EFFECT OF COOKING FUELS USE ON INCREASED MATERNAL CAROTID INTIMA MEDIA THICKNESS AND PREECLAMPSIA AMONG SELF-COOKING PREGNANT WOMEN IN NAY PYI TAW AREA, MYANMAR: A COHORT STUDY

Mr. Myo Min

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ผลของการใช้เชื้อเพลิงในการหุงต้มต่อการเพิ่มขึ้นของความหนาหลอดเลือดแดงคาโรติดที่ลำคอและภาวะครรภ์เป็นพิษในกลุ่มหญิงตั้งครรภ์ในเมืองเนปิดอร์ ประเทศเมียนมา: การศึกษาไปข้างหน้าจากเหตุไปหาผล

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By	Mr. Myo Min
Field of Study	Public Health
Thesis Advisor	Assistant Professor NUTTA TANEEPANICHSKUL, Ph.D.
Thesis Co Advisor	Associate Professor VITOOL LOHSOONTHORN, Ph.D.

Accepted by the COLLEGE OF PUBLIC HEALTH SCIENCES, Chulalongkorn University in Partial Fulfillment of the Requirement for the Doctor of Philosophy

.... Dean of the COLLEGE OF PUBLIC HEALTH SCIENCES
(Professor SATHIRAKORN PONGPANICH, Ph.D.)

DISSERTATION COMMITTEE

.... Chairman
(Associate Professor Ratana Somrongthong, Ph.D.)

.... Thesis Advisor
(Assistant Professor NUTTA TANEEPANICHSKUL, Ph.D.)

.... Thesis Co-Advisor
(Associate Professor VITOOL LOHSOONTHORN, Ph.D.)

.... Examiner
(Associate Professor WATTASIT SIRIWONG, Ph.D.)

.... Examiner
(THANAPOOM RATTANANUPONG, Ph.D.)

.... External Examiner
(Professor Wichai Aekplakorn, Ph.D.)

เมียว มิน :
ผลของการใช้เชื้อเพลิงในการหุงต้มต่อการเพิ่มขึ้นของความหนาหลอดเลือดแดงคาโรติดที่ลำคอและภาวะครรภ์เป็นพิษในกลุ่มหญิงตั้งครรภ์ในเมืองเนปิดอร์ ประเทศเมียนมา: การศึกษาไปข้างหน้าจากเหตุไปหาผล. (EFFECT OF COOKING FUELS USE ON INCREASED MATERNAL CAROTID INTIMA MEDIA THICKNESS AND PREECLAMPSIA AMONG SELF-COOKING PREGNANT WOMEN IN NAY PYI TAW AREA, MYANMAR: A COHORT STUDY) อ.ที่ปรึกษาหลัก : ณัฏฐา ฐานีพานิชสกุล, อ.ที่ปรึกษาร่วม : วิฑูรย์ โล่ห์สุนทร

การใช้เชื้อเพลิงเผาไหม้เพื่อการประกอบอาหารในครัวเรือนก่อให้เกิดมลภาวะทางอากาศในบ้านเรือนผ่านการสัมผัสมลพิษซึ่งปลดปล่อยมาจากการใช้เชื้อเพลิงเผาไหม้ซึ่งก่อให้เกิดความเสี่ยงทางสุขภาพในมนุษย์รวมถึงภาวะความดันโลหิตสูงในขณะตั้งครรภ์เป็นพิษ (pre-eclampsia) โดยทำให้เกิดความหนาตัวของผนังชั้นในและชั้นกลางของเส้นเลือดแดงแคโรทิด (carotid intima-media) ผ่านกระบวนการอักเสบทั่วทั้งร่างกายซึ่ง surrogate arthrosclerosis ซึ่งเป็นข้อบ่งชี้ทางชีวภาพที่สำคัญของการศึกษานี้ ซึ่งมีวัตถุประสงค์เพื่อหาความสัมพันธ์ระหว่างการใช้เชื้อเพลิงเผาไหม้เพื่อการประกอบอาหารในครัวเรือนและภาวะความหนาตัวเพิ่มขึ้นของผนังชั้นในและชั้นกลางของเส้นเลือดแดงแคโรทิด (carotid intima-media) ในหญิงตั้ งครรภ์ รวมถึงการหาความสัมพันธ์ต่อภาวะตั้งครรภ์เป็นพิษและภาวะความดันโลหิตสูงที่ในประเทศเมียนม่าร์ การศึกษานี้เป็นการศึกษาไปข้าง หน้าแบบจากเหตุไปหาผล (cohort study) ในเขตพื้นที่เนปยีดอ (Nay Pyi Taw) ประเทศเมียนม่าร์ในระหว่างเดือนกันยายน 2019 ถึงเดือนมีนาคม 2020 กลุ่มตัวอย่างเป็นหญิงตั้งครรภ์ซึ่งอายุมากกว่า 18 ปีที่มีอายุครรภ์มากกว่า 18 สัปดาห์ ณ จุดเริ่มต้นการศึกษาจำนวน 192 คน โดยกลุ่มตัวอย่างถูก เลือกจากศูนย์สุขภาพในเขตชนบท 15 แห่งในเขตพื้นที่เนปยีดอ (Nay Pyi Taw) โดยเมื่อสิ้นสุดการศึกษามีกลุ่มตัวอย่างที่ยังอยู่ในการศึกษา ต่อเนื่องทั้งสิ้น 176 คน หญิงตั้งครรภ์ที่เป็นกลุ่มตัวอย่างถูกแบ่งตามชนิดของเชื้อเพลิงเผาไหม้ที่ใช้เพื่อการประกอบอาหารในครัวเรือนเป็น 3 กลุ่ม คือ กลุ่มที่ใช้ฟืน, กลุ่มที่ใช้ถ่านและกลุ่มที่ใช้อุปกรณ์ไฟฟ้าประกอบอาหารในครัวเรือนการเก็บข้อมูลลักษณะพื้นฐานทางสังคมข้อมูลการพักอาศัยและข้อมูลเกี่ยวกับการใช้เชื้อเพลิงใช้แบบสอบถามเก็บข้อมูลด้วยวิธีสัมภาษณ์แบบตัวต่อตัวการเก็บข้อมูลกายภาพของร่างกาย, ข้อมูลเกี่ยวกับระบบไหลเวียนโลหิต, ข้อมูลการตรวจความสมบูรณ์ของเม็ดเลือดแดง,ข้อมูลไขมันในเลือดและข้อมูลผลอัลตราซาวน์เพื่อวัดภาวะความหนาตัวเพิ่มขึ้นขอ งผนังชั้นในและชั้นกลางของเส้นเลือดแดงแคโรทิด (CIMT) ที่จุดเริ่มต้นและระหว่างติดตามศึกษาและจัดเก็บข้อมูลภายใต้เกณฑ์วิธีมาตรฐานและศึกษาความเกี่ยวข้องโดยปรับอิทธิพลของปัจจัยกวนด้วยวิธีวิเคราะห์หลายตัวแปร ผลการวิจัยพบว่าหลังจากปรับปัจจัยที่เกี่ยวข้องกับการตั้งครรภ์แล ะปัจจัยที่เกี่ยวกับการตรวจ CIMT พบว่าที่จุดเริ่มต้นการศึกษาค่า CIMT ทุกชนิด (combined mean CIMT, mean CIMT of the LCCA และ mean CIMT of the RCCA) ของหญิงที่ใช้ฟืนเป็นเชื้อเพลิงเผาไหม้เพื่อการประกอบอาหารเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ โดยเฉพาะการเพิ่มขึ้นของค่า (mean CIMT RCCA(RCCA; $\beta=0.033$ mm; 95%CI: 0.006, 0.058; $P<0.05$) ซึ่งมีความเกี่ยวข้องกับการใช้ถ่านเป็นเชื้อเพลิงเผาไหม้เพื่อการประกอบอาหารเปรียบเทียบกับการใช้ฟืนเป็นเชื้อเพลิงเผาไหม้เพื่อการประกอบอาหาร ($\beta=0.029$ mm; 95%CI: 0.010, 0.049; $P<0.05$) ในระหว่างการติดตามศึกษาพบว่าเฉพาะการใช้ถ่านเป็นเชื้อเพลิงเผาไหม้เพื่อการประกอบอาหารเท่านั้นที่มีความเกี่ยวข้องอย่างมีนัยสำคัญกับการเพิ่มขึ้นของค่า CIMT ทุกชนิด (combined mean CIMT $\beta=0.035$ mm; 95%CI: 0.010, 0.060; $P<0.05$), mean CIMT of the LCCA ($\beta=0.029$ mm; 95%CI: 0.004, 0.054; $P<0.05$) and mean CIMT of the RCCA ($\beta=0.041$ mm; 95%CI: 0.012, 0.071; $P<0.05$). และไม่มีความเกี่ยวข้องอย่างมีนัยสำคัญระหว่างการใช้ฟืนเป็นเชื้อเพลิงเผาไหม้เพื่อการประกอบอาหารและการเพิ่มขึ้นของค่า CIMT ยิ่งไปว่านั้น ค่า CIMT ของหญิงตั้งครรภ์ที่ใช้ถ่านเป็นเชื้อเพลิงเผาไหม้เพื่อ การประกอบอาหารและค่า CIMT ของหญิงตั้งครรภ์ใช้อุปกรณ์ไฟฟ้าเพื่อการประกอบอาหารในครัวเรือนไม่มีการเปลี่ยนแปลงจากจุดเริ่มต้น

สาขาวิชา	สาธารณสุขศาสตร์	ลายมือชื่อนิสิต	....
ปีการศึกษา	2562	ลายมือชื่อ อ.ที่ปรึกษาหลัก	....
		ลายมือชื่อ อ.ที่ปรึกษาร่วม	....

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Myo Min : EFFECT OF COOKING FUELS USE ON INCREASED MATERNAL CAROTID INTIMA MEDIA THICKNESS AND PREECLAMPSIA AMONG SELF-COOKING PREGNANT WOMEN IN NAY PYI TAW AREA, MYANMAR: A COHORT STUDY. Advisor: Asst. Prof. NUTTA TANEEPANICHSKUL, Ph.D. Co-advisor: Assoc. Prof. VITOOL LOHSOONTHORN, Ph.D.

Fuels burned in households for cooking causes indoor air pollution. Exposure to pollutants emitted from burning cooking fuels poses a considerable risk for human health including preeclampsia through systemic inflammation process for which carotid intima-media thickness (CIMT) is an important surrogate arthrosclerosis biomarker. This study aimed to examine the association of cooking fuels use with increased maternal carotid intima-media thickness and preeclampsia among cooking pregnant women in Myanmar. A cohort study was conducted in Nay Pyi Taw Area, Myanmar from September 2019 to March 2020. A total of 192 pregnant women over 18 years with gestational weeks less than 18 at baseline were recruited by a purposive sampling from 15 rural health centers in Nay Pyi Taw, and 176 completed the follow-up. Based on the type of cooking fuels use, pregnant women were grouped as firewood user, charcoal user and electricity user. Sociodemographic data, residential data and fuels use data were collected with semi-structured questionnaires in face-to-face interviews. At baseline and at follow-up, anthropometry, hemodynamics, Complete Blood Count, blood lipids and ultrasound CIMT measurements were performed under standard protocols. Multivariate linear regression analysis was used to explore associations with adjustments for potential confounding factors. The results revealed that, after adjusting for pregnancy-related factors and factors related to CIMT, firewood use had a significant association with increase of all CIMT (combined mean CIMT, mean CIMT of the LCCA and mean CIMT of the RCCA). More specifically, a greater increase of mean CIMT of the right common carotid artery (RCCA; β=0.033mm; 95%CI: 0.006, 0.058; $P<0.05$) had significant association with charcoal use compared to firewood use (β=0.029mm; 95%CI: 0.010, 0.049; $P<0.05$). At follow-up, only charcoal use was significantly associated with increase of all CIMT; combined mean CIMT (β=0.035mm; 95%CI: 0.010, 0.060; $P<0.05$), mean CIMT of the LCCA (β=0.029mm; 95%CI: 0.004, 0.054; $P<0.05$) and mean CIMT of the RCCA (β=0.041mm; 95%CI: 0.012, 0.071; $P<0.05$). There was no significant association between firewood use and increased CIMT. Moreover, in firewood users, combined mean CIMT at baseline 0.42±0.05mm was reduced to 0.41±0.06 mm at follow-up ($P=0.039$) and mean CIMT of RCCA at baseline 0.43±0.06mm was decreased to 0.41±0.07mm at follow-up ($P=0.008$). CIMT levels of charcoal and electricity users at baseline and at follow-up remains unchanged ($P>0.05$). No significant association between fuels use and preeclampsia was found. In addition, there was no significant association between CIMT and preeclampsia in this study. Our findings demonstrate that the indoor use of cooking fuels that cause indoor air pollution, such as firewood and charcoal, is a considerable risks factor for human health and is associated with increased CIMT, wherein charcoal use was consistently associated with increase of CIMT. However, no association between fuels use and preeclampsia; and no association between CIMT and preeclampsia was found. Therefore, measures to prevent health risks related to the use of such fuels especially charcoal use should be instituted early on during pregnancy and beyond. Further studies to examine the exposure effects of pollution on acute and later health problems of women burning solid fuels in cooking are suggested.

Field of Study:	Public Health	Student's Signature ....
Academic Year:	2019	Advisor's Signature ....
		Co-advisor's Signature ....

