတဲ့ပညာအရည်အချင်းက

☐ ၁။ ရေးတတ်၊ ဖတ်တတ်ရုံ

☐ ၂။ မူလတန်း

☐ ၃။ အလယ်တန်း

☐ ၄။ အထက်တန်းနှင့်အထက်

(၅) သင့်မှာ လက်ရှိအလုပ်အကိုင်ရှိပါသလား။

☐ ၁။ ရှိပါတယ်

☐ ၂။ အလုပ်မရှိသေးပါ

(၆) အလုပ်ရှိတယ်ဆိုလျှင် ဘယ်လိုအလုပ်မျိုးမှာလုပ်ရတာလဲ။

☐ ၁။ စက်ရုံလုပ်ငန်း

☐ ၂။ ဆောက်လုပ်ရေး

☐ ၃။ အိမ်အကူ

☐ ၄။ ငါးနှင့် ရေထွက်ကုန်လုပ်ငန်း

☐ ၅။ စိုက်ပျိုးရေး

☐ ၆။ အခြား (ကျေးဇူးပြုပြီးဖော်ပြပါ) ----------

(၇) သင့်မိသားစုတစ်လဝင်ငွေ ဘယ်လောက်ရှိလဲ။----------(ထိုင်းဘတ်)

(၈) စမွတ်ဆခွန်မှာနေတာ ဘယ်လောက်ကြာပြီလဲ။ ---------- (နှစ်)

ကျန်းမာရေးရာဇဝင်နှင့် ကျန်းမာရေးနှင့်သက်ဆိုင်သောအမူအကျင့်များ

(၉) အရင်က ကိုယ်ဝန်ဆောင်ဖူးပါသလား။

☐ ၁။ ဆောင်ဖူးပါတယ်

☐ ၂။ မဆောင်ဖူးပါ

(၁၀) သင့်မှာ လက်ရှိမွေးထားပြီးကလေးဘယ်နှစ်ယောက်ရှိလဲ။----------(ယောက်)

(၁၁)အရင်က အမျိုးသမီးရောဂါ (ဥပမာ။ ။ဓမ္မတာပုံမှန်မပေါ်ခြင်း၊ သားအိမ်၊ သားဥပြွန်တွင် အကျိတ်လုံး တွေ့ခြင်း) ဖြစ်ဖူးလား။

☐ ၁။ ဖြစ်ဖူးတယ်

☐ ၂။ မဖြစ်ဖူးပါ

ဖြစ်ဖူးတယ်ဆိုလျှင် ဘယ်တုန်းက ---------- ဘာဖြစ်တာလဲ ----------

(၁၂) အရင်က သွေးတိုးရောဂါဖြစ်ဖူးလား။

☐ ၁။ ဖြစ်ဖူးတယ်

☐ ၂။ မဖြစ်ဖူးပါ

(၁၃) မိသားစုမျိုးရိုးထဲမှာ သွေးတိုးရောဂါဖြစ်တဲ့သူရှိလား။

☐ ၁။ ရှိတယ်

☐ ၂။ မရှိပါ

(၁၄) မိသားစုမျိုးရိုးထဲမှာ စိတ်ကျရောဂါဖြစ်ဖူးတဲ့သူရှိလား။

☐ ၁။ ရှိတယ်

☐ ၄။ မရှိပါ

(၁၅) ဆေးလိပ်သောက်ဖူးလား။

☐ ၁။ အခုလောလောဆယ်သောက်တယ်

☐ ၂။ အခုမသောက်ဘူး၊ အရင်တုန်းကတော့သောက်တယ်

☐ ၃။ ဘယ်တုန်းကမှမသောက်ဘူး

(၁၆) ဒီကိုယ်ဝန်ဆောင်ချိန်မှာ တခြားသူတွေဆေးလိပ်သောက်တဲ့အနားနေတာ၊ ဆေးလိပ်ငွေ့ ရှူမိတာ ရှိလား။

☐ ၁။ ရှိတယ်

☐ ၂။ မရှိဘူး

(၁၇) အရက်ဘီယာသောက်ဖူးလား။

☐ ၁။ အခုလောလောဆယ်သောက်တယ်

☐ ၂။ အခုမသောက်ဘူး၊ အရင်တုန်းကတော့သောက်တယ်

☐ ၃။ ဘယ်တုန်းကမှမသောက်ဘူး

(၁၈) ဒီကိုယ်ဝန်ဆောင်စဉ် (သို့မဟုတ်) ကိုယ်ဝန်မဆောင်ခင် ၃လအတွင်းမှာ ဆံပင် အရောင်ဆိုးဖူးလား။

☐ ၁။ ဆိုးဖူးတယ်

☐ ၂။ မဆိုးဖူးဘူး

(၁၉) ဒီကိုယ်ဝန်ဆောင်စဉ် (သို့မဟုတ်) ကိုယ်ဝန်မဆောင်ခင် ၃လအတွင်းမှာ သွားမှာ အပေါက်ဖြစ်လို့ သွားအပေါက်ဖာတဲ့ ကုသမှုမျိုး ခံယူဖူးလား။

☐ ၁။ ခံယူဖူးတယ်

☐ ၂။ မခံယူဖူးဘူး

(၂၀)ဒီကိုယ်ဝန်ဆောင်ထားချိန်မှာ လမ်းလျှောက်လေ့ကျင့်ခန်း (အနည်းဆုံးတနေ့မိနစ်၂၀ခန့်) လုပ်ဖြစ် ပါသလား။

☐ ၁။ လုပ်ဖြစ်တယ်

☐ ၂။ မလုပ်ဖြစ်ဘူး

လုပ်ဖြစ်တယ်ဆိုလျှင် ဘယ်လိုလုပ်ဖြစ်လဲ။

☐ ၁။ နေ့စဉ်

☐ ၂။ နေ့စဉ်မဟုတ်

(၂၁) ဒီကိုယ်ဝန်ဆောင်ထားချိန်မှာ ပင်လယ်စာတွေ ဘယ်လိုစားဖြစ်လဲ။

☐ ၁။ တစ်ပါတ်ကို တစ်ကြိမ်တောင် မစားဖြစ်ဘူး

☐ ၂။ တစ်ပါတ်ကို တစ်ကြိမ်တော့ စားဖြစ်တယ်

☐ ၃။ တစ်ပါတ်ကို ၂ကြိမ် ၃ကြိမ် စားဖြစ်တယ်

☐ ၄။ တစ်ပါတ်ကို ၃ကြိမ်အထက် စားဖြစ်တယ်

ပါတ်ဝန်းကျင်ဆိုင်ရာအချက်များ

(၂၂) သင်အခုနေတဲ့အိမ်၊ အခန်းက စက်ရုံနဲ့နီးလား။ (၁ ကီလိုမီတာအတွင်း)

☐ ၁။ နီးတယ်

☐ ၂။ မနီးဘူး

နီးတယ်ဆိုလျှင် ဘယ်လိုစက်ရုံတွေနဲ့နီးတာလဲ။ (အဖြေတစ်ခုထက်မက ရွေးလို့ ရပါတယ်)

☐ ၁။ သတ္တုစပ် (အလွိုင်း) စက်ရုံ

☐ ၂။ ဘက်ထရီထုတ်စက်ရုံ

☐ ၃။ ကြွေထည်မြေထည်ထုတ်စက်ရုံ

☐ ၄။ အီလက်ထရောနစ်ပစ္စည်းထုတ်စက်ရုံ

☐ ၅။ ဖန်စက်ရုံ

☐ ၆။ ပိုးသတ်ဆေးထုတ်စက်ရုံ

☐ ၇။ သတ္တုပိုက်ထုတ်စက်ရုံ

☐ ၈။ အိမ်သုတ်ဆေးထုတ်စက်ရုံ

☐ ၉။ စာရွက် စက္ကူထုတ်စက်ရုံ

☐ ၁၀။ ဆိုးဆေး၊ အရောင်ဆိုးဆေးထုတ်စက်ရုံ

☐ ၁၁။ ပလတ်စတစ်ထုတ်စက်ရုံ

☐ ၁၂။ အထည်ချုပ်စက်ရုံ

☐ ၁၃။ အခြား (ကျေးဇူးပြုပြီးဖော်ပြပါ) ----------

(၂၃) သင်အခုနေတဲ့ အိမ်၊ အခန်းက အောက်ပါနေရာတွေနဲ့နီးလား။ (၁ ကီလိုမီတာအတွင်း) (အဖြေ တစ်ခုထက်ပိုပြီးရွေးလို့ရပါတယ်)

☐ ၁။ ဆောက်လုပ်ရေးလုပ်ငန်း

☐ ၂။ ပိုးသတ်ဆေးတွေသုံးတဲ့လယ်ယာစိုက်ပျိုးရေး

☐ ၃။ အမှိုက်မီးရှို့တဲ့နေရာ

ကိုယ်တိုင်ဖတ်ဖြေရသော ဒုတိယမေးခွန်းလွှာ (ကိုယ်ဝန်သက် ဒုတိယဥလ)

မေးခွန်းများကိုကိုယ်တိုင်ဖတ်ပြီးဖြေဆိုပေးဖို့ သင့်အားဖိတ်ခေါ်ပါတယ်။ သင်ရွေးချယ်သည့် အဖြေမှန်ဘေးရှိ အကွက်ထဲတွင် ကြက်ခြေခတ်သင်္ကေတထည့်ခြင်းဖြင့် မှန်ကန်သည့် အဖြေများကို ရွေးချယ်ဖြေဆိုပါ။ ပါဝင်မည့်မေးခွန်းများမှာ ကျန်းမာရေးနှင့်သက်ဆိုင်သော အမူအကျင့်များပြောင်းလဲမှု၊ အလုပ်အကိုင်နှင့် နေထိုင်ရာပြောင်းလဲမှု စသည်တို့ဖြစ်သည်။ မေးခွန်းများကိုဖြေဆိုရာတွင် ဆက်လက်ဖြေဆိုလိုစိတ်မရှိတော့ပါက လွတ်လပ်စွာ ငြင်းပယ်ခွင့်ရှိပါသည် (သို့မဟုတ်) သင်မဖြေဆိုလိုသောမေးခွန်းများကို ကျော်လိုက ကျော်သွားနိုင်သည်။ သင့်အဖြေများကို စနစ်တကျလုံခြုံစွာ ထိန်းသိမ်းပေးသွားမည်ဖြစ်ပြီး သင်ဟုသိစေနိုင်မည့် အမည်၊ နေရပ်လိပ်စာ၊ အခြားမည်သည့်အရာမှလည်း ဖော်ပြသွားမှာ မဟုတ်ပါ။

(၁) ဒီကိုယ်ဝန်ကာလအတွင်း လမ်းလျှောက်လေ့ကျင့်ခန်း (အနည်းဆုံးတနေ့မိနစ် ၂၀ခန့်) လုပ်ဖြစ်လား။

☐ ၁။ လုပ်ဖြစ်တယ်

☐ ၂။ မလုပ်ဖြစ်ဘူး

လုပ်ဖြစ်တယ်ဆိုလျှင် ဘယ်လိုလုပ်ဖြစ်လဲ။

☐ ၁။ နေ့စဉ်

☐ ၂။ နေ့စဉ်မဟုတ်

(၂) အခုကိုယ်ဝန်ကာလအတွင်း ပင်လယ်စာတွေဘယ်လိုစားဖြစ်လဲ။

☐ ၁။ တစ်ပါတ်ကို တစ်ကြိမ်တောင် မစားဖြစ်ဘူး

☐ ၂။ တစ်ပါတ်ကို တစ်ကြိမ်တော့ စားဖြစ်တယ်

☐ ၃။ တစ်ပါတ်ကို ၂ကြိမ် ၃ကြိမ် စားဖြစ်တယ်

☐ ၄။ တစ်ပါတ်ကို ၃ကြိမ်အထက် စားဖြစ်တယ်

(၃) အခုကိုယ်ဝန်ကာလအတွင်း သင်အလုပ်အကိုင်ရှိသေးလား။

☐ ၁။ ရှိသေးတယ်

☐ ၂။ မရှိတော့ပါ

ရှိသေးတယ်ဆိုလျင် တခြားအလုပ်ပြောင်းသေးလား။

☐ ၁။ ပြောင်းတယ်

☐ ၂။ မပြောင်းပါ

ပြောင်းတယ်ဆိုလျင် အခုလက်ရှိအလုပ်ကဘယ်လိုမျိုးလဲ။

☐ ၁။ စက်ရုံလုပ်ငန်း

☐ ၂။ ဆောက်လုပ်ရေး

☐ ၃။ အိမ်အကူ

☐ ၄။ ငါးနှင့် ရေထွက်ကုန်လုပ်ငန်း

☐ ၅။ စိုက်ပျိုးရေး

☐ ၆။ အခြား (ကျေးဇူးပြုပြီး ဖော်ပြပါ) ----------

(၄) အခုကိုယ်ဝန်ကာလအတွင်း အိမ်၊ အခန်းပြောင်းသေးလား။

☐ ၁။ ပြောင်းတယ်

☐ ၂။ မပြောင်းဘူး

ပြောင်းတယ်ဆိုလျှင် သင်အခုနေတဲ့အိမ်၊ အခန်းက အောက်ပါအရာတွေနဲ့နီးလား။

(၁ ကီလိုမီတာအတွင်း) (အဖြေတစ်ခုထက်မကရွေးလို့ရပါတယ်)