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Myo Min

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LIST OF ABBREVIATIONS

IAP	-	Indoor Air Pollution
LPG	-	Liquid petroleum gas
BMI	-	Body Mass Index
WHO	-	World Health Organization
EMC	-	Emerging Market Consulting
CIMT	-	Carotid intima-media thickness
$PM_{2.5}$	-	Particulate Matter with aerodynamic diameter less than 2.5 µm
PM_{10}	-	Particulate Matter with aerodynamic diameter less than 10 µm
CO	-	Carbon monoxide
CO_2	-	Carbon dioxide
WHO	-	World Health Organization
MOHS	-	Ministry of Health and Sports
DOP	-	Department of Populations
SPB	-	Systolic Blood Pressure
DBP	-	Diastolic Blood Pressure
mmHg	-	Millimeter Mercury
HH	-	Households
CBC	-	Complete Blood Count
PE	-	Preeclampsia
COPD	-	Chronic Obstructive Pulmonary Disease
CVD	-	Cardiovascular Diseases
CCA	-	Common Carotid Artery
RCCA	-	Right Common Carotid Artery
LCCA	-	Left Common Carotid Artery

mm	-	millimeters
OR	-	Odds Ratio
aOR	-	Adjusted Odds Ratio
CI	-	Confidence Intervals
P	-	P-value
MRI	-	Magnetic resonance imaging
RHC	-	Rural Health Center
HDL	-	High Density Lipoprotein
LDL	-	Low Density Lipoprotein
TG	-	Triglycerides

CHAPTER 1

INTRODUCTION

1.1 Background and rationale

Indoor air pollution (IAP) has drawn attention on rising diseases and premature deaths in developing countries, which is concerned as global and local issue. According to World Health Organization statistics, globally, deaths due to only indoor air pollution accounts for 3.8 million from pneumonia (27%), stroke (18%), ischemic heart disease (27%), chronic obstructive pulmonary disease (COPD) (20%) and lung cancer (8%) (WHO, 2018b) while more than 3 billion of global population rely on unqualified fuels of biomass as a primary energy source (WHO). Cooking stoves on different types of solid fuels plays as primary polluting source in households, whereby emit pollutants such as carbon dioxide (40%), carbon monoxide (32%), particles (20%) and PAHs (50%) (L Curtis, 2002). Moreover, ($PM_{2.5}$ or smaller size), ozone, methane, nitrous oxides, sulphur dioxides (principally from coal) and Volatile Organic Compounds (VOC) are among also other emitted pollutants from burning sources, which are substantially compounded by environmental tobacco smokes worsening indoor pollution (Zhang & Smith, 2003). Furthermore, existing literatures show several air pollutants and using different types of cooking fuels are associated with increased carotid-intima media thickness (Adar et al., 2013; X. Liu et al., 2015; Provost, Madhloum, Panis, De Boever, & Nawrot, 2015; Su, Hwang, Shen, & Chan, 2015), elevated blood pressure (Burroughs Peña et al., 2015; Ofori, Fobil, & Odia, 2018; Painschab et al., 2013) risks of preeclampsia (Agrawal & Yamamoto, 2015; Pereira et al., 2012) and several cardiovascular diseases.

Carotid intima-media thickness (CIMT) is a state of carotid artery walls thickened as a result of structurally hypertrophic changes in response to metabolic insults from many factors including pollutants in prolonged manner. The increased thickness of arteries can be identified by non-invasive ultrasound scan. CIMT is also believed to be an independent cardiovascular risk marker important to predict cardiovascular diseases (Simova, 2015). Degree of intima-media thickness and presence of plagues may serve as additional aid, and they help improve predicting cardiovascular diseases risks apart from using mere traditional risk factors in risk prediction (Øygarden, 2017). In such cardiovascular and respiratory diseases, reactions and systematic inflammation (Von Bornstädt, Kunz, & Endres, 2014) induced by air pollutants inhalation results in elevated blood pressure from vascular tone disruption leading to increasing cardiovascular accidents (Gill et al., 2011), central nervous system diseases (e.g. strokes, Parkinson's diseases, Alzheimer's diseases) (Block & Calderón-Garcidueñas, 2009), and higher inflammatory biomarkers (e.g. TNF-α) in the placenta of pregnant women who use firewood or kerosene fuels compared to ethanol fuels (Olopade et al., 2017).

Carotid intima-media thickness (CIMT) is in fact found to be associated with air pollutants of Ozone, CO_2 and $PM_{2.5}$ (Adar et al., 2013; X. Liu et al., 2015; Provost et al., 2015; Su et al., 2015), biomass fuels uses (Ofori et al., 2018; Painschab et al., 2013) and incense burning (Kammoolkon, 2018; Kammoolkon, Taneepanichskul, Pitaknoppakul, Lertmaharit, & Lohsoonthorn, 2018). Additionally, traditional risks factors for increased CIMT include age, sex, race, smoking, alcohol drinks, exercise, blood pressure, abnormal lipid profiles, diet consumption, taking lipid lowering agents, glycaemia, hyperuricemia and obesity related conditions. Novel risks factors are genetics, some inflammatory diseases, lipid metabolism, blood cells functions, job stress and vitamin-D (Qu & Qu, 2015). Furthermore, nulliparity (Wolff et al., 2005), bearing of more children (Skilton et al., 2010), and diabetic condition (Freire et al., 2012; Lorenz et al., 2015) are found to be in association with CIMT.

Preeclampsia is "a pre pregnancy specific disorder characterized by hypertension ≥ 140/90 mmHg on at least two occasions 6-hour apart, and proteinuria of 300 mg or greater in

24-hour urine after 20 weeks of gestation" (Garovic & August, 2013). According to gestational terms, preterm-preeclampsia is meant for preeclampsia developed from 34+1 weeks through 37 weeks, and that of 37+1 is considered as term-preeclampsia (Tranquilli, Brown, Zeeman, Dekker, & Sibai, 2013). Regarding with preeclampsia onset, early-onset preeclampsia is used to mean the episode at 20 weeks gestation onwards and, late-onset preeclampsia entitles to the event at 34 weeks gestation onwards (You et al., 2018). Including air pollution (Agrawal & Yamamoto, 2015; Pereira et al., 2012), preeclampsia complicating (3-5%) of all pregnancies (Hutcheon, Lisonkova, & Joseph, 2011; Mol et al., 2016) has factors associated with it, include unmarried mother (Tessema, Tekeste, & Ayele, 2015), prior cesarean section (Cho et al., 2015), and other factors such as age, nulliparity, presence of family hypertension, hypertension , diabetes (Coghill, Hansen, & Littman, 2011; Kiondo et al., 2012; Shegaze, Markos, Estifaons, Taye, & Gemeda, 2016; Yi, Jing, Gang, & Weiwei, 2017; You et al., 2018) and increased CIMT (Blaauw et al., 2006; Milic et al., 2017).

Myanmar, a developing country in South East Asia region, extensively and massively uses biomass as its primary source. Heavy dependency of Myanmar on solid fuels is ascertained by some usage figures for cooking reason (85%) in which include fire woods (59%), charcoal (24%) and electricity (15%) (Emerging Markets Consulting Group, 2015). At national level report, Myanmar relies on biomass fuels such as firewood (69.2%), charcoal (11.8%), coal (0.3%) for cooking with electricity (16.4%), LPG (0.4%), biogas (0.3%), kerosene (0.2%) and others (1.4%) (Department of Population, 2015b). In Nay Pyi Taw Area, energy source for cooking is revealed as firewood (53.8%), charcoal (11.1%), coal (0.2%), electricity (34.0%), LPG (0.1%), kerosene (0.1%), biogas (0.1%) and others (0.6%) (Department of Population, 2015a).

In terms of fuels combustion in Myanmar, the fuels are mostly burned in traditional cook stoves to produce desired energy. The stoves namely three-stone open fire stoves, multipurpose stoves and charcoal stoves are traditional appliances prevalently used in the whole country whereas electric stoves and improved stoves types are preferentially used in urban areas where electricity and other clean fuels are favorably available. Across Myanmar, different types of stoves in use are statistically three-stone open fire stove (35%), the charcoal/multipurpose stove (27%) and the electric stove (15%). While charcoal stoves (46%) and electric stoves (35%) are prevalent in peri-urban areas, three-stone stove type largely dominates in rural environments (50%) (Emerging Markets Consulting Group, 2015).

In Myanmar, non-communicable disease previously accounting for 48% of all mortality increased to over 51% in 2016, comprising of CVD (20.6%), Respiratory diseases (4.9%), Cancer (4.9%), other NCD (20%) (MoHS, 2018) for which air pollution cannot be ruled out. With regard to maternal mortality, Myanmar has high maternal deaths MMR 281.6 at union level; MMR 298.1 in Nay Pyi Taw area (Department of Population, 2015c), is triggered by several pregnancy related causes including preeclampsia being responsible for 11.3% maternal deaths (MoHS, 2018; Thein et al., 2012) at its prevalence (6-8%) expected (Tin Tin Thein, 2008), and even more higher deaths 21% is reported among mothers referred for preeclampsia/eclampsia (15%) of all emergency referral cases due to postpartum hemorrhage, antepartum hemorrhage and uterine rupture and abortion (3MDG report, 2012).

With the knowledge of burning different types of cooking fuels contributes to both indoor air pollution and health consequences including increased CIMT among women with preeclampsia (Milic et al., 2017; Tessema et al., 2015), few studies report increased CIMT along the course of pregnancy (Niemczyk et al., 2018). Myanmar using different type of cooking fuels widely also has limited studies with a focus on investigating associations between types of cooking fuels use and maternal CIMT and preeclampsia among pregnant women in particular. Hence, this study aims to examine the association between type of cooking fuels use and increased maternal CIMT and preeclampsia among self-cooking pregnant women in Nay

Pyi Taw Area, Myanmar. This study would be beneficial in adding further evidence to cooking fuels use and its health consequences.

1.2 Research questions

1. Is there an association between types of cooking fuels use and maternal CIMT at early trimester (baseline) among self-cooking pregnant women in Nay Pyi Taw area, Myanmar?

2. Is there the changes of CIMT at the baseline and at the follow-up among fuels use groups of self-cooking pregnant women in Nay Pyi Taw area, Myanmar?

3. Are there any associations between types of cooking fuels use and increased maternal CIMT at the third trimester (follow-up) among self-cooking pregnant women in Nay Pyi Taw area, Myanmar?

4. Are there any associations between types of cooking fuels use and preeclampsia among self-cooking pregnant women in Nay Pyi Taw area, Myanmar?

5. Are there any associations between increased maternal CIMT in early and third trimesters and preeclampsia among self-cooking pregnant women in Nay Pyi Taw area, Myanmar?

1.3 Statistical hypothesis

Alternative hypothesis 1:

There is an association between type of cooking fuels use and increased maternal CIMT among self-cooking pregnant women in Nay Pyi Taw area, Myanmar.

Alternative hypothesis 2:

There is the changes of CIMT at the baseline and at the follow-up among fuels use groups of self-cooking pregnant women in Nay Pyi Taw area, Myanmar.

Alternative hypothesis 3:

There is an association between type of cooking fuels use and increased maternal CIMT at the follow-up among self-cooking pregnant women in Nay Pyi Taw area, Myanmar.

Alternative hypothesis 4:

There is an association between type cooking fuels use and preeclampsia among self-cooking pregnant women in Nay Pyi Taw area, Myanmar.

Alternative hypothesis 5:

There is an association between increased maternal CIMT in early and third trimesters and preeclampsia among self-cooking pregnant women in Nay Pyi Taw area, Myanmar.

1.4 Objectives

1.4.1 General objective

To investigate associations between types of cooking fuels use and increased maternal CIMT and preeclampsia among self-cooking pregnant women in Nay Pyi Taw area, Myanmar

1.4.2 Specific objectives

(i) To find association between types of cooking fuels use and maternal CIMT at early trimester (baseline) among self-cooking pregnant women in Nay Pyi Taw area, Myanmar

(ii) To examine changes of carotid intima-media thickness from the baseline to the follow-up among self-cooking pregnant women in Nay Pyi Taw area, Myanmar

(iii) To find association between types of cooking fuels use and increased maternal CIMT at third trimester (follow-up) among self-cooking pregnant women in Nay Pyi Taw area, Myanmar

(iv) To find association between types cooking fuels use and preeclampsia among self-cooking pregnant women in Nay Pyi Taw area, Myanmar

(v) To find an association between increased maternal CIMT in early and third trimesters and preeclampsia among self-cooking pregnant women in Nay Pyi Taw area, Myanmar

1.5 Conceptual framework

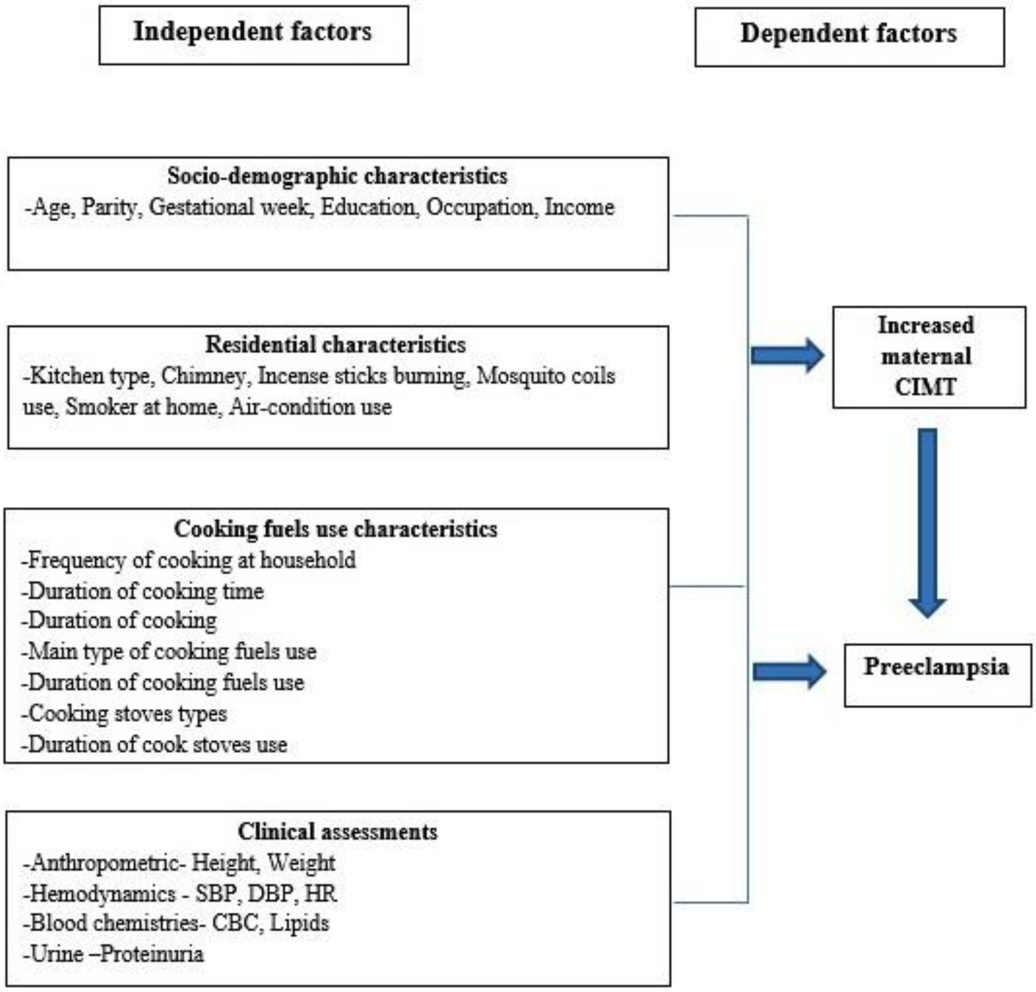


Figure 1 Conceptual framework

1.6 Operational definitions

1.6.1 Sociodemographic characteristics

Age is the completed years reported by participants at interview.