- ☐ ၁။ သတ္တုစပ် (အလွိုင်း) စက်ရုံ
- ☐ ၂။ ဘက်ထရီထုတ်စက်ရုံ
- ☐ ၃။ ကြွေထည်မြေထည်ထုတ်စက်ရုံ
- ☐ ၄။ အီလက်ထရောနစ်ပစ္စည်းထုတ်စက်ရုံ
- ☐ ၅။ ဖန်စက်ရုံ
- ☐ ၆။ ပိုးသတ်ဆေးထုတ်စက်ရုံ
- ☐ ၇။ သတ္တုပိုက်ထုတ်စက်ရုံ
- ☐ ၈။ အိမ်သုတ်ဆေးထုတ်စက်ရုံ
- ☐ ၉။ စာရွက် စက္ကူထုတ်စက်ရုံ
- ☐ ၁၀။ ဆိုးဆေး၊ အရောင်ဆိုးဆေးထုတ်စက်ရုံ
- ☐ ၁၁။ ပလတ်စတစ်ထုတ်စက်ရုံ
- ☐ ၁၂။ အထည်ချုပ်စက်ရုံ
- ☐ ၁၃။ ဆောက်လုပ်ရေးလုပ်ငန်း
- ☐ ၁၄။ ပိုးသတ်ဆေးတွေသုံးတဲ့လယ်ယာစိုက်ပျိုးရေး
- ☐ ၁၅။ အမှိုက်မီးရှို့တဲ့နေရာ
- ☐ ၁၆။ အခြား (ကျေးဇူးပြုပြီးဖော်ပြပါ) ----------

ကိုယ်တိုင်ဖတ်ဖြေရသော တတိယမေးခွန်းလွှာ (ကိုယ်ဝန်သက် တတိယခုလ)

မေးခွန်းများကိုကိုယ်တိုင်ဖတ်ပြီးဖြေဆိုပေးဖို့ သင့်အားဖိတ်ခေါ်ပါတယ်။ သင်ရွေးချယ်သည့်အဖြေမှန်ဘေးရှိ အကွက်ထဲတွင် ကြက်ခြေခတ်သင်္ကေတထည့်ခြင်းဖြင့် မှန်ကန်သည့်အဖြေများကို ရွေးချယ်ဖြေဆိုပါ။ ပါဝင်မည့်မေးခွန်းများမှာ ကျန်းမာရေးနှင့်သက်ဆိုင်သော အမူအကျင့်များပြောင်းလဲမှု၊ အလုပ်အကိုင်နှင့် နေထိုင်ရာပြောင်းလဲမှု စသည်တို့ဖြစ်သည်။ မေးခွန်းများကိုဖြေဆိုရာတွင် ဆက်လက် ဖြေဆိုလိုစိတ်မရှိတော့ပါက လွတ်လပ်စွာ ငြင်းပယ်ခွင့်ရှိပါသည် (သို့မဟုတ်) သင်မဖြေဆိုလိုသောမေးခွန်းများကို ကျော်လိုက ကျော်သွားနိုင်သည်။ သင့်အဖြေများကို စနစ်တကျလုံခြုံစွာ ထိန်းသိမ်းပေးသွားမည်ဖြစ်ပြီး သင်ဟုသိစေနိုင်မည့် အမည်၊ နေရပ်လိပ်စာ၊ အခြားမည်သည့်အရာမှလည်း ဖော်ပြသွားမှာ မဟုတ်ပါ။

(၁) ဒီကိုယ်ဝန်ကာလအတွင်း လမ်းလျှောက်လေ့ကျင့်ခန်း (အနည်းဆုံးတနေ့မိနစ် ၂၀ခန့်) လုပ်ဖြစ်လား။

☐ ၁။ လုပ်ဖြစ်တယ်

☐ ၂။ မလုပ်ဖြစ်ဘူး

လုပ်ဖြစ်တယ်ဆိုလျှင် ဘယ်လိုလုပ်ဖြစ်လဲ။

☐ ၁။ နေ့စဉ်

☐ ၂။ နေ့စဉ်မဟုတ်

(၂) အခုကိုယ်ဝန်ကာလအတွင်း ပင်လယ်စာတွေဘယ်လိုစားဖြစ်လဲ။

☐ ၁။ တစ်ပါတ်ကို တစ်ကြိမ်တောင် မစားဖြစ်ဘူး

☐ ၂။ တစ်ပါတ်ကို တစ်ကြိမ်တော့ စားဖြစ်တယ်

☐ ၃။ တစ်ပါတ်ကို ၂ကြိမ် ၃ကြိမ် စားဖြစ်တယ်

☐ ၄။ တစ်ပါတ်ကို ၃ကြိမ်အထက် စားဖြစ်တယ်

(၃) အခုကိုယ်ဝန်ကာလအတွင်း သင်အလုပ်အကိုင်ရှိသေးလား။

☐ ၁။ ရှိသေးတယ်

☐ ၂။ မရှိတော့ပါ

ရှိသေးတယ်ဆိုလျှင် တခြားအလုပ်ပြောင်းသေးလား။

☐ ၁။ ပြောင်းတယ်

☐ ၂။ မပြောင်းပါ

ပြောင်းတယ်ဆိုလျှင် အခုလက်ရှိအလုပ်ကဘယ်လိုမျိုးလဲ။

☐ ၁။ စက်ရုံလုပ်ငန်း

☐ ၂။ ဆောက်လုပ်ရေး

☐ ၃။ အိမ်အကူ

☐ ၄။ ငါးနှင့် ရေထွက်ကုန်လုပ်ငန်း

☐ ၅။ စိုက်ပျိုးရေး

☐ ၆။ အခြား (ကျေးဇူးပြုပြီး ဖော်ပြပါ) ----------

(၄) အခုကိုယ်ဝန်ကာလအတွင်း အိမ်၊ အခန်းပြောင်းသေးလား။

☐ ၁။ ပြောင်းတယ်

☐ ၂။ မပြောင်းဘူး

ပြောင်းတယ်ဆိုလျှင် သင်အခုနေတဲ့အိမ်၊ အခန်းက အောက်ပါအရာတွေနဲ့နီးလား။

(၁ ကီလိုမီတာအတွင်း) (အဖြေတစ်ခုထက်မကရွေးလို့ရပါတယ်)

☐ ၁။ သတ္တုစပ် (အလွိုင်း) စက်ရုံ

☐ ၂။ ဘက်ထရီထုတ်စက်ရုံ

☐ ၃။ ကြွေထည်မြေထည်ထုတ်စက်ရုံ

☐ ၄။ အီလက်ထရောနစ်ပစ္စည်းထုတ်စက်ရုံ

☐ ၅။ ဖန်စက်ရုံ

☐ ၆။ ပိုးသတ်ဆေးထုတ်စက်ရုံ

☐ ၇။ သတ္တုပိုက်ထုတ်စက်ရုံ

☐ ၈။ အိမ်သုတ်ဆေးထုတ်စက်ရုံ

☐ ၉။ စာရွက် စက္ကူထုတ်စက်ရုံ

☐ ၁၀။ ဆိုးဆေး၊ အရောင်ဆိုးဆေးထုတ်စက်ရုံ

☐ ၁၁။ ပလတ်စတစ်ထုတ်စက်ရုံ

☐ ၁၂။ အထည်ချုပ်စက်ရုံ

☐ ၁၃။ ဆောက်လုပ်ရေးလုပ်ငန်း

☐ ၁၄။ ပိုးသတ်ဆေးတွေသုံးတဲ့လယ်ယာစိုက်ပျိုးရေး

☐ ၁၅။ အမှိုက်မီးရှို့တဲ့နေရာ

☐ ၁၆။ အခြား (ကျေးဇူးပြုပြီးဖော်ပြပါ) ----------

Appendix I: Participant Information sheet (Myanmar)

သုတေသနတွင်ပါဝင်သူများ၊ လူနာများအတွက် သတင်းအချက်အလက်စာလွှာ

သုတေသနခေါင်းစဉ်

ထိုင်းနိုင်ငံ၊ စမွတ်ဆခွန်ခရိုင်ရှိ ရွှေ့ပြောင်းမြန်မာနိုင်ငံသားများ၌ ကိုယ်ဝန်ဆောင်မိခင်သွေး အတွင်း သတ္တုလေးပါဝင်မှုပမာဏ၏ အာရုံကြောဖွံ့ဖြိုးရေးအထောက်အပံ့ပေးပရိုတင်းနှင့် ကိုယ်ဝန်ဆောင်မိခင်ကျန်းမာရေးရလဒ်များအပေါ် သက်ရောက်မှုကိုလေ့လာသောသုတေသန။

သုတေသနခေါင်းဆောင်အမည်

ရဲထက်ဇော်

လက်ရှိတာဝန်

ပါရဂူဘွဲ့လွန်ကျောင်းသား၊ ပြည့်သူ့ကျန်းမာရေးအထူးပြု၊ ပြည်သူ့ကျန်းမာရေးသိပ္ပံကောလိပ်၊ ချူလာလောင်ကွန်းတက္ကသိုလ်။

လက်ရှိနေရပ်လိပ်စာ

CUihouse၊ ၂၆၈၊ ချူလာလမ်းသွယ် ၉၊ ချရာမူရမ်လမ်း၊ ဝမ်မိုင်၊ ပသူဝမ်၊ ဗန်ကောက်၊ ၁၀၃၃၀၊ ထိုင်းနိုင်ငံ၊ လက်ကိုင်ဖုန်းနံပါတ် +၆၆၉ ၂၄၇၄ ၇၀၃၃၊ အီးမေးလ် yehtet.roman@gmail.com

၁။ ဤသုတေသနမှာပါဝင်ဖို့ သင့်ကို ကမ်းလှမ်းဖိတ်ခေါ်ပါတယ်။ ပါဝင်ဖို့မဆုံးဖြတ်ခင် ဘာ့ကြောင့် သုတေသနကိုလုပ်ရကြောင်း၊ ဘယ်လိုအစီအစဉ်တွေပါဝင်သွားမှာဖြစ်ကြောင်းကို သင်သိရှိနားလည်ထားဖို့ အရေးကြီးပါတယ်။ အောက်ပါသတင်းအချက်တွေကို အချိန်ပေးပြီး

ဂရုတစိုက်ဖတ်ပေးပါ။ အကယ်၍ မရှင်းလင်းတာ၊ နားမလည်တာရှိလျှင်၊ အခြားအချက်တွေ ထပ်သိချင်လျှင်လည်း မေးမြန်းဖို့ အားမနာပါနှင့်။

၂။ ဤသုတေသနဟာ ထိုင်းနိုင်ငံ၊ စမွတ်ဆခွန်ခရိုင်နေ ရွှေ့ပြောင်းမြန်မာနိုင်ငံသားတွေရဲ့ ကိုယ်ဝန်ဆောင်မိခင်သွေးထဲ သတ္တုလေးပါဝင်မှုပမာဏက အာရုံကြောဖွံ့ဖြိုးရေး အထောက်အပံ့ပေးပရိုတင်းနဲ့ ကိုယ်ဝန်ဆောင်မိခင်ကျန်းမာရေးရလဒ်တွေအပေါ် ဘယ်လို ဆက်စပ်သက်ရောက်မှုတွေဖြစ်နိုင်သလဲဆိုတာကို လေ့လာမှာဖြစ်တယ်။ ဒီသုတေသနမှာ သတ္တုလေးဆိုတဲ့အသုံးအနှုန်းက ခဲ၊ပြဒါး၊ ကတ်ဒမီယံနဲ့ စိန်အဆိပ်တို့ကိုဆိုလိုတာဖြစ်ပြီး ကိုယ်ဝန်ဆောင်ကျန်းမာရေးရလဒ်တွေဆိုတာကတော့ ကောင်းတဲ့ရလဒ် (ကိုယ်ဝန်ဆိပ်မတက်ခြင်း၊ နေ့စေ့လစေ့မွေးခြင်း၊ ကလေးပေါင်ချိန်ပြည့်ခြင်း) နဲ့ မကောင်းတဲ့ရလဒ် (ကိုယ်ဝန်ဆိပ်တက်ခြင်း၊ လမစေ့မွေးခြင်းနဲ့ ကလေးပေါင်မပြည့်ခြင်း) တွေကို ဆိုလိုတာ ဖြစ်ပါတယ်။ သုတေသနရဲ့ယေဘူယျရည်ရွယ်ချက်ကတော့ ထိုင်းနိုင်ငံ၊ စမွတ်ဆခွန်ခရိုင်နေ ရွှေ့ပြောင်းမြန်မာနိုင်ငံသားတွေရဲ့ ကိုယ်ဝန်ဆောင်မိခင်သွေးထဲ သတ္တုလေးပါဝင်မှုပမာဏက အာရုံကြောဖွံ့ဖြိုးရေးအထောက်အပံ့ပေးပရိုတင်းနဲ့ မိခင်ကျန်းမာရေးရလဒ်တွေအပေါ် ဘယ်လိုဆက်စပ်မှုတွေ ဖြစ်နိုင်လဲဆိုတာကို လေ့လာဖို့ ဖြစ်ပါတယ်။