Gestational week at entry refers to the weeks of pregnancy at enrolment which was calculated from last menstrual period of participant or by ultrasound scan.

Body Mass Index is the computed parameter by the formula of weight in kilograms divided by height in meter squared.

Parity refers to the number of times the participants have delivered a baby (alive or death) over 24 weeks or more of gestation.

Education refers to the education level of participants reported at interview.

Occupation refers to the occupation of participants for a living.

Monthly income refers to the average income of the whole family in kyats per month.

1.6.2 Residential characteristics

Household type refers to the types of household - Dhani/Theke/In leaf, Bamboo, Earth, Wood, Corrugated sheet, Tile/Brick/Concret and Other.

Air-condition use refers to the use of any type of air-conditioners installed in order to create cool environment in the bedrooms or living rooms.

Incense stick burning refers to the practice of burning different types of incense sticks inside home for various reasons.

Mosquito coils use refers to the practice of burning different types of mosquito coils inside home to repel mosquitoes.

Smoker at household refers to any member of family who is a current active smoker.

Duration of living at current household is self-report of participant living at the current home in years.

1.6.3 Cooking fuel use characteristics

Cooking at home means the usual cooking conduct at home.

Cooking fuels refer to any materials used to produce heat for cooking.

Cooking fuels use refers to the practice of burning fuels such as firewood, charcoal, coal, gas, LPG or electricity for cooking purpose.

Type of cooking fuels is categorized as firewood, charcoal and coal in unclean fuels group; biogas, LPG and electricity in clean fuels group (Agrawal & Yamamoto, 2015; Kurmi et al., 2014; Ofori et al., 2018; Painschab et al., 2013; Wylie et al., 2014) .

Self-cooking refers to participant's self-cooking practices done at household. It will be defined as always (> 14 times a week), often (14-11 times a week), sometimes (10-7 times a week) seldom (6-2 times a week) and rare cooking (< 1 time a week).

Frequency of cooking at home refers to participants' self-report of self-cooking practice happened at home per week. It will be defined as always (> 14 times a week), often (14-11 times a week), sometimes (10-7 times a week) seldom (6-2 times a week) and no cooking (< 1 time a week).

Duration of cooking per time refers to the participant's self-report average time taken from the beginning of cooking to the end of cooking per time of cooking. It will be less than 30 minutes, 30- 60 minutes, 60-120 minutes, 120-180 minutes, more than 180 minutes.

Duration of cooking refers to participant's self-report of total duration (years) on the practice of cooking in her life course.

Cooking stoves types refer to stoves used for cooking- charcoal/multipurpose stove, three-stones open fire stove, electric stove or gas stove.

Kitchen type refers to 2 types of kitchen attached home and separated from home.

Chimney refers to structures attached to kitchen or cooking stoves to pass smokes out.

Blood chemistries refer to complete blood count (CBC), lipid profiles and blood sugar in mg/dl by standard analysis.

Hemodynamics parameters refer to systolic blood pressure and diastolic blood pressure measured digitally in millimeters of mercury (mmHg); and heart rate/minute measured digitally while taking blood pressure.

Urinary protein refers to concentration of protein in urine detected in dipstick analysis and/or laboratory analysis; and expressed in mg/day. The 24-hour urine protein is calculated by multiplying urinary protein with normal urine output in 24 hour period.

Blood sugar refers to concentration of sugar in blood detected in standard laboratory analysis expressed in mg/dl.

Carotid intima-media thickness (CIMT) refers to the interface between media-adventitial and intima-lumen of far wall of both right common carotid artery and left common carotid artery taken from (anterior, lateral, posterior) angles captured at 10 millimeters proper length of proximally 1 cm away from carotid bulb produced by validated Ultrasound (SAMSUNG MEDISON CO.,LTD, Korea) (Darabian, Hormuz, Latif, Pahlevan, & Budoff, 2013; Simova, 2015). Specific terms are as follows:

1. Combined mean CIMT = (Combined mean CIMT of both LCCA and RCCA at baseline or at follow-up)

2. Mean CIMT of the LCCA = (Ant+Lat+Post views) at baseline or at follow-up

3. Mean CIMT of the RCCA = (Ant+Lat+Post views) at baseline or at follow-up

4. Overall mean CIMT of the LCCA = (Ant+Lat+Post views) at baseline and at follow-up

5. Overall mean CIMT of the RCCA = (Ant+Lat+Post views) at baseline and at follow-up

6. Overall mean CIMT = [Combined mean CIMT of the RCCA (Ant+Lat+Post views) at baseline and at follow-up + Combined mean CIMT of the LCCA (Ant+Lat+Post views) at baseline and at follow-up]

Preeclampsia (PE) is defined as a disorder characterized by a presence of hypertension ≥ 140/90 mmHg on at least two occasions taken 6 hours apart, and proteinuria of 3+ (>300 mg/24h) or greater in urine samples after 20 weeks of gestation (American College of Obstetricians and Gynecologists, 2013; Mol et al., 2016; WHO, 2011) .

Trimesters include three periods defined by gestational weeks where first trimester is first 13 weeks from conception; second trimester is 14 weeks to 26 weeks; and third trimester is from 27 weeks to delivery (Becerra, Wilhelm, Olsen, Cockburn, & Ritz, 2012).

Pregnant women refer to any woman known to conceive a child ascertained by either of Last Menstrual Period (LMP) or UCG tests or Ultrasound.

Rural health centers (RHC) refers to the basic health units established for maternal, reproductive and immunization services for community.

Urinary tract infection refers to diagnosis with ICD-10 code of O23.

Kidney disease refers to diagnosis with ICD-10 code of O26.9.

Liver disease refers to diagnosis with ICD-10 code of O10-O16.

CHAPTER 2

LITERATURE REVIEW

2.1 Cooking fuels

Fuels are used in daily lives for several purposes, including for heating, cooking and lighting. Different types of common fuels are woods, charcoal, animal dung, various types of crop wastes, coal, electricity, Liquid Petroleum Gas (LPG), biogas and kerosene being used all over the world depending on the situation. Woods, charcoal, animal dung, crop wastes, coal, and even kerosene are categorized in the non-clean fuels while electricity, LPG and biogas are listed in the category of clean fuels from the environmental pollution perspectives (Agrawal & Yamamoto, 2015; Kurmi et al., 2014; Ofori et al., 2018; Wylie et al., 2014).

Biomass fuels burnt by humans in multiple settings are of any material derived from plants, agricultural products and animals. International Energy Agency predicted that about 2.6 billion people would be relying on biomass fuels as a primary energy source by 2015, which would then conservatively increase to 2.7 billion by 2030 along with growing population (International Energy Agency, 2006). Currently, approximately 3 billion of world population is reported to rely on solid fuels according to World Health Organization (WHO). Of stated biomass fuels, wood is a commonly cited solid fuel which is extensively used while other fuels are also widely combusted for domestic heating. Regions such as sub-Saharan Africa, nearly all parts of Asia and larger parts of Latin America have population, of which over 50% is biomass fuels user. Furthermore, not less than 90% of people in some countries such as Nepal, Sri Lanka, Africa, Haiti, Myanmar, Indonesia, Brazil and Nicaragua are dependent on biomass fuels (Banzaert, 2013). Other solid fuel such as coal is massively used in China, India and South Africa (Bruce, Perez-Padilla, & Albalak, 2000). Biomass fuels usage are mostly in (not limited to) rural areas especially in countries where clean energy is a challenge in many aspects (International Energy Agency, 2006).

Even though energy demand and sources are not dramatically similar country to country, Myanmar, a lower middle income country, uses biomass mainly and massively as its primary energy source. Some literature reports that majority of Myanmar people uses solid fuels for cooking purposes (85%) for which include firewood (59%), charcoal (24%) and electricity (15%) (Emerging Markets Consulting Group, 2015). According to Population and Housing Census 2014, Myanmar substantially relies on biomass fuels such as firewood (69.2%), charcoal (11.8%), coal (0.3%) for cooking with electricity (16.4%), LPG (0.4%), biogas (0.3%), kerosene (0.2%) and others (1.4%) at national level (Burroughs Peña et al., 2015). In Nay Pyi Taw Area, firewood (53.8%), charcoal (11.1%), coal (0.2%) are energy sources for cooking with electricity (34.0%), LPG (0.1%), kerosene (0.1%), biogas (0.1%) and others (0.6%) (Department of Population, 2015a). The figures mentioned highlights heavy dependency of Myanmar on solid fuels.

Using fuels by combustion of particularly biomass as cooking fuels is more common in low-and middle income countries including Myanmar and, these fuels are mostly burned in traditional cook stoves to produce desired energy. The stoves such as three-stone open fire stoves, multipurpose stoves and charcoal stoves are prevalently used throughout the country. Stoves such as electric stoves and improved stoves types are preferentially used in urban areas where electricity and other clean fuels are favorably available. Across Myanmar, different types of stoves use are three-stones open fire stove (35%), charcoal or multipurpose stove (27%) and electric stove (15%). While charcoal using stoves (46%) and electrical stoves (35%) are prevalent in peri-urban areas, three-stones stove type largely dominates in rural environments (50%) (Emerging Markets Consulting Group, 2015).

Cook stoves which are not effective and efficient may fail to completely burn all fuel components. Incomplete combustion of fuels, especially biomass fuels in hearths and inefficient stoves, profusely emits health damaging pollutants. The level of pollution with toxic substances may be intensified by the absence of proper ventilation system in the cooking spaces as evidenced by higher odds (OR=1.8) of children deaths due to using polluting fuels in kitchens not separated from households (Naz, Page, & Agho, 2017). Variety of pollutants produced from burning fuels includes particulate matters ($PM_{2.5}$ or smaller size), ozone, methane, carbon monoxide, carbon dioxide, nitrous oxides, sulphur dioxides (principally from coal), polyaromatic hydrocarbons (PAHs) and volatile organic compounds. These pollutants are becoming part of environmental pollutions (Luke Curtis, Rea, Smith-Willis, Fenyves, & Pan, 2006).

2.2 Air pollution

Air pollution has become one of environmental problems locally and globally due to high content of monitored toxics in the environment despite using different gauges. Broadly, air pollution is 'introduction of chemicals, particulate matter, or biological materials into the atmosphere that cause harm or discomfort to humans or other living organisms, or cause damage to the natural environment or built environment'. In the air pollution scenario includes both man-made and natural causes (Hutton, 2011). Despite air pollution virtually divided into outdoor and indoor air pollutions of different sources, both conditions are interrelated and tend to be not much different in rendering immediate and long term health problems.

2.2.1 Indoor air pollution (IAP)

Indoor air pollution (IAP) is caused mainly by burning several types of fuels for cooking and heating purposes in most parts of the world. In almost all developing countries, biomass fuels still remain a major fuel type, and continuation of heavy usage of these fuels is prospective due to free, relatively low costs, and easy availability. Different pollutants such as carbon dioxide (40%), carbon monoxide (32%), particles (20%) and PHAs (50%) playing in air pollution come from all sources of biomass burning in the world (L Curtis, 2002). Indoor recommended standards in the United States Environmental Protection Agency for some pollutants such as PM_{10} and $PM_{2.5}$ in 24-hours cooking time are 150µg/m³ and 65µg/m³; and 8-hour carbon monoxide is 10mg/m³ respectively (Bruce et al., 2000).

Indoor air pollutants are measured in most parts of the world in different settings. In China, a study measured personal level exposure to PM indoor of rural households. Reliable apparatus was utilized in particle measurement for 2 consecutive days excluding possible long activity holidays. Among random 10 percent of 280 women, the $PM_{2.5}$ levels were measured, which presents the levels of personal average 24-hour exposure within the range in winter of 22 to 634µg/m³; and in summer of 9 to 492µg/m³ (Baumgartner et al., 2011). In Sri Lanka, on measuring $PM_{2.5}$ and CO level in 58 households using cook stoves, it observed that these pollutants concentrations are varying depending on the type of stoves and chimney presence. Among those using traditional cook stoves without chimney, it had the maximum 24-hour CO (8.66ppm), indoor $PM_{2.5}$ (940µg/m³) and personal $PM_{2.5}$ (522µg/m³) (Chartier et al., 2017). In Tanzania study including 239 pregnant women, CO was measured 72-hours and $PM_{2.5}$ was measured 48-hours. The measured values of personal CO (25.5ppm), cooking area CO (56.2ppm) from charcoal burning, and personal $PM_{2.5}$ (528µg/m³) were reported, where 87% of $PM_{2.5}$ measurements were above recommended value (Wylie et al., 2017).