၃။ သုတေသနမှာပါဝင်မည့်သူများ၏ အသေးစိတ်အချက်အလက်များ

ပါဝင်မည့်သူတွေဟာ ထိုင်းနိုင်ငံ၊ စမွတ်ဆခွန်ခရိုင်အတွင်းနေထိုင်ပြီး ခထွန်းဘမ်မြို့နယ်၊ ခထွန်းဘမ်ဆေးရုံ ကိုယ်ဝန်ဆောင်ကျန်းမာရေးစောင့်ရှောက်မှုဆေးခန်းကို လာပြတဲ့ ရွှေ့ပြောင်းမြန်မာနိုင်ငံသားအဖြစ်စာရင်းသွင်းထားပြီးသူ ကိုယ်ဝန်ဆောင်မိခင်များ ဖြစ်ပါမယ်။

ပါဝင်ရန်အကျုံးဝင်သည့် အချက်များ

(၁) ကိုယ်ဝန်ဆောင်မိခင်စောင့်ရှောက်ရေးဆေးခန်းကို ကိုယ်ဝန်သက် ပထမ၃-လ အတွင်း လာရောက်ပြသသူ

(၂) ဆေးခန်းလာမပြခင် အနည်းဆုံး၃လအတွင်း စမွန်ဆခွန်ခရိုင်မှာနေထိုင်ခဲ့သူ

(၃) အသက် ၁၈နှစ်မှ ၃၅နှစ်အတွင်း

(၄) ခထွန်းဘမ်ဆေးရုံမှာ မွေးဖွားဖို့ စီစဉ်ထားသူ

(၅) မြန်မာဘာသာစကားကို ဖတ်တတ်၊ ရေးတတ်၊ ပြောတတ်သူ

(၆) သုတေသနမှာ ပါဝင်ဖို့ဆန္ဒရှိသူ

ပါဝင်ရန် အကျုံးမဝင်သည့်အချက်များ

(၁) ကလေး၅ယောက်နဲ့အထက် မွေးထားပြီးသူ

(၂) အရင်ကိုယ်ဝန်နဲ့ အခုကိုယ်ဝန်ကြားကာလ ၁နှစ်မရှိသေးသူ

(၃) အမြွာကိုယ်ဝန်ဟု ဓါတ်မှန်ဖြင့် အတည်ပြုထားပြီးသူ

(၄) အရင်တုန်းက ကိုယ်ဝန်ဆိပ်တက်ခြင်း၊ လမစေ့မွေးခြင်း၊ ကလေးပေါင်ချိန်မပြည့်ခြင်း၊ စိတ်ဓါတ်ကျခြင်း စတာတွေဖြစ်ဖူးသူ

ဤသုတေသနအတွက် ပါဝင်မည့်သူ စုစုပေါင်း ကိုယ်ဝန်သည် ၁၂၄-ယောက် လိုအပ်ပါတယ်။

၄။ သုတေသနဆောင်ရွက်မည့်နည်းများ

သုတေသနခေါင်းဆောင်က သုတေသနဆောင်ရွက်မည့်နည်းလမ်းတွေကို စီမံကြီးကြပ်သွားပါမယ်။ ကိုယ်တိုင်ဖတ်ဖြေဆိုရမည့်မေးခွန်းလွှာတွေကိုတော့ သုတေသနအကူက

ဖြန့်ဝေပေးပါမယ်။ သွေးဖောက်ခြင်းကို ကျွမ်းကျင်သူနာပြုက ပြုလုပ်ပါမယ်။ သွေးခါတ်ခွဲစစ်ဆေးခြင်းကို ခါတ်ခွဲခန်းပညာရှင်မှ ပြုလုပ်ပါမယ်။ သုတေသနကာလ အနေနဲ့ကတော့ ကိုယ်ဝန်ဆောင်မိခင်တွေဟာ ၄င်းတို့ကလေးမွေးဖွားချိန်အထိ ပါဝင်ပါမယ်။

သုတေသနအစီအစဉ်ကိုတော့ စုစုပေါင်း ၄ကြိမ် ပြုလုပ်ပါမယ်။

(၁) ကိုယ်ဝန်ဆောင်မိခင်စောင့်ရှောက်ရေးဆေးခန်းသို့ ကိုယ်ဝန်သက်ပထမဝုလအတွင်း လာရောက် ပြသချိန်တွင်ပြုလုပ်မည့် ပထမအစီအစဉ်

(၁.၁) ခထွန်းဘမ်ဆေးရုံ ကိုယ်ဝန်ဆောင်မိခင်စောင့်ရှောက်ရေးဆေးခန်းမှာ သုတေသနခေါင်းဆောင်ဟာ လူနာစာရင်းတွေကတဆင့် အကျိုးဝင်၊မဝင်အချက်တွေကို ကြည့်ပြီး ပါဝင်မည့်သူတွေကို ရွေးချယ်ပါလိမ့်မယ်။ ပါဝင်မည့်သူတွေသိထားရမည့် သတင်းအချက်အလက်စာရွက်ကို ထုတ်ပေးမှာဖြစ်ပြီး၊ သဘောတူဝန်ခံကတိကိုလည်း မေးမြန်းတောင်းဆိုသွားပါမယ်။ မြန်မာဘာသာနဲ့ ရှင်းလင်းအောင်ရေးထားတဲ့ မေးခွန်းတွေ ဖြစ်ပါမယ်။ ဖြေဆိုချိန်ကတော့ ၁၅ မိနစ်လောက် ကြာပါလိမ့်မယ်။

(၁.၂) ကျွမ်းကျင်သူနာပြုက ကိုယ်ဝန်ဆောင်တွေရဲ့ သွေးနမူနာ လက်ဖက်ရည်ဇွန်း တစ်ဇွန်း ပမာဏကို တခါသုံးဆေးထိုးအပ်နဲ့ဖောက်ယူပြီး ပိုးသတ်သန့်စင်ထားတဲ့ ထည့်စရာ ပြွန် ၂ခုထဲ ခွဲထည့်ပါမယ်။ (သုတေသနပြီးဆုံးတဲ့အခါ သွေးနမူနာအားလုံးကို စနစ်တကျ ဖျက်ဆီးသွားမှာဖြစ်တယ်။)

(၂) ကိုယ်ဝန်ဆောင်မိခင်စောင့်ရှောက်ရေးဆေးခန်းသို့ ကိုယ်ဝန်သက်ဒုတိယဥလအတွင်း လာရောက် ပြသချိန်တွင်ပြုလုပ်မည့် ဒုတိယအစီအစဉ်

(၂. ၁) ကိုယ်ဝန်ဆောင်မိခင်စောင့်ရှောက်ရေးဆေးခန်းသို့ ကိုယ်ဝန်ဒုတိယဥလအတွင်း ထပ်မံလာရောက် ပြသချိန်မှာ သုတေသနအကူမှ ပါဝင်သူကိုယ်ဝန်ဆောင်တွေကို သေချာအောင်ပြန်စီစစ်ပြီး မေးခွန်းတွေ ဖြန့်ဝေပေးပါမယ်။ ဖြေဆိုချိန်ကတော့ ၃-မိနစ်လောက်သာ ကြာမြင့်ပါလိမ့်မယ်။

(၃) ကိုယ်ဝန်ဆောင်မိခင်စောင့်ရှောက်ရေးဆေးခန်းသို့ ကိုယ်ဝန်သက်တတိယဥလ အတွင်း လာရောက်ပြသချိန်တွင်ပြုလုပ်မည့် တတိယအစီအစဉ်

(၃. ၁) ကိုယ်ဝန်ဆောင်မိခင်စောင့်ရှောက်ရေးဆေးခန်းကို ကိုယ်ဝန်တတိယဥလအတွင်း ထပ်မံလာရောက် ပြသချိန်မှာ သုတေသနအကူမှ ပါဝင်သူကိုယ်ဝန်ဆောင်တွေကို သေချာအောင်ပြန်စီစစ်ပြီး မေးခွန်းတွေ ဖြန့်ဝေပေးပါမယ်။ ဖြေဆိုချိန်ကတော့ ၃-မိနစ်လောက်သာ ကြာမြင့်ပါလိမ့်မယ်။

(၃. ၂) ကျွမ်းကျင်သူနာပြုက ကိုယ်ဝန်ဆောင်တွေရဲ့ သွေးနမူနာလက်ဖက်ရည်ဇွန်းတစ်ဇွန်း ပမာဏကို တခါသုံးဆေးထိုးအပ်နဲ့ဖောက်ယူပြီး ပိုးသတ်သန့်စင်ထားတဲ့ ထည့်စရာ ပြွန် ၂ခုထဲ ခွဲထည့်ပါမယ်။ (သုတေသနပြီးဆုံးတဲ့အခါ သွေးနမူနာအားလုံးကို စနစ်တကျဖျက်ဆီး သွားမှာဖြစ်တယ်)

(၄) ကလေးမွေးဖွားပြီးချိန်တွင် ပြုလုပ်မည့် စတုတ္ထအစီအစဉ်

ကလေးမွေးခန်းမှကျွမ်းကျင်သူနာပြုဟာ ကလေးမွေးဖွားမှုမှတ်တမ်းထဲက ကလေးမွေးတဲ့နည်းလမ်း [ရိုးရိုးမွေး (သို့မဟုတ်) ခွဲမွေး)]၊ ကလေးမွေးချိန်ကိုယ်ဝန်သက်၊

မွေးကင်းစကလေးပေါင်ချိန်စတဲ့ ကလေးမွေးဖွားမှုကျန်းမာရေးရလဒ်တွေကို မှတ်သားကောက်ယူပါမယ်။

၅။ သတင်းအချက်အလက်များ ထုတ်ပြန်ပေးသွားမည့် အစီအစဉ်

၅.၁ သုတေသနခေါင်းဆောင်ဟာ ဆေးရုံစီမံအုပ်ချုပ်ရေးအဖွဲ့နဲ့ညှိနှိုင်းကာ ပါဝင်သူကိုယ်ဝန်ဆောင်တွေကို တွေ့ဆုံဆွေးနွေးပြီး လိုအပ်တဲ့သတင်းတွေ ပေးသွားမှာ ဖြစ်ပါတယ်။

၅.၂ ပါဝင်မယ့်ကိုယ်ဝန်ဆောင်တွေဟာ မြန်မာဘာသာစကားကို ဖတ်တတ်၊ ရေးတတ်၊ ပြောတတ်ရမှာ ဖြစ်ပါတယ်။

၅.၃ သုတေသနကာလတလျှောက်မှာ ကိုယ်ဝန်ဆောင်မိခင်တဦးဦးဟာ အကျိုးဝင်အချက်တွေနဲ့ မကိုက်ညီတာ၊ ပြဿနာတခုခုရှိတာ၊ အကြံဉာဏ်အကူအညီတစုံတရာ လိုအပ်တာတွေ ဖြစ်လာခဲ့သော် သုတေသနခေါင်းဆောင်မှ ကိုယ်ဝန်ကျန်းမာရေးစောင့်ရှောက်မှုအကြောင်းကို ပညာပေးပြောပြသွားမှာ ဖြစ်သလို လိုအပ်တဲ့ကျန်းမာရေးဆေးစစ်မှုတွေလုပ်ဖို့ကိုလည်း ခထွန်းဘမ်ဆေးရုံရှိ သက်ဆိုင်ရာအထူးကုဆရာဝန်ထံ အချိန်မီလွှဲပြောင်းပေးသွားမှာလည်း ဖြစ်ပါတယ်။

၆။ ပါဝင်မည့်သူများအား စီစစ်ရွေးချယ်ခြင်း

ခထွန်းဘမ်ဆေးရုံ၊ ကိုယ်ဝန်ဆောင်မိခင်ကျန်းမာရေးစောင့်ရှောက်မှုဆေးခန်းမှ ရွှေ့ပြောင်းမြန်မာတွေကို ကိုယ်ဝန်ဆောင်ကျန်းမာရေးစောင့်ရှောက်မှုများ ပေးလျက်ရှိပါတယ်။ ဆေးခန်းသို့လာပြတဲ့ ကိုယ်ဝန်ဆောင်မိခင်များဟာ ပထမဆုံးအကြိမ်မှာ ဆေးရုံ၏ လူနာအဖြစ်စာရင်းသွင်းရပြီး နောက်ထပ်မံ ပြတဲ့အချိန်တိုင်းမှာလည်း ကုသစစ်ဆေးမှုခံယူဖို့

ပြန်လည်တန်းစီစောင့်ဆိုင်းကြရပါတယ်။ သုတေသန စတင်ချိန်အတွင်း ပါဝင်မည့်သူများ ရွေးချယ်တဲ့အခါ ဆေးခန်းကလူနာစာရင်းတွေကို ခွင့်တောင်းအသုံးပြုမှာဖြစ်ပြီး ပါဝင်မည့်သူများရဲ့ ခွင့်ပြုချက်ကိုလည်း တောင်းခံမှာဖြစ်ပါတယ်။