According to the finding from the study based on 74 random households in slums of Nairobi, the pollution sources were fuels such as kerosene, wood, LPG and electricity, cigarette smoke and lighting fuel (i.e. kerosene). Specifically, level of $PM_{2.5}$ was found to be varying at higher level with different types of fuel use. For example, the highest level reported in the cohort was in overall households (82.2µg/m³), in kerosene households (181.7µg/m³), and in

LPG households below (50µg/m^3) (Muindi, Kimani-Murage, Egondi, Rocklov, & Ng, 2016). In Peru study quantifying $PM_{2.5}$ and CO concentrations indoors, the levels were found to be different depending on urban and rural settings, not much between chimney presence and absence. Median 24-h $PM_{2.5}$ in urban Vs rural households were 22µg/m^3 Vs 130µg/m^3; and that of CO was 0.4ppm Vs 5.8ppm. Extended stay in rural households with high pollution level has potential higher exposure exemplified by median higher exhaled carbon monoxide (eCO=10ppm) and carboxyhemoglobin (eHbCO=1.6%) than urban value (eCO=6ppm) and (eHbCO=1.0%) (Pollard et al., 2014). Study measuring CO and PM in convenient samples of households using biomass fuels (n=12) in Nepal showed 24-hour overall average CO concentration of 5.4, SD=4.3ppm, and $PM_{2.5}$ of 417.6, SD=686.4µg/m^3 of which higher levels again are associated with cooking activities of the day (Bartington et al., 2017). The findings of all these study support presence of pollutants indoors at higher concentrations than recommendations.

Among documented factors influencing IAP, building with recent renovation can modify the pollutant concentration detected indoor. Relating to this, level of formaldehyde and volatile organic compound (VOC), which are risky for cancers on exposure, were examined if they are different in newly built-schools or renovated schools in Osaka. Measurements were done at 1, 3, 10, 22 months of renovation completion, which showed that formaldehyde level remained higher even after 22 months of completion. Moreover, VOC was found to rise soon after renovation process. It was also reported that the higher the level of the layer in 3-4 story structure, the higher the concentration of pollution, and more sickness reported (Yura, Iki, & Shimizu, 2005). Moreover, a study in Slovakia showed similar findings where CO_2 and total volatile compound (TVOC) levels were objectively measured before and after renovation of 20 residential buildings. The study reported that maximum CO_2 levels were 2050ppm before innovation and 2,770 ppm after renovation (i.e. completion of energy saving installation). Maximum TVOC concentration were (1,805µg/m^3) and (2,362µg/m^3) before and after renovation, which exceeds guideline limit of 300$\mu g/m^3$. Although this study has unknown materials used in buildings and small sample size as limitations, standardized procedure application and similar characteristics of building chosen are strengths to exhibit pollution in connection to building renovation (Sánka & Földváry, 2017).

2.2.2 Air pollution and diseases burden

The air breathed in by humans requires as clean as possible. In light of the growing burden of diseases, particularly non-communicable diseases such as ischemic heart diseases, COPD, lung cancer and strokes, CVD has taken a larger share of all diseases prompting to uncover what is behind. According to global and local facts and figures of adverse health problems stemmed out from environmental problems, air pollution is stepping as one massive environmental issue at present tending to alert the world of its impacts and consequences.

Air pollution known to be contributed by indoor and outdoor sources broadly does matter on accounts from daily living to climate change. So far, air pollution becomes at concerned level as pollutants on exposure are evidently reported to have health consequences. World Health Organization (WHO, 2018a) describes the role of outdoor air pollution which is estimated to cause nearly 4.2 million premature global deaths worldwide in year 2016. The deaths are due to mostly non-communicable diseases such as stroke and ischemic heart diseases (58%), chronic obstructive pulmonary diseases (18%), lung cancer (6%) and acute lower respiratory infections. Almost 91% of premature deaths are from low and middle income countries bearing heavy burden in countries of South-East Asia and Western Pacific regions. Deaths attributable to indoor air pollution include pneumonia (27%), stroke (18%), ischemic heart disease (27%), chronic obstructive pulmonary disease (COPD) (20%) and lung cancer (8%). Around 3.8 million premature deaths are accountable for exposure to air pollution (WHO, 2018b).

The effect of indoor smokes exposure is explicitly reported to have increased blood pressure in many studies of different settings. Even the short term exposure (24-hour) to carbon monoxide raises blood pressure as evidenced in Ghanaian cohort. In the study, 44 pregnant women less than 28 weeks of gestation enrolled, and BP of participants in the improved cook stoves and traditional stoves were measured with validated BP monitors before study. Personal real-time CO measurement was conducted along with BP monitoring sections of the study by using Lascar EL-USB-CO which provides CO concentration in parts per million (ppm). The analysis showed that transient increase of SBP (4.3 mmHg) and DBP (4.5 mmHg) has been in association with exposure to 4.1ppm CO level prior 2 hour blood pressure taken. Only CO data on small sample size was a limitation, however, the study shows association of transient increase of BP with CO exposure from biomass use (Quinn et al., 2017). This study was followed by the GRAPH, a community experimental trial, where every 1ppm increase in CO exposure in households was found to be associated with 0.43 mmHg (95%CI: 0.01, 0.86) higher in DBP, not in SBP according to 72-hour BP and CO monitoring among 817 adult women in Ghana (Quinn et al., 2016).

Other studies in China and Peru reported increased BP in relationship with indoor air pollution. According to a study in 280 rural women (≥25 years) of China, 24-hour personal average measured level of one of the indoor pollutants, $PM_{2.5}$, was found to have association with increase in SBP (4.1 mmHg higher, 95%CI: 1.5, 6.6); DBP (1.8 mmHg higher, 95%CI: 0.4, 3.2) among women (>50 years) exposed to 1-log-µg/m³ increase in $PM_{2.5}$ exposure (Baumgartner et al., 2011). In Peru, a study exploring the association of biomass fuel use and hypertension was conducted with 1004 adults recruited by stratification of age, sex and location (urban and rural). Validated questionnaires for biomass use and standardized instruments for blood pressure were utilized, and data analyzed by multiple linear and multinominal logistic models revealed biomass user had higher (SBP=3.0mmHg, DBP=2.5mmHg) in unadjusted model; (SBP=6.1mmHg, DBP=4.7mmHg) in minimally adjusted model (i.e. age, sex, BMI);

(SBP=7.0 mmHg, DBP=5.9mmHg) in fully adjusted model (i.e., plus height, smoking, pack years, wealth indexes, alcohol use and physical activities) when compared with non-biomass user. The blood pressure was not different among gender (Burroughs Peña et al., 2015). These study findings support the knowledge of effects of indoor air pollution by different pollutants on hypertension, which is a risk factor for cardiovascular events.

Abundant literatures importantly mention some pollutants are harmful and causing more deaths. WHO reports that 1 in 9 deaths is attributable to air pollution where role of particulate matters is accounted for in larger scale. Particulate matters in coarse and fine forms are two important particles involved in the air quality assessment. In technical terms, particles' diameter larger than 10µm is termed as PM_{10}, so is $PM_{2.5}$ for particles smaller than 2.5 µm. Although both particles are responsible for aggravation of existing diseases, they are believed to involve in promotion of potential diseases and initiation of diseases, because these particles especially $PM_{2.5}$ can travel to deeper parts of body particularly respiratory system (Von Bornstädt et al., 2014) . Recently, the global burden of disease study 2015 described that figures of adverse health attributed to air pollution is escalating, and $PM_{2.5}$ exposure alone is reported to have left nearly 4.2 million global deaths with 103.1 million disability-adjusted life-years, of which 59% is happening in East and South Asia regions (Cohen et al., 2017).

However, Crouse et al. made an effort to investigate whether there is association between $PM_{2.5}$, NO_2 and Ozone exposure and mortality in CanCHEC study and found after 16 years of follow-up on 2.5 million people in Canada that $PM_{2.5}$ alone does not have enough power to cause high mortality, but positive correlation is observed if $PM_{2.5}$ combines with other pollutants. Their single pollutant model and multiple pollutant model analysis provided a conclusion that long term exposure to these specific chemicals enhanced risk of deaths (Crouse et al., 2015). In another study known as NIH-AARP Diet and Health Cohort showed inconsistent findings- total and CVD mortality risk is increased; but respiratory mortality risk except in never-smoker is not statistically significant on exposure to outdoor $PM_{2.5}$ (Thurston et al., 2016). Similarly, in damage estimation of air pollution (1990-2050) conducted by Hutton based on the maximum available resources, it was predicted that the use of solid fuels would be going down in 2050 (Hutton, 2011) with prospect of low exposure to unclean air by solid fuels burnings then.

Regarding the impacts, though, brought about by air pollution and climate change on health, Perera commented that fossil fuel burning which is a significant polluting source, has been a great threat to health of children based on obvious evidence of developmental defects and genetic damage documented recently (Perera, 2017). In fact, although toxic air inhalation tends to be unequal based on the locations, ethnicity and socioeconomic status (Rosofsky, Levy, Zanobetti, Janulewicz, & Fabian, 2018), health impacts ranging from child development to immediate health risks remain high following air pollution exposure. When high mortality, high morbidity, high health cost and compromised economic outputs are with no much doubt responsible for environmental pollution, increased prevalence of vascular disorder such as carotid intima-media thickness (CIMT) in particular is not excused from the influence of environmental substances despite their fluctuations in concentrations.

2.3 Studies related to measured pollutants levels and, some pollutants in association with high blood pressure

Growing number of literatures show increased indoor pollutants levels which is related to different fuels use. The summary of studies in relation to air pollution are summarized in Table 1.

Table 1 Summary of related studies for pollutants levels and blood pressure

First author, location, study design	Population	Study factor	Outcome factor	Results
(Chartier et al., 2017) Sri Lanka Cross-sectional study	n=58 HH	Households using different cook stoves	48-hour personal $PM_{2.5}$ exposure, measured by MicroPEM developed by RIT Indoor CO level measured by electrochemical logger (Lascar Electronics EL-USB-CO)	-Measured median 48-hour average indoor $PM_{2.5}$ concentration was 64µg/m³ in HH with Anagi stoves and a chimney presence; 181µg/m³ without chimney. In traditional stoves HH, the concentrations were 70µg/m³ if a chimney was present and 371µg/m³ if not. -Overall, measured indoor $PM_{2.5}$ concentrations were from a minimum of 33µg/m³ to a maximum of 940µg/m³, while that of personal exposure concentrations were from 34 to 522µg/m³. -Linear mixed effects modeling of the dependence of indoor concentrations on stove type and presence or absence of chimney showed a significant chimney effect (65% reduction; P<0.001) and an almost significant stove effect (24% reduction; P=0.054). -Primary cooks in households without chimneys were exposed to substantially higher levels of HAP than those in households with chimneys, while exposures in households with traditional stoves were moderately higher than those with improved Anagi stoves.

First author, location, study design	Population	Study factor	Outcome factor	Results
(Wylie et al., 2017) Tanzania Cross-sectional study	n=239 pregnant women	Women cooking with different fuels	Personal exposure to CO Draeger carbon monoxide 50/a-D (Draeger USA, Andover, MA, USA) Personal $PM_{2.5}$ Casella Apex Lite Personal Sampling Pump (Casella USA, Amherst, NH, USA).	-CO and $PM_{2.5}$ exposures during pregnancy were moderately high (geometric means 2.0ppm and 40.5µg/m³); 87% of $PM_{2.5}$ measurements exceeded WHO air quality guidelines. -Median and high (75th centile) CO exposures were increased for those cooking with charcoal and kerosene versus kerosene alone in quintile regression. -High $PM_{2.5}$ exposures were increased with charcoal use. -Outdoor cooking reduced median $PM_{2.5}$ exposures. -For $PM_{2.5}$, a 0.15kg reduction in birth weight per interquartile increase in exposure (23.0µg/m³) in multivariable linear regression was observed with borderline statistical significance (95%CI: 0.30, 0.00 kg; P=0.05). -$PM_{2.5}$ was neither significantly associated with birth length or head circumference nor, was CO exposures associated with newborn anthropometrics.
(Muindi et al., 2016) Kenya Cross-sectional study	n=72 HH	HH Pollution sources	Level of 72 hours households $PM_{2.5}$ measured by DustTrak™ II Model 8532 monitor	-Kerosene (69.7%) used in majority of HH as a cooking fuel. -Overall, the mean $PM_{2.5}$ levels measured within homes at both sites (108.9µg/m³

First author, location, study design	Population	Study factor	Outcome factor	Results
				SD=371.2 in Korogocho; 59.3µg/m³ SD=234.1 in Viwandani) were high. -Air quality ($PM_{2.5}$) measured in HH varied widely, especially during the evenings (124.6µg/m³ SD: 372.7 in Korogocho and 82.2µg/m³ SD=249.9 in Viwandani), and in households using charcoal (126.5µg/m³ SD=434.7 in Korogocho and 75.7µg/m³ SD=323.0 in Viwandani).
(Bartington et al., 2017) Nepal Cross-sectional study	N=12 HH using biomass	HH using biomass	CO and $PM_{2.5}$ concentrations measured at by EL-USB-CO monitor and TSI DustTrack II 8530/Sidepack AM 510	-Average measured kitchen $PM_{2.5}$ level in 24-hours was 417.6, SD=686.4µg/m³ (8 households), CO was 5.4, SD=4.3ppm)(12 households). -Higher concentrations were associated with cooking activities. -Average $PM_{2.5}$ and peak 1-hour CO levels were above the WHO guidelines. -Average hourly CO and $PM_{2.5}$ concentrations were in moderate correlation (r=0.52).
(Pollard et al., 2014) Peru Cross-sectional study	n= 86 HH	Factors associate with higher exposure to CO and $PM_{2.5}$ in rural and urban setting	24 hours $PM_{2.5}$, CO and PM_{10} in selected HH	-Median 24-hour indoor $PM_{2.5}$ and CO concentrations were 130 vs. 22µg/m³ and 5.8 vs. 0.4ppm (all P<0.001) in rural vs. urban households. -No significantly reduced median concentrations in 24-hour indoor $PM_{2.5}$ (119 vs. 137µg/m³; P=0.40) or CO (4.6 vs. 7.2ppm; P=0.23) among rural households with and without chimneys.

First author, location, study design	Population	Study factor	Outcome factor	Results
				-Having a chimney did not significantly reduce median cook-time $PM_{2.5}$ (360 vs. 298µg/m³, P=0.45) or cook-time CO concentrations (15.2 vs. 9.4ppm, P=0.23). -Having a thatched roof (P=0.007) and hours spent cooking (P=0.02) were associated with higher 24-hour average PM concentrations. -Rural participants had higher median exhaled CO (10 vs. 6 ppm; P=0.01) and exhaled carboxyhemoglobin (1.6% vs. 1.0%; p=0.04) than urban participants.
(Baumgartner et al., 2011) China Cross-Sectional study	n=280 women > 25 years	42-hour HH $PM_{2.5}$ exposure measured by portable, battery operated apparatus (Apex Pro, Casella CEL, Bradford, UK)	SBP and DBP measured by Omron BP monitor (Omron-705 CP, Omron Corp, Tokyo, Japan)	-Ranges of personal average 24-hr exposure to $PM_{2.5}$ are 22 to 634µg/m³ in winter; 9 to 492µg/m³ in summer. -Association between a 1-log-µg/m³ increase in $PM_{2.5}$ exposure with 2.2mmHg higher in SBP (95% CI: 0.8 to 3.7; P=0.003) and 0.5mmHg higher in DBP (95% CI, –0.4 to 1.3; P=0.31) among all women were revealed. -Varying estimated effects by age group was found (i.e. among women >50 years of age, a 1-log-µg/m³ increase in $PM_{2.5}$ exposure was associated with 4.1 mmHg higher SBP (95% CI: 1.5 to 6.6; P=0.002) and 1.8 mmHg higher DBP (95% CI: 0.4 to 3.2; P=0.01).

First author, location, study design	Population	Study factor	Outcome factor	Results
(Burroughs Peña et al., 2015) Peru Longitudinal cohort study	n=1004 male and female >35 years	Biomass fuels use	Blood pressure level	-The results on 1004 participants of mean age 55.3 years and female (51.7%) showed an association between biomass fuel use with both prehypertension (adjusted relative risk ratio 5.0, 95% CI: 2.6-9.9) and hypertension (adjusted relative risk ratio 3.5, 95% CI: 1.7 to 7.0). -Biomass fuel users had a higher SBP (7.01 mmHg, 95% CI: 4.4 to 9.6) and a higher DBP (5.9 mmHg, 95% CI: 4.2 to 7.6) when compared to nonusers. -Biomass fuel use was associated with an increased risk of hypertension and higher blood pressure in Peru. -Reducing exposure to household air pollution from biomass fuel use represents an opportunity for cardiovascular prevention.
(Quinn et al., 2016), Ghana Cross-sectional study	n=817 women	72 hour CO exposure	Blood pressure level	-Carbon monoxide exposure and diastolic blood pressure (DBP) was found to have a significant positive association. -There was an association of average of each 1 ppm increase in exposure to CO with 0.43 mmHg higher DBP (95% CI: 0.01, 0.86). -A positive association but no significance was observed for systolic blood pressure (SBP).

First author, location, study design	Population	Study factor	Outcome factor	Results
				-Household air pollution from wood-burning fires was found to be associated with higher DBP in pregnant women at early to mid-gestation.
(Quinn et al., 2017) Ghana Community randomized trial	N= 44 women	Personal CO exposure	Increased ambulatory blood pressure (ABPM) in 24 hour	-Exposing to peak Carbon monoxide defined as ≥4.1ppm 2 hours before taking blood pressure was associated with hourly systolic BP elevation of 4.3 mmHg (95%CI: 1.1, 7.4), and that of diastolic BP of 4.5 mmHg (95%CI: 1.9, 7.2), in comparison to blood pressure of women with lower carbon monoxide exposures. -Lower systolic blood pressure at post-intervention among women receiving improved cook stoves was observed within-subject change of −2.1 mmHg (95% CI: -6.6, 2.4) when compared to controls, but not statistically significant.

2.4 Carotid intima-media thickness (CIMT)

Carotid intima-media thickness (CIMT) is a state of carotid artery walls thickened as a result of structurally hypertrophic changes in response to metabolic insults in prolonged manner. In normal arteries following arthrosclerosis caused by several risk factors, increased intima-media thickness can be identified. The intima-media thickness is believed to be an independent cardiovascular risk marker important to predict cardiovascular diseases (Simova, 2015). Degree of intima-media thickness identified and presence of plagues may serve as additional aid, and they improve predicting cardiovascular diseases apart from mere traditional risk factors in risk prediction (Øygarden, 2017).

Atherosclerosis in its gradual development can occur at any age, but more commonly in growing age, whereby susceptibility and complications may vary partly due to flow and velocity thresholds. Increased thickness of intima-media being an important atherosclerotic risk marker is firstly detected structural change in the lengthy pathogenesis of atherosclerosis, coupled with concurrent plague formation. In clinical terms however, IMT increase and subclinical atherosclerosis are different synonyms despite the fact that both are related and complement to each other. In acute state, IMT can occur as a result of adaptive response to changes in blood flow, arterial wall tension or lumen diameter which is a non-atherosclerotic process in which the processes known to be arterial smooth muscle hyperplasia and fibrocellular hypertrophy occurs which lead to medial thickness and compensatory arterial remodeling. Therefore, CIMT alone still should not be the subject of treatment by assuming it as the only risk factor, thereby requiring considerations for other influences (e.g. age, body weight) (Simova, 2015).

2.4.1 Pollutants and inflammatory process on vascular diseases and preeclampsia

Diseases such as cardiovascular diseases are shown in many studies to date that they are associated to not only short term exposure but also long term exposure to elevated level of environmental pollutants. The mechanism in the association of diseases with air pollutant exposure is in part described due to inflammation process induced by toxic properties of different pollutants in body systems. With the exposure to pollutants, and entry to body in different routes, following systematic inflammation by means of reactions, metabolic and biologic imbalances causing changes in the target organs especially in vascular structure occur. This is explained in the Multi Ethnic Study of Atherosclerosis (MESA) that inhaled particles which down-graded nitric oxide synthase which has vasodilating action and, following its low bioavailability results in high blood pressure and, automatic dysfunction impairing automatic tone of vasculatures as well (Gill et al., 2011) One study suggested that central nervous system diseases including ischemic strokes were in the key process of changes in microglia and blood brain barrier on exposing to air pollutants. Among many air pollutants, ground level ozone and particulate matters have rapid effects on brain key vasoregulatory pathways by modulating genes expression, resulting in to substantiate that the cerebrovascular accidents are importantly induced by air pollutants. No single pathway is responsible for these processes though, complex inflammatory process(Von Bornstädt et al., 2014) is overwhelmingly implicating, in which inflammatory mediators (cytokines, TNF-α, Interleukins, granulocyte-macrophage colony-stimulating factor) originated and activated in the lungs, which consequently induce further systematic inflammation and cellular changes to cause brain cells deaths resulting in many CNS diseases (e.g. strokes, Parkinson's diseases, Alzheimer's diseases) (Block & Calderón-Garcidueñas, 2009).

A pregnancy specific syndrome, preeclampsia, despite many possible causes (Redman & Sargent, 2003), is broadly hypothesized to follow inflammatory process induced by many factors. As has been shown air pollution has implicated in the inflammation process with its toxic properties which initiate the cascade of systematic inflammation including placenta. Exposing to air pollutants has shown increased risks of having markers of chronic placenta hypoxia such as hypoxia- inducible factors, syncytial knots are found to be higher in the placenta of women using firewood, kerosene users than ethanol user. Additionally, inflammatory markers (TNF-α) is found to be higher in pregnant women using firewood (7.17pg/ml, SD=32.6) than ethanol user (3.72 pg/ml, SD=37.2) in clean stove trial in Nigeria (Olopade et al., 2017). These randomized controlled trials in Nigeria concluded that household air pollution has caused oxidative stress favoring undesirable oxygen deprivation in placenta (Dutta et al., 2018). Furthermore, one study measuring coronary flow reserve (CFR) which represents microvascular functions, found that CFR is significantly impaired in PE patients, and high sensitivity CRP being a marker of inflammation is revealed high in PE patients as well. These findings suggested the important role of chronic inflammation which contributes to endothelial dysfunction and arthrosclerosis in PE (Ciftci et al., 2014).

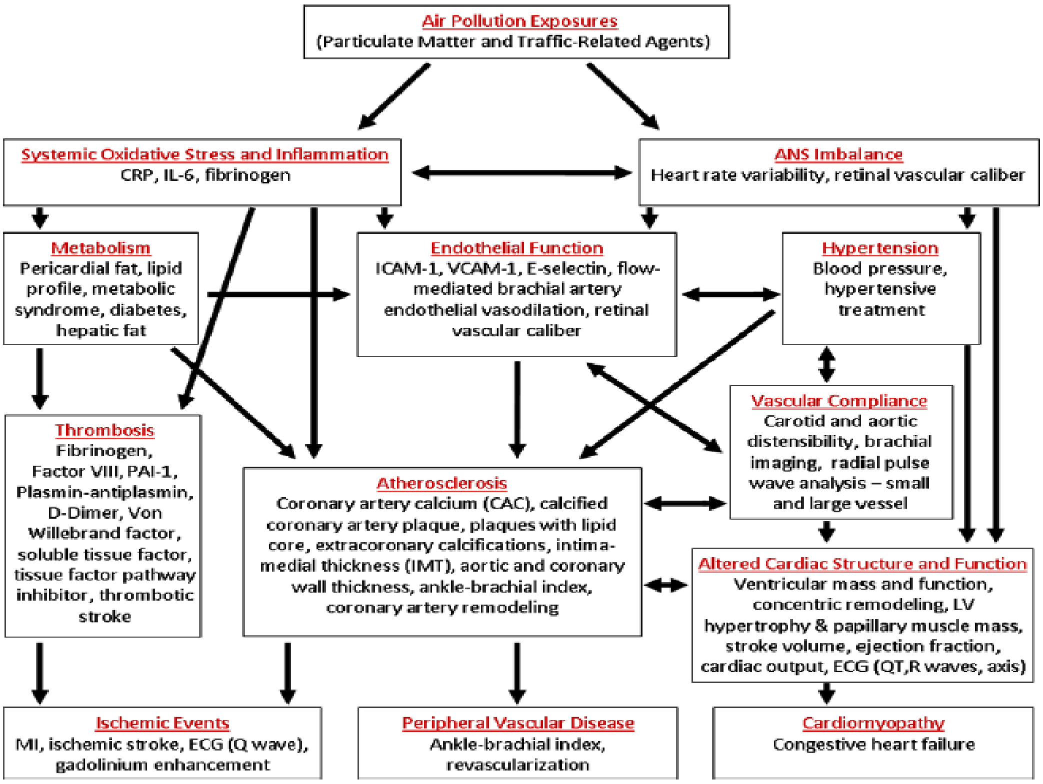


Figure 2 Air pollutants affecting diseases through multiple pathways

2.4.2 Risks factors associated with CIMT

The hallmark of arthrosclerosis is reflected by thickened or harden arterial walls which again are found to be associated with several both traditional and novel cardiovascular risk factors. In traditional cardiovascular risk factors includes age, sex, race, smoking, alcohol drinks, exercise, blood pressure, abnormal lipid profiles, diet consumption, taking lipid lowering agents, glycaemia, hyperuricemia and obesity related conditions. Novel cardiovascular risk factors among many others are genetics, some inflammatory diseases, lipid metabolism, blood cells functions, job stress and vitamin-D. Inconsistencies of these associations are in need of further studies and clear mechanism for explanations.

The presence of such traditional risks on changes of CIMT was analyzed in the meta-analysis recently (Qu & Qu, 2015). It revealed that increased CIMT predisposed by older age lower cardiac functions in women, having no obvious difference between Asians and Europeans. Despite males reported to have thicker CIMT, it could not provide statistical significance. Alcohol is protective for CMIT and, exercises improve cardiovascular risks, however, still has no evidence to reduce age related arthrosclerosis. High blood pressure of both systolic and diastolic pressure is reported to be associated with CIMT where BP variations have stronger correlation with thickness or plague number of left common carotid artery than the right one. Dyslipidemia with non-high density lipoprotein influences on CIMT where familial hypercholesterolemia (FH) in childhood is associated with higher CIMT. Hyperglycemia and low HbA1c levels among type 2 diabetes are found to be positively associated with CIMT where impaired glucose favoring insulin resistance supports early arthrosclerosis development. Obesity and its parameters such as BMI, waist circumference, waist hip ratio are reported to be associated with CIMT which is more significant in metabolically abnormal obese people while this association cannot be well established among those with minor cardiovascular risks. Obesity related diseases (e.g. Polycystic Ovary Syndrome -PCOS) are independent risk factor for obesity which may contribute to increased CIMT via direct effect of higher androgen.

Similarly, CIMT has associations with novel cardiovascular risk factors. Certain genotypes such as telomere shortening in adults over 50 years, hepatoglobin (Hp) 2-2 genotype in beta thalassemia major children, and single nucleotide polymorphisms (SNPs) in 7-dehydrocholesterol reductase/NAD synthetase-1 interacted with type 2 diabetes are particularly observed to be predictor of early arthrosclerosis and associated with early increased CIMT. Some inflammatory diseases found to be associated with arthrosclerosis are Rheumatoid Arthritis, Behcet diseases, Systematic Lupus Erythematous and Psoriasis, which all elevates risks for cardiovascular diseases by complex immunologically inflammatory mechanisms. Effects of Cytokines, interleukin-17, leucocyte counts are considered in the case of CIMT. HIV infection, H-pylori, tooth loss, and chronic periodontitis in men are shown to be associated with arthrosclerosis. Stress posed by job appears to be risky for subclinical arthrosclerosis in some studies; nevertheless, it is inappropriate for high demand job requiring more strong evidences. Regarding with vitamin-D, low levels of serum 25-hydroxyvitamin D3 (25(OH) D during childhood is found to be associated with increased CMIT in adulthood. That serum level in fact is not independently associated with cardiovascular diseases and CIMT, although its increased level is useful in predicting subclinical arthrosclerosis in non-smokers. Complementary effect of Vitamin-D and statin may be beneficial in cardiovascular diseases prevention while only Vitamin-D cannot be assumed to have a protective effect against subclinical arthrosclerosis (Qu & Qu, 2015).

Moreover, women's parity tends to be susceptible to higher CIMT, which is reported in some literature. For instance, a study in Germany showed the significant association between parity and increased CIMT, which did analysis on randomly selected women (n=1195) of 45-79 years. The study examined the associations based on number of children (0-4) with CIMT. It found out that nulliparous women had associations with thicker CIMT (mean CIMT=0.81mm, 95%CI: 0.78, 0.84); (maximum CIMT=1.04mm, 95%CI: 1.00, 1.09) adjusted for age. Regarding with number of children on CIMT, those with more number of children tended to have higher CIMT, and while women with a single child had the thinnest CIMT of mean value=0.73mm, and of maximum value=0.91mm in the cohort (Wolff et al., 2005).

It is worth noting that child bearing itself is found to be a risk of increased CIMT. In Finland, the assessment was conducted on 1786 eligible participants with female (n=1786), and male (n=781) as control to estimate the effect of child rearing on CIMT. Under control for cardiovascular risk factors of (e.g. age, occupation, marital status, CIMT at baseline), and in stratification by sex, the 6-year cohort showed that females with children born in 6-years period had their CIMT progressed by mean and maximum thickness of 7.5±3.2μm (P=0.02); and

8.3±34µm (P=0.02) respectively for every child delivered (Skilton et al., 2010). This study highlighted possible influences of child bearing on the progress of CIMT among women. It however recommended serial measurements of parameters including CIMT along the course of pregnancy stressing its current study's limitations.

Other factors relating to metabolic functions are documented in risks of increased CIMT. A study in Brazil assessed if CIMT is increased among those women having past history of gestational diabetes (n=79), and it was compared with other women diagnosed as having metabolic syndrome (n=30) and healthy women (n=60). Following standard protocols for blood chemistry and CIMT measured by ultrasound, among all women between 18 and 47 years, it was found to have more increased CIMT in gestational group (mean CIMT=0.53mm, (95%CI: 0.49, 0.58) which this CIMT is similar to that of metabolic disease group (mean CIMT=0.55mm, (95%CI: 0.46, 0.59), than health women (mean CIMT=0.50mm, (95%CI: 0.46, 0.55). Further in the multivariate analysis on the assumption of possible predictors which will be related to higher composite CIMT, variables such as age, total cholesterol, presence of previous gestational diabetes and presence of metabolic syndrome have been revealed as independent predictor for increased composite CIMT (Freire et al., 2012). Although nature of cross-sectional study has limitations in terms of participants selection, results from measurements of respective groups showed significant difference in CIMT values more higher in women with gestational diabetes histories, which implies diabetes being associated with increased CIMT.

Moreover, diabetes mellitus by which CIMT can be in more progression which is favorable for cardiovascular events. This was explained by a recent meta-analysis on 21 population based cohorts out of 2,278 publications by 18 July 2014. Among many selection criteria, papers that performed at least 2 times ultrasound measurement in diabetes population were selected. Analysis based on data aggregated from 3,092 participants between 33-92 years revealed that not only average mean common carotid artery IMT (0.041mm higher, 95%CI: 0.036, 0.045) but also average maximal common carotid artery IMT (0.046mm higher, 95%CI: 0.041, 0.051) was found in diabetes than non-diabetes population. Further analysis showed only (-0.09 and 0.04mm/year) progression in average annual mean common carotid artery IMT progression in people with and without diabetes (Lorenz et al., 2015). Although studies are mostly focused on western countries, their CIMT measurement differences are indicating diabetic people to have a higher CIMT.

2.4.3 Air pollution and carotid intima-media thickness (CIMT)

In addition to risks factors mentioned in the case of increased CIMT, air pollution is increasingly staged forward in considering health risks. Either high concentrations of, presence of, exposing to, or breathing in of unclean air has been claimed for several health risks including thickened wall of vessels (e.g. CIMT) which has been independent risk marker in predicting cardiovascular diseases.

For example, a study in America investigated the association between Ozone, particulate matters, NO_2 and CIMT with 861 non-smoking university students. Air pollutants exposure was estimated by a method of geocoding residential addresses linked to the database of the United States Environmental Protection Agency's Air Quality System. After analysis under adjustments for other factors (e.g. lipids), it revealed that increased CIMT and air pollutants is associated among age increment. Exposure to Ozone during childhood (0-5 years) is associated with increased CIMT of 7.8μm which is however not statistically significant, that of exposure in 6-12 years showed increased CIMT of 10.1μm (95%CI: 1.8, 18.5, p=0.02) while no significant associations revealed for particulate matters and NO_2 in their study (Breton et al., 2012).

On the other hand, there existed studies showing associations between pollutants such as PM and NO_2 and CIMT. One prospective study known as Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA) provided association between $PM_{2.5}$ pollutants exposure and higher CMIT. The study enrolled initially 6814 participants with 83% complete follow-up in six sites- Winston Salem, New York, Baltimore, St. Paul, Chicago and Los Angeles. The spatio-temporal model was used to estimate $PM_{2.5}$ concentrations for two times ultrasound measurements at the baseline and follow up from 2000 to 2005. By controlling age, sex, race, smoking, and socioeconomic status, analysis on (n=5362) with mean annual progression of 14µm/year showed that a higher residential $PM_{2.5}$ level of 2.5µg/m^3 is associated with greater CIMT of 5µm per year in these same urban areas. Moreover, $PM_{2.5}$ level reduction from its baseline measurement in the course of 2.5 years follow-up is associated with slow rate of IMT progression (-2.8µm/year (95%CI: -1.6, -3.6) for even 1µg/m^3 reduction of $PM_{2.5}$ concentration. Despite the study limited by surrogate measure of atherosclerosis, drop-outs and deficient estimate of prior study air pollution status, the findings of that 5-year cohort highlighted the associations of air pollutant with CIMT: decreased progression and increased progression (Adar et al., 2013).

Similar in Taiwan study, traffic related particulate matters of size less than 2.5 is found to be associated with increased CIMT. That cross-sectional design from 2009-2011 focused on the 689 middle aged (35-65) volunteers in Taipei. One-year average exposure to $PM_{2.5}$, and $PM_{2.5}$ absorbance level, PM_{10}, NO_2 and NO_x related to traffics was assessed by land use regression model. In the left CIMT, not right CIMT, maximum average percentage increase was, for every 1.0×10^{-5}/m increase in $PM_{2.5}$ absorbance level, 4.23% (95%CI: 0.32, 8.13); for every 10-µg/m^3 increase in PM_{10}, 3.72% (95%CI: 0.32, 7.11); for every 20µg/m^3 increase in NO_2, 2.81% (95%CI: 0.32, 5.31); and 0.74% for every 10µg/m^3 increase in NO_x, 0.74% (95%CI: 0.08, 1.41) respectively. The study showed positive associations of exposures to the mentioned pollutants and increased CIMT among middle aged populations (Su et al., 2015).

Due to high probability of several literatures to have heterogeneous results with respect to $PM_{2.5}$ exposure and CIMT, a meta-analysis was conducted so as to determine the strength of associations between $PM_{2.5}$ exposure and CIMT by applying random effect models. One meta-analysis with 8 eligible studies out of 42 reviewed studies, results of combined cross-sectional studies were that every 5μg/m^3 increase in $PM_{2.5}$ is associated with 1.66% (95%CI: 0.86, 2.46; P<0.0001) increase in CIMT, which equates to 12.1μm average increase in thickness. Results of combined longitudinal studies revealed that a greater CIMT progression of 1.04μm per year (95%CI: 0.01, 2.07; P=0.048) if more $PM_{2.5}$ concentration of every 5μg/m^3 is exposed (Provost et al., 2015). Another meta-analysis compiling 11 studies out of 56 studied identified, focused on exposure to $PM_{2.5}$ and PM_{10}. It reported that increase in CIMT of 16.79μm (95%CI: 4.95, 28.63) is associated with $PM_{2.5}$ increasing 10μm/m^3; and increase in 4.13μm (95%CI: -5.79, 14.04) is associated with PM_{10} increasing 10μm/m^3 in overall analysis. These analyses provide stronger evidence that air pollution is involved in increased CIMT with obvious effect of $PM_{2.5}$ in female population (X. Liu et al., 2015).

More recently, papers to find associations between fuel use and increased CIMT elicited that using biomass fuels has associations with CIMT. A study conducted in Peru was cross-sectional in design performed on 266 of adults aged ≥35 years, stratified by groups of chronic exposure to biomass fuel and clean fuel. It revealed in biomass groups that thicker CIMT (0.66 vs 0.60mm; P<0.001), high percentage of carotid plagues (26% vs 14%; P=0.03), and higher medium households concentration of $PM_{2.5}$ (280 vs 14μg/m^3; P<0.001) were reported than clean fuel group. Higher systolic blood pressure (118 mmHg vs 111 mmHg; P=0.001) was in the biomass fuel group than clean fuel group. In multiple regression analysis, it was found on comparison between groups, that the group using biomass fuel revealed higher mean CIMT (mean difference=0.03mm (95%CI: 0.01, 0.06; P=0.02), more carotid plagues at OR=2.6 (95%CI: 1.1, 6.0; P=0.03), more elevated systolic pressure of mean difference=9.92 mmHg (95%CI: 5.4, 13.0; P<0.001) (Painschab et al., 2013).

Furthermore, consistent associations of biomass fuel use with increased CIMT and hypertension were reported in a study in Nigeria. The cross-sectional study involving 389 women older than 18 years living in rural area revealed the differences in CIMT and blood pressure levels between users of biomass fuel and clean fuels. Biomass fuel user compared to clean fuel user had higher significant mean CIMT (0.63mm, SD=0.16 vs 0.56, SD=0.014; P=0.004), mean SBP in mmHg (135.3, SD=26.7 vs 123.8, SD=22.6; p=0.01), and mean DBP (83.7, SD=18.5 vs 80.1, SD=13.8; P=0.043). The regression analysis method showed biomass users are associated with 2.7mmHg more increased in SBP, 0.04mm thicker in CIMT and elevated odds of prehypertension at OR=1.67, all are statistically significant at ($P<0.05$). This study provides evidence of increased CIMT possibly due to exposure to pollutants from biomass fuels burning, for which larger cohort studies is proposed (Ofori et al., 2018).

A very recent cross-sectional study was conducted on Thai-Vietnamese adults (n=132) of 35 years and above with a focus on examining an association between burning incense sticks and increased CIMT. Eligible participants were categorized into non-exposed, non-daily-exposed and daily-exposed group, where high exposed group was found to experience more thickened CMIT with mean thickness (0.04mm; P=0.01) and combined maximum thickness (0.09mm; P=0.01) at left common carotid artery, which were significantly different from CMIT of other groups in comparison. The results of the study added more strength in suggesting the indoor pollution by incense smoke may be a risk factor for cardiovascular diseases (Kammoolkon et al., 2018). Similarly, a cohort study on participants (n=132) in Mueang district of Thailand left consistent results showing the incense smoke was associated with increased left CIMT. Moreover, measured indoor households PM_{10} concentration was 24±11.4$\mu m/m^3$, of which 1 $\mu m/m^3$ average increase had associations with 8% more risks for increased mean common carotid artery (aOR=1.08; 95%CI: 1.01, 1.15); 7% more risks for increased maximum common carotid artery (aOR=1.07; 95%CI: 1.01, 1.12); and 3% more risks for increased maximum left common carotid artery (aOR=1.03; 95%CI: 1.01, 1.09) (Kammoolkon, 2018).

This study mentioned shows that PM_{10} found to be household pollutants produced partly from burning incense is mainly associated with CIMT progression, and incense smoke alone did not show such association despite its risk for increased CIMT on prolonged exposure as small sample size, unknown incense brands and incomplete followers may potentially limit findings.

In the advent of CIMT being found to be associating with traditional risks factors, novel risks factors and environmental pollutants, the proposition of CIMT as a screening tool in assessing risk of cardiovascular diseases demands robust handling of these risk factors. Furthermore, influences of associated risks factors, methodological and analysis issues are of importance and still deserve intensive considerations including CIMT measurements methods by imaging techniques.

2.4.4 Assessment of carotid intima-media thickness

CIMT may be asymptomatic despite its presence and progression in slow pace. However, the thickness of carotid intima media can be assessed by imaging technique. Ultrasound (USG) is a noninvasive tool which can measure CIMT as precisely as possible by following standard protocols. The technological advancement in ultrasound imaging brings real-time, safe, reliable, fast and less cost measurements in both outpatient and inpatients settings. Dependency on the operators in fact warrants following strict protocols in measuring CMIT for accurate parameters. Mean thickness and maximum thickness are used to assess the degree of thickness (Darabian et al., 2013).

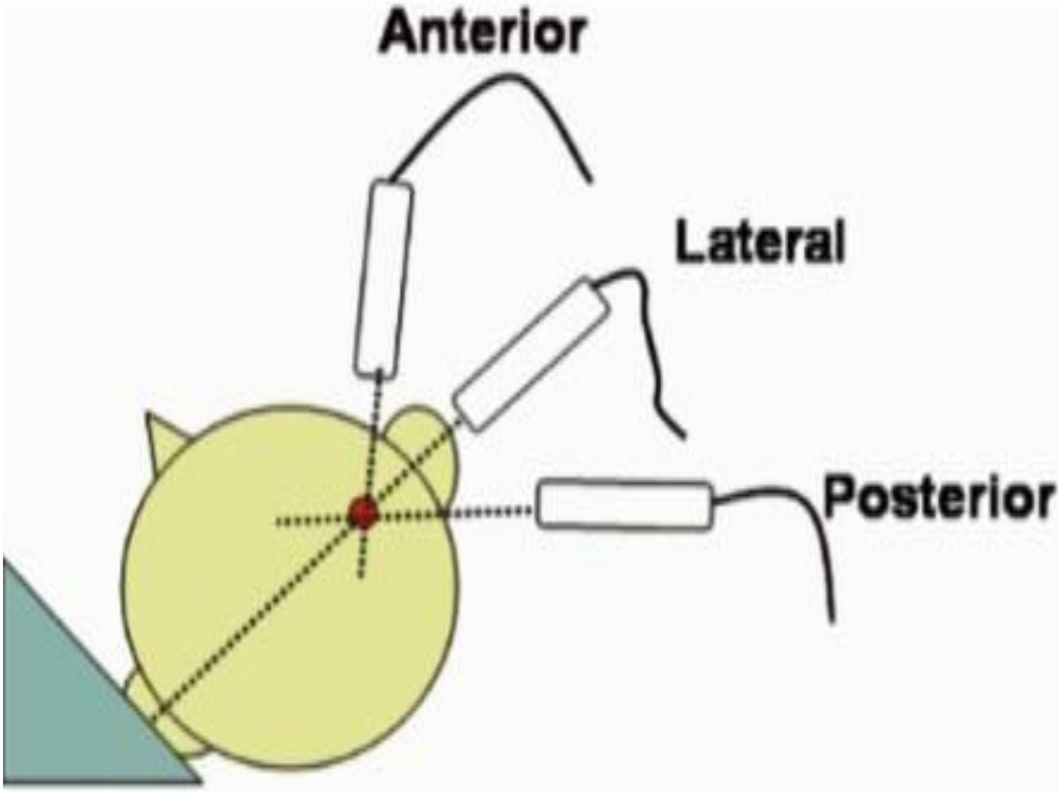


Figure 3 Right sided position of head and probe orientation in carotid ultrasound imaging

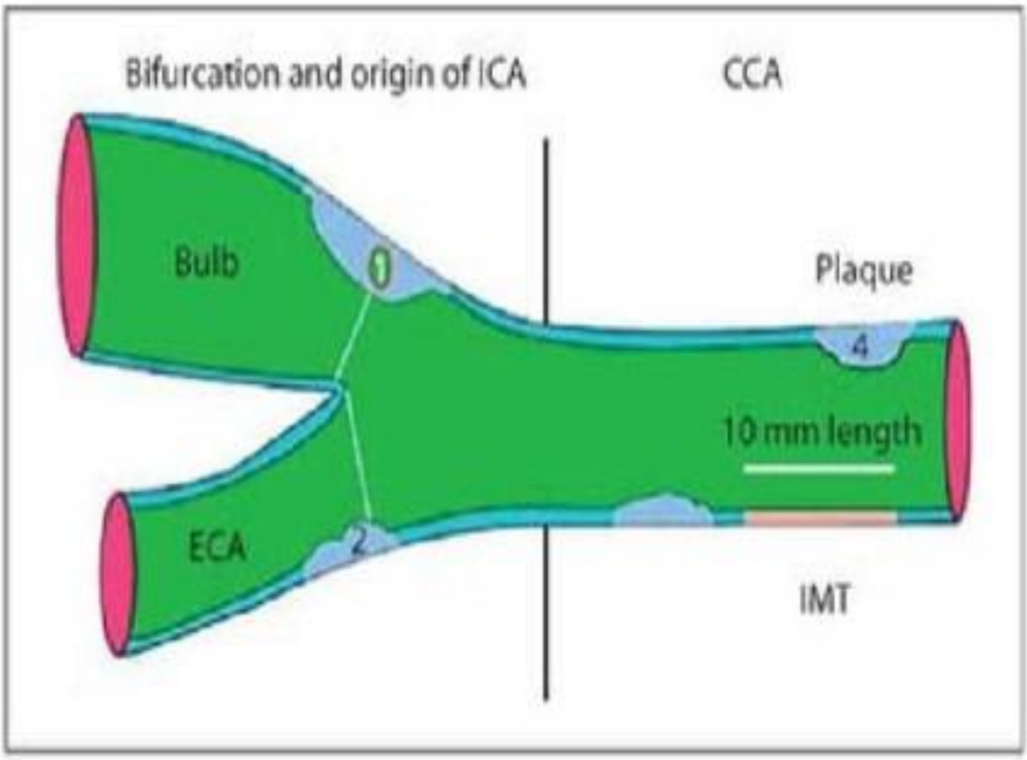


Figure 4 Site and segment of carotid artery for CIMT measurements

Other noninvasive methods applicable for CIMT are flow-mediated dilation (FMD), electron-beam computed tomography (EBCT) measurement, and Magnetic Resonance Imaging. FMD is a portable device useful in assessing endothelium function early of atherosclerotic changes. However, absence of standards, procedure's dependence on operator and few studies for its outcome are some limitations of FMD. EBCT can be used to detect the coronary artery calcification status which its presence means cardiovascular disease probability. Identifying soft plagues, however, not calcified ones deter the uses of EBCT according to experts at American Heart Association/American College of Cardiology. MRI technology provides high sensitivity and specificity in characterizing plagues, which cannot yet overcome high costs creating less use in routine basis (Barth, 2002).

Different brands and origins of ultrasound can be used in assessing CMIT. Most of all, carotid ultrasound applied in CMIT assessment fundamentally has B-mode transducer with frequency of 7 to 15 MHz (Darabian et al., 2013). Exact sites of carotid artery segments predetermined are primary focus in capturing CIMT images. As being sensitive to sonographer, Inter- and intra-observer reliability to avoid man-induced artifacts as well as machine calibrations are essentially required in assessing the credibility of reported images.

Hemodynamic phenomenon of individuals may have effects on CIMT measurements, thus requires ample knowledge of substantial thickness changed during cardiac cycle. For instance, CIMT tends to have difference (0.041mm) between measurements of end diastole and peak systole when the mean IMT was 0.66mm (95%CI: 0.039-0.042) among multi ethnic participants (n=5633) aging from 48-84 years. It also stressed the need to pay considerable attention on the time of capturing the image either at end systole or at peak systole because measurements taken at end systole tended to place individuals at high risks of cardiovascular diseases due to risks overestimate (31.3%). One important finding from this study is that female had higher CMIT changes (mean CIMT=0.042±0.044 vs 0.039±0.047mm; P<0.008) than male (Polak et al., 2012).

2.5 Studies related to factors associated with increased CIMT

There are many burgeoning studies which revealed that many factors are associated with increased CIMT, which is summarized in Table 2.

Table 2 Summary of related studies for factors associated with increased CIMT

First author, location, study design	Population	Study factor	Outcome factor	Results
(Wolff et al., 2005) Germany Cross sectional study	n=1195 male and female between 45-79 years	Parity	CIMT	-Number of children (from 0 to 4) and mean and maximum IMT was found to be associated in U-shape association. -Nulliparous women had the highest age-adjusted mean IMT=0.81mm (95%CI: 0.78 to 0.84) and maximum IMT=1.04mm (95%CI: 1.00 to 1.09), -Women with single parity the lowest mean IMT=0.73 (95% CI: 0.72, 0.74); maximum IMT=0.91mm (95%CI: 0.89, 0.93); P<0.001 compared to nulliparity for both parameters. -Following adjustments for socioeconomic factors, lifestyle variables and biological variables in stepwise multivariate analysis, the magnitude of this association was lowered, yet significance remained.
(Skilton et al., 2010)	n=1786 male and female	Childbearing	CIMT	-Childbirth during the 6-year follow-up in females was associated with increased

First author, location, study design	Population	Study factor	Outcome factor	Results
Finland Cohort study				progression of carotid intima-media thickness of 7.5±3.2μm/birth (mean±SEM), P=0.02 in addition to concurrent reductions in high-density lipoprotein cholesterol (P_{trend}<0.0001), apolipoprotein A-I (P_{trend}<0.0001), apolipoprotein B (P_{trend}=0.01); a redistribution of adiposity to abdominal deposits. -The association of childbirth with carotid intima-media thickness progression did not alter much by adjustment for concurrent changes in cardiovascular risk factors when fully adjusted, P=0.05. -This association was significantly stronger in females than males ($P_{heterogeneity}$=0.001), who served as a control group exposed to the social and lifestyle influences of child-rearing but not the biological influences of childbearing.
(Freire et al., 2012) Brazil Cross sectional study	N=79 with pregastational diabetic history (pGDM) , N = 30 with metabolic syndrome (MS), n=60 healthy control (18-47 years)	pGDM, MS and Healthy controls	CMIT	-Significantly higher CIMT in pGDM when compared to CG in all sites of measurements (P<0.05) except for the right common carotid artery. -Women with pGDM showed similar CIMT measurements to MS in all sites of measurements, except for the left carotid bifurcation, where it was significantly higher than MS (P<0.001). -In a multivariate analysis by including classical cardiovascular risk factors,

First author, location, study design	Population	Study factor	Outcome factor	Results
				pGDM was shown to be independently associated with increased composite CIMT ($P<0.01$). -Analysis of pGDM without risk factors further showed similar CIMT to MS ($P>0.05$) and an increased CIMT when compared to controls ($P<0.05$).
(Lorenz et al., 2015) Australia Systematic Review and Meta-analysis	n = 22 population based cohorts	CMIT and Common Carotid Artery CCA-IMT changes	CVD risks	-Average mean CCA-IMT ranged from 0.72 to 0.97 mm across cohorts in people with diabetes. -The HR of CVD events was 1.22 (95%CI: 1.12–1.33) per SD difference in mean CCA-IMT, after adjustment for age, sex, and cardiometabolic risk factors. -Average mean CCA-IMT progression in people with diabetes ranged between 20.09 and 0.04mm/year. The HR per SD difference in mean CCA-IMT progression was 0.99 (0.91–1.08).
(Su et al., 2015) Cross-sectional study	n = 689 volunteers	Air pollution	CMIT	-One-year mean air pollution exposures were 44.21±4.19$\mu g/m^3$ for PM_{10}, 27.34±5.12$\mu g/m^3$ for $PM_{2.5}$, and (1.97±0.36)×10–5/m for $PM_{2.5abs}$. -Multivariate regression analyses showed average percentage increases in maximum left CIMT of 4.23% (95%CI: 0.32, 8.13) per 1.0×10–5/m increase in $PM_{2.5abs}$; 3.72% (95%CI: 0.32, 7.11) per 10-$\mu g/m^3$ increase in PM_{10}; 2.81% (95%CI: 0.32, 5.31) per 20-$\mu g/m^3$ increase in

First author, location, study design	Population	Study factor	Outcome factor	Results
				NO_2; and 0.74% (95%CI: 0.08, 1.41) per 10-µg/m^3 increase in NO_x. -The associations were not evident for right CIMT, and $PM_{2.5}$ mass concentration was not associated with the outcomes.
(Provost et al., 2015) Systematic reviews and Meta-analysis	n=8 publications	$PM_{2.5}$	CIMT	-$PM_{2.5}$ average exposure ranged from 4.1 to 20.8µg/m3, and average CIMT was 0.73mm with SD=0.14 mm. -In pooled estimate from a random-effects model, combined cross-sectional studies showed an increase of 5µg/m^3 $PM_{2.5}$ was associated with a 1.66% (95%CI: 0.86, 2.46; P<0.0001) thicker CIMT, which corresponds to an average increase of 12.1µm. -Combined longitudinal estimate showed each 5µg/m^3 higher $PM_{2.5}$ exposure had a greater CIMT progression of 1.04µm per year (95%CI: 0.01, 2.07; P=0.048).
(Liu et al., 2015) Systematic reviews and Meta-analysis	N= 11 publications	Effect of $PM_{2.5}$ and PM_{10}	Subclinical arthrosclerosis by CIMT measurements	-11/56 met inclusion criteria. -Overall analysis showed increment of 10µg/m^3 in $PM_{2.5}$ was associated with an increase of CIMT=16.79µm (95%CI: 4.95, 28.63µm), that of PM_{10} was 4.13µm (95%CI: −5.79 to 14.04µm).
(Painschab et al., 2013) Peru	n=266 male and female ≥ 35 years	Exposure to biomass fuels smoke	-Increased CIMT	-Biomass fuel group had greater unadjusted mean CIMT (0.66mm) compared with clean fuel group (0.60mm) at p<0.001.

First author, location, study design	Population	Study factor	Outcome factor	Results
Cross-sectional study			-Carotid plague	-Biomass fuel group had greater carotid plaque prevalence (26%) compared with clean fuel group (14%) at p=0.03). -Biomass fuel group had slightly SBP (118 mmHg) compared with clean fuel group (111 mmHg) at p<0.001). - Biomass fuel group had higher medium household $PM_{2.5}$ concentration (280µg/m^3) compared with clean fuel group (14µg/m^3) at p<0.001. -In multivariate regression, greater mean CIMT (mean difference=0.03mm, 95%CI: 0.01, 0.06; P=0.02), higher prevalence of carotid plaques (OR=2.6, 95%CI: 1.1, 6.0; P=0.03) and higher systolic blood pressure (mean difference=9.2 mmHg, 95%CI: 5.4 to 13.0; p<0.001) were found in biomass fuel group.
(Ofori et al., 2018) Nigeria Cross-sectional study	n=389 women aged 18 and above	Biomass fuels user (BMF) Non-BMF user	-Blood pressure -CIMT	-Mean systolic blood pressure between biomass users (mean SBP=135.3, SD=26.7 mmHg) and non-biomass users (mean SBP=123.8, SD=22.6 mmHg were significantly different at P<0.01). -Mean diastolic blood pressure between biomass users (mean DBP=83.7, SD=18.5 mmHg) and non-biomass users (mean DBP=80.1, SD= 13.8 mmHg) at p=0.043. -CIMT between biomass users (mean CIMT=0.63mm,

First author, location, study design	Population	Study factor	Outcome factor	Results
				SD=0.16mm) and non-biomass users (mean CIMT=0.56mm, SD=0.14mm) were significantly different at P=0.004). -In regression analysis, Biomass fuel use was significantly associated with 2.7 mmHg higher systolic BP (P=0.040); and 0.04mm thicker CIMT (P=0.048). It was also observed that biomass fuel use had increased odds of pre-hypertension (OR=1.67, 95%CI: 1.56, 4.99; P=0.035), but not hypertension (OR=1.23; 95%CI: 0.73, 2.07; P=0.440).

2.6 Preeclampsia

2.6.1 Definitions of preeclampsia

Preeclampsia is a systematic syndrome mostly manifested among pregnant women in their pregnancy courses, of which sufferings can extend beyond pregnancy period. Despite discrepancy in defining preeclampsia (Tranquilli et al., 2013) in terms of onset, blood pressure level, urine protein level and other associated symptoms and signs, new onset hypertension and proteinuria during pregnancy are major constituents. Widely accepted definitions for preeclampsia is described as "onset of a new episode of hypertension during pregnancy (with persistent diastolic blood pressure >90 mmHg) with the occurrence of substantial proteinuria (>0.3g/24h)" (WHO, 2011), "de-novo hypertension presenting after 20 weeks of gestation combined with proteinuria (>300mg/day)" (Mol et al., 2016), "a pre pregnancy specific disorder characterized by hypertension ≥140/90 mmHg on at least two occasions 6-hour apart, and proteinuria of 300 mg or greater in 24-hour urine after 20 weeks of gestation" (Garovic &

August, 2013). According to gestational terms, preterm preeclampsia is meant for preeclampsia developed from 34+1 weeks through 37 weeks, and that of 37+1 is considered as term preeclampsia (Tranquilli et al., 2013). Regarding with preeclampsia onset, early onset preeclampsia is used to mean the episode at 20 weeks gestation onwards and, late onset preeclampsia entitles to the event at 34 weeks gestation onwards (You et al., 2018).

Preeclampsia convinced by worldwide clinicians as more than "pregnancy induced hypertension" (Tranquilli et al., 2013) can be identified separately or in conjunction with other comorbidities during pregnancy. In addition to hypertension and presence of proteins in the urine, preeclampsia may be accompanied by any of cluster features related to severe renal, liver, neurological and hematological malfunctions due to respective organ's dysfunctions. The significant presentation is HELLP syndrome (i.e. Haemolysis, Elevated Liver enzymes and Low Platelet count). Additionally, generalized seizure is recognized among pregnant women with preeclampsia as the characteristics of eclampsia unless that seizure is related to other diseases conditions (WHO, 2011).

2.6.2 Definitions for similar conditions in preeclampsia

Preeclampsia having similar features as other hypertensive disorders thus requires more attention not only for clinical diagnosis but also for public health interests particularly to have clear insight into its classifications. Terminology of 1) chronic hypertension, 2) gestational hypertension, 3) chronic hypertension with superimposed preeclampsia and 4) eclampsia are indeed hypertensive disorders in pregnancy which can be in ambiguity. Therefore, specific definitions for each condition are as follows (Hutcheon et al., 2011)-

- Chronic hypertension is defined as preexisting hypertension with SBP 140 mmHg and DBP ≥90 mmHg prior 20-weeks pregnancy. That level of blood pressures diagnosed after 20 weeks gestation persisting up to 12 weeks after delivery can also be defined as chronic hypertension.

- Gestational hypertension is referred to the development of hypertension in pregnancy after 20 weeks gestation persisting throughout and restoring to normal blood pressure level within 12 weeks after delivery.

- Chronic hypertension with superimposed preeclampsia is called when new onset of proteinuria and thrombocytopenia is detected in pregnant women with chronic hypertension, which may or may not be manifested by other severe features.

Eclampsia, severe progression of preeclampsia, can be in the state of involving neurological features such as generalized fits in pregnant women with preeclamptic diagnosis in the absence of possible seizures causes (e.g. brain tumor, brain infections, epilepsy). At this stage, HELLP syndrome comprising of (Haemolysis, Elevated Liver enzymes and Low Platelet count) will be further manifestations indicating liver cells damage.

2.6.3 Complications and symptoms of preeclampsia

Preeclampsia that occurs beyond high blood pressure during pregnancy typically plays major role in both maternal morbidity and mortality in addition to perinatal morbidity and mortality. Pregnancy hypertensive disorders including preeclampsia impact on 10% of all pregnant women globally (Duley, 2009; WHO, 2011). Among maternal deaths amounting to one million each year are due to pregnancy related causes, and nearly 99% are in lower and middle income countries, which is the major cause of deaths of reproductive women. In statistics, hypertensive disorders leaves nearly 150 annual maternal deaths in developed countries, whereas Latin America and the Caribbean, Africa and Asia has maternal deaths of 38,000, 25,000 and 22,000 every year respectively (Hutcheon et al., 2011).

Preeclampsia alone accounts for 2-8% of pregnancy complications (Duley, 2009; Hutcheon et al., 2011; Mol et al., 2016). Out of pregnancies, preeclampsia related maternal complications are estimated 3% in America, 3.3% in New Zealand, 3% in Swedish, 4.5% in Denmark and 3% in Norway according to studies cited in J.A.Hutcheon et al. Fatal complications include liver rupture, stroke, pulmonary oedema, or kidney failure (Mol et al., 2016). Postpartum depression risk is higher and quality of life is decreased as well. Delay in taking necessary actions at initial stage leading to placenta affected, placental function is damaged to result in fetal complications partly due to insufficient placental blood flow and face maternal death while novel therapy is in development (Mol et al., 2016). Symptoms and signs associated with PE can be noticed as hypertension, proteinuria, severe headache, disturbed visions, vomiting, stomach pain, swollen extremities, hyperreflexia, anaemia and liver enzyme disturbances, which might vary with the severity of PE (Duley, 2009). Apart from maternal deaths, increased future hypertension risks (Garovic & August, 2013), later life cognitive impairment (Fields et al., 2017) could follow. Moreover, preeclampsia is reported to adversely affect fetal health (Madazli et al., 2014) such as fetal growth restrictions, preterm delivery/ birth, low birth weight, higher risk of bronchopulmonary dysplasia, cerebral palsy (Mol et al., 2016) and new born death (Yi et al., 2017).

2.6.4 Risks factors associated with preeclampsia

Preeclampsia with unidentifiable causes yet among pregnant women being a pivot for maternal and children wellbeing has several potential risks factors to be associated with. Among important risks factors, a population-based case-control study confirmed that mother age (<20 and ≥35 years (aOR=1.69), nulliparous (aOR=3.04), low maternal education (aOR=2.95), BMI ≥30 (aOR=1.73), weight gain >35lbs in pregnancy (aOR=1.68), longer birth interval >5 years (aOR=1.92) and gestational diabetes (aOR=1.79) produced elevated risks of eclampsia at when analyzed 3905 women in Washington state. Interestingly, smoking (aOR=0.53) had less risks explained by its anti-inflammatory effect. Chronic hypertension had 3 folds the risks of eclampsia in sensitivity analysis (Coghill et al., 2011). In a hospital based case-control study in Uganda, it pointed out that education (aOR=3.39), alcohol, chronic hypertension (aOR=2.29), family hypertension (aOR=2.25), parity status of primiparity (aOR=2.26) and multiparity (aOR=3.71) (Kiondo et al., 2012). Despite presence of limitations such as some missing data and recall bias, these studies, under adjusted analysis, reinforced the consistent results that education, parity, maternal age and hypertension are associated with preeclampsia.

Another hospital based cross-sectional study in Southern Ethiopia stated that preeclampsia was associated with presence of some factors such as maternal age ≥35 years (aOR=4.5), family hypertension history (aOR=7.9), chronic hypertension (aOR=4.3), family diabetes history (aOR=2.4) and unmarried mother (aOR=3.03). The study was based on 490 eligible women attending to the local hospital (Tessema et al., 2015). Another cross-sectional study with 422 pregnant in another hospital of Ethiopia showed that family hypertension history (aOR=3.25), alcohol use (aOR=8.06) and age < 24 (aOR=0.47) and recent paternity change (aOR=4.08) (Shegaze et al., 2016). The former study enrolled eligible participants in a specified period, and the second study used multistage random sampling to obtain required sample size. Given design limitations and no biomarkers tests for objective measurement, they substantially provide risks for preeclampsia.

Studies in China and Taiwan also discovered risks factors associated with preeclampsia. A hospital-based case-control study in China investigated predictor risks for preeclampsia among case (n=850) and control (n=31147) from hospital records. The analysis reported that factors such as gestational diabetes, family history of diabetes, urinary tract infections, hypertension and stress scores were significantly associated with preeclampsia (Yi et al., 2017). Another population-based retrospective cohort study was conducted in Taiwan, by collecting required data from Birth registers and national insurance database (n=2884347) within 4 years, to explore risks factors of preeclampsia. Maternal age, primiparity, diabetes, chronic hypertension, stroke and hyperthyroidism are document as risks factors of preeclampsia. In separate analysis in early onset and late onset preeclampsia, association between primiparity (relative risk ratio=0.71; 95%CI: 0.68-0.75) and late onset preeclampsia existed. Advanced age and chronic hypertension each were found to be strongly associated with early onset preeclampsia at (relative risk ratio=1.41; 95%CI: 1.29-1.54) and (relative risk ratio=1.71; 95%CI: 1.55-1.88) respectively among Taiwanese pregnant women (You et al., 2018).

Operative delivery is another risks factor for preeclampsia in following pregnancies among women. As an attempt to investigate the impact of prior caesarian section on preeclampsia, a study was conducted in Korea. The required data for first operative delivery and second pregnancy were taken from the Korean National Health Insurance database which holds 97% coverage for 50 million population. Women of 222,137 were analyzed by multivariate logistic regression method for final outcomes, and it observed that women having preeclampsia in the first pregnancy had higher chance of preeclampsia again in second pregnancy at 13.3% while 0.85% in women without PE. The risk of preeclampsia to have in the second pregnancy was (aOR=1.67, 95%CI: 1.31, 2.11 in Older age ≥35 years), (aOR=16.90, 95%CI: 14.93, 19.12 in preeclampsia in first pregnancy), (aOR=3.98, 95%CI: 2.84, 5.56 in multiple pregnancy in second pregnancy), and (aOR=1.48, 95%CI: 1.24, 1.77 in pregnancy interval of 4 years). On analysis of caesarian section, women who had first caesarian section had odds of preeclampsia in the second pregnancy (aOR=1.26, 95%CI: 1.13, 1.41); and it also showed increased risks of PE (aOR=1.35, 95%CI: 1.09, 1.67) on analysis among women who had PE in their first pregnancy (Cho et al., 2015).

2.6.5 Studies showing associated risk factors with CIMT and preeclampsia

Recent literatures show associations between many factors and preeclampsia. Findings are summarized in Table 3.

Table 3 Summary of related studies for factors for CIMT and preeclampsia

First author, Location, study design	Population	Study factor	Outcome factor	Results
(Coghill et al., 2011) Washington State, USA Population-based case-control study	Case=781 pregnant women Control=3124 pregnant women (1:4)	Several risk factors	PE	-Higher risk of preeclampsia was observed in nulliparous women compared to parous women. -Young mother of (20 years) or an older mother of (35 years) was found to be associated with elevated eclampsia risk. -Other risks in positive association with eclampsia were Longer birth interval, low socioeconomic status, gestational diabetes, pre-pregnancy obesity, and weight gain during pregnancy above or below recommended guidelines. -Multiparity and smoking had negative association with eclampsia risk.
(Kiondo et al., 2012) Uganda Hospital-based case-control study	Case=207 pregnant women Control=352 pregnant women	Several risks factors	PE	Risk factors for preeclampsia were plasma vitamin C (OR=3.19, 95%CI: 1.54–6.61), chronic hypertension (OR=2.29, 95%CI: 1.12, 4.66), family history of hypertension (OR=2.25, 95%CI: 1.53, 3.31), primiparity (OR=2.76, 95%CI: 1.84, 4.15) and parity>5 (OR=3.71, 95%CI: 1.84, 7.45) and low education level

First author, Location, study design	Population	Study factor	Outcome factor	Results
				(OR=1.67, 95%CI: 1.12, 2.48).
(Tessema et al., 2015) Ethiopia Hospital-based Cross-sectional	N= 490 pregnant women	Several risk factors	PE	-Preeclampsia prevalence was 8.4% among referred pregnant women in Dessie referral hospital. -Pregnant women were found to be associated with preeclampsia if they had age ≥35 years (aOR=4.5, 95%CI: 1.56, 12.8), chronic hypertension (aOR