၇။ ဆေးမှတ်တမ်းများ အသုံးပြုခြင်း

ဤသုတေသနမှာ ပါဝင်သူကိုယ်ဝန်ဆောင်တွေရဲ့ဆေးမှတ်တမ်းတွေကို အသုံးပြုသွားပါမယ်။ (က) ကိုယ်ဝန်ဓါတ်မှန်အဖြေ၊ အပေါ်သွေး၊ အောက်သွေး သွေးပေါင်ချိန်၊ ဆီးအနည်ထိုင်မှုအခြေအနေတွေသိရှိဖို့ ကိုယ်ဝန်ဆောင်မိခင်ကျန်းမာရေး စောင့်ရှောက်မှုမှတ်တမ်းစာအုပ် (ခ) ကလေးမွေးဖွားမှု ကျန်းမာရေးရလဒ်တွေသိရှိဖို့ ကလေးမွေးဖွားမှုမှတ်တမ်းစတဲ့ဆေးမှတ်တမ်းတွေကို အသုံးပြုဖို့ ဆေးရုံမှခွင့်ပြုချက်ကိုလည်း တောင်းပါမယ်။ ဆေးမှတ်တမ်းတွေ ယူသုံးခွင့်အတွက် ပါဝင်သူကိုယ်ဝန်ဆောင်များထံမှ သဘောတူညီမှုဝန်ခံကတိကိုလည်း တောင်းဆိုသွားပါမယ်။

၈။ ဖြစ်လာနိုင်သည့် ဆိုးကျိုးအန္တရာယ်များအတွက် ကြိုတင်စီမံခန့်ခွဲခြင်း

သုတေသနကာလအတွင်း ပါဝင်သူကိုယ်ဝန်ဆောင်မိခင်ဟာ ကိုယ်ဝန်ပျက်ကျတာ (သို့မဟုတ်) အခြားကိုယ်ဝန်နဲ့ဆိုင်တဲ့ပြဿနာတခုခု ဖြစ်လာခဲ့သော် ဆေးရုံရှိသက်ဆိုင်ရာအထူးကုဆရာဝန်ထံ အမြန်ဆုံးလွှဲပြောင်းပြသမှာဖြစ်သလို သုတေသနမှလည်း ထုတ်ပယ်အနားပေးမှာဖြစ်ပါတယ်။

၉။ ဤသုတေသနမှ ပြည်သူ့ကျန်းမာရေးအတွက် အကျိုးကျေးဇူးများ

သင့်ရဲ့ပူးပေါင်းပါဝင်မှုနဲ့ သုတေသနမှရရှိလာမယ့်ရလဒ်တွေဟာ ထိုင်းနိုင်ငံတွင်း နေထိုင်သူ ရွှေ့ပြောင်းမြန်မာများရဲ့ကျန်းမာရေး၊ ကိုယ်ဝန်ဆောင်မိခင်ကျန်းမာရေး၊ ပတ်ဝန်းကျင်ကျန်းမာရေးတို့ကိုတိုးတက်စေဖို့ များစွာအထောက်အကူဖြစ်စေမှာ ဖြစ်ပါတယ်။

၁၀။ သုတေသနမှာပါဝင်ဖို့က သင့်သဘောဆန္ဒအတိုင်းသာ ဖြစ်ပါတယ်။ ပါဝင်မည့်သူတွေဟာ အကြောင်းပြချက်ပေးစရာမလိုဘဲ သုတေသနကနေ အချိန်မရွေး နုတ်ထွက်နိုင်သလို နုတ်ထွက်ခွင့်လည်း ရှိပါတယ်။ အဲ့ဒီအတွက် သင့်အပေါ် ဘာမှ မထိခိုက်နိုင်ပါ။

၁၁။ သင်မေးမြန်းချင်တာ၊ ထပ်ပြီးသိချင်တာရှိလျင် သုတေသနခေါင်းဆောင်က အချိန်မရွေးရှင်းပြပေးနိုင်ပါတယ်။ အကယ်၍ သုတေသနနဲ့ပက်သက်တဲ့ ဆိုးကျိုးကောင်းကျိုးတွေအကြောင်း သတင်းအသစ်တွေရှိလာမယ်ဆိုရင်လည်း ပါဝင်သူတွေကို အချိန်မီ အသိပေးသွားမှာပါ။ အဲ့ဒီအခါမှာ ပါဝင်သူတွေဟာ သုတေသနတလျောက် ဆက်ပါဖို့၊ မပါဖို့ ဆုံးဖြတ်နိုင်မှာဖြစ်ပါတယ်။

သုတေသနခေါင်းဆောင်

ရဲထက်ဇော်၊ ပါရဂူဘွဲ့လွန်ကျောင်းသား၊ ပြည့်သူ့ကျန်းမာရေးအထူးပြု၊ ပြည်သူ့ကျန်းမာရေးသိပ္ပံကောလိပ်၊ ချူလာလောင်ကွန်းတက္ကသိုလ်။ ဖုန်းနံပါတ် +၆၆၉ ၂၄၇ ၄၇၀ ၃၃၊ အီးမေးလ် yehtet.roman @gmail.com

၁၂။ သင့်ကိုယ်ရေးသတင်းအချက်အလက်တွေကို စနစ်တကျ လျို့ဝှက်သိမ်းဆည်းပေးသွားမှာပါ။ ရလာတဲ့ရလဒ်တွေကိုလည်း ဇယားနဲ့စုပေါင်းဖော်ပြသွားမှာပါ။ သင်ဖြစ်ကြောင်းသိရှိစေမဲ့ အချက်အလက် တခုတလေမှ ဖော်ပြမှာမဟုတ်ပါဘူး။

၁၃။ အကယ်၍ သုတေသနခေါင်းဆောင်ဟာ သတင်းအချက်အလက်စာလွှာပါ အချက်တွေအတိုင်း မဆောင်ရွက်ဘူးဆိုလျှင်၊ ချုပ်လာလောင်ကွန်းတက္ကသိုလ် ကျန်းမာရေးသိပ္ပံအဖွဲ့၏ လူပုဂ္ဂိုလ်များအပေါ် သုတေသနပြုခြင်းကျင့်ဝတ်ဆိုင်ရာ ဘုတ်အဖွဲ့ထံ ချက်ချင်းသတင်းပို့တင်ပြနိုင်ပါသည်။ ၄င်းဘုတ်အဖွဲ့၏ ဆက်သွယ်ရန်လိပ်စာမှာ ချမ်ချုရီ အဆောက်အဦ (၁)၊ ဒုတိယထပ်၊ အမှတ် (၂၅၄)၊ ပရာထိုင်းလမ်းမ၊ ပတ်သူဝမ်၊ ဗန်ကောက် ၁၀၃၃၀၊ ထိုင်းနိုင်ငံ။ တယ်လီဖုန်း၊ ဖက်စ်နံပါတ် ၀၂၂၁၈၃၂၀၂၊ အီးမေးလ် eccu@chula.ac.th

Appendix J: Informed Consent Form (Myanmar)

သုတေသနတွင်ပါဝင်ရန်သဘောတူကြောင်း ဝန်ခံကတိ

နေရပ်လိပ်စာ----------

ရက်စွဲ----------

သုတေသနတွင်ပါဝင်သူ၏လျှို့ဝှက်ကုတ်နံပါတ်----------

ဤသုတေသနတွင်ပါဝင်ရန် သဘောတူညီပြီး အောက်တွင် လက်မှတ်ရေးထိုးပါသည်။

သုတေသနခေါင်းစဉ်

ထိုင်းနိုင်ငံ၊ စမွတ်ဆခွန်ခရိုင်ရှိ ရွှေ့ပြောင်းမြန်မာနိုင်ငံသားများ၌ ကိုယ်ဝန်ဆောင်မိခင်သွေး အတွင်း သတ္တုလေးပါဝင်မှုပမာဏ၏ အာရုံကြောဖွံ့ဖြိုးရေးအထောက်အပံ့ပေးပရိုတင်းနှင့် ကိုယ်ဝန်ဆောင်ကျန်းမာရေးရလဒ်များအပေါ် သက်ရောက်မှုကိုလေ့လာသော သုတေသန။

သုတေသနခေါင်းဆောင်အမည်

ရဲထက်ဇော်

ဆက်သွယ်ရန်နေရပ်လိပ်စာ

CUihouse ၊ ၂၆၈၊ ချူလာလမ်းသွယ် ၉၊ ချုရာမူရမ်လမ်း၊ ဝမ်မိုင်၊ ပသူဝမ်၊ ဗန်ကောက် ၁၀၃၃၀၊ ထိုင်းနိုင်ငံ၊ လက်ကိုင်ဖုန်းနံပါတ် +၆၆ ၉၂၄၇၇၇၀၃၃၊ အီးမေးလ်

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ဤသုတေသန၏ အသေးစိတ်အချက်များ၊ ရည်ရွယ်ချက်၊ လုပ်ဆောင်မည့် နည်းလမ်းများနှင့် အစီအစဉ်များ၊ အကျိုးကျေးဇူးများ၊ ဖြစ်လာနိုင်သောဆိုးကျိုးများ စသည့် သတင်းအချက်အလက်များပါသောစာလွှာကို လက်ခံရရှိပြီးဖြစ်ပါသည်။ ၄င်းစာလွှာပါ

သုတေသနခေါင်းဆောင်၏ ရှင်းလင်းဖော်ပြချက်များကို ဖတ်ရှုပြီး၊ သတင်းလက်ခံရရှိပြီး ကောင်းစွာနားလည်သဘောပေါက်ပါသည်။

ကိုယ်ဝန်ဆောင်စောင့်ရှောက်ရေးဆေးခန်းသို့လာပြချိန်၃ကြိမ်အတွင်း မေးခွန်းများကို ဖြေဆိုရန်နှင့် သွေးနမူနာများပေးရန် (ကိုယ်ဝန်သက်ပထမ၃လအတွင်းနှင့် ကိုယ်ဝန်သက် တတိယ၃လအတွင်း တစ်ကြိမ်စီမှာ သွေးလက်ဖက်ရည်တစ်ဇွန်းပမာဏ) သဘောတူညီပြီး ဝန်ခံကတိပေးပါသည်။ သုတေသန ပြီးဆုံးသည့်အခါ သွေးနမူနာများကို ဖျက်ဆီးသွားလိမ့်မည်ဟုလည်း သိရှိပြီးဖြစ်ပါသည်။

ကျွန်ုပ်သည် ဤသုတေသနမှ မည်သည့်အကြောင်းပြချက်မျှပေးစရာမလိုဘဲ အချိန်မရွေး နှုတ်ထွက်ခွင့်ရှိပါသည်။ ယင်းကြောင့် ကျွန်ုပ်အပေါ်တွင် ဆိုးကျိုးတစုံတရာ သက်ရောက်နိုင်လိမ့်မည် မဟုတ်ပါ။

စာလွှာတွင်ဖော်ပြထားသည့်အတိုင်း စီစဉ်ဆောင်ရွက်သွားမည်ဟု သုတေသန ခေါင်းဆောင်မှ ကတိပြုဖော်ပြထားပြီးဖြစ်သည်။ ကျွန်ုပ်နှင့်ပက်သက်သည့် အတွင်းရေး အချက်အလက်များကိုလည်း စနစ်တကျလျှို့ဝှက်သိမ်းဆည်းပေးသွားမည် ဖြစ်သည်။ ရလဒ်များကို ရုပ်ပုံကားချပ်ဇယားဖြင့်သာ ဖော်ပြသွားမည်။ ထိုသို့ဖော်ပြရာတွင် ရလဒ်များမှ ကျွန်ုပ်မည်သူဖြစ်ကြောင်း သိနိုင်မည့် အမှတ်အသားအချက်အလက် တစုံတရာမျှ ပါဝင်လိမ့်မည်မဟုတ်ပါ။

အကယ်၍ ကျွန်ုပ်အား သတင်းအချက်အလက်ဖော်ပြစာလွှာပါအတိုင်း ပြုမူခြင်း မရှိလျှင် ချူလာလောင်ကွန်းတက္ကသိုလ်ကျန်းမာရေးသိပ္ပံအဖွဲ့၏ လူပုဂ္ဂိုလ်များအပေါ် သုတေသနကျင့်ဝတ်ဆိုင်ရာ ပညာရှင်အဖွဲ့ထံ သတင်းပို့တင်ပြနိုင်ပါသည်။ ယင်းအဖွဲ့၏

လိပ်စာမှာ ချန်ချူရီအဆောက်အဦ အမှတ် (၁)၊ ဒုတိယထပ်၊ အမှတ် (၂၅၄)၊ ဖရာထိုင်းလမ်းမ၊ ပတ်သူဝမ်၊ ဗန်ကောက် ကုတ်နံပါတ် ၁၀၃၃၀၊ ထိုင်းနိုင်ငံ၊ တယ်လီဖုန်း ဝ၂၂၁၈၃၂၀၂၊ အီးမေးလ် eccu@chula.ac.th

သတင်းအချက်အလက်စာလွှာနှင့် သဘောတူဝန်ခံကတိမိတ္တူကိုလည်း လက်ခံရရှိပြီး ဖြစ်ပါသည်။

လတ်မှတ်----------

(----------)

သုတေသနခေါင်းဆောင်

လတ်မှတ်----------

(----------)

သုတေသနတွင်ပါဝင်သူ

လတ်မှတ်----------

(----------)

အသိသက်သေ

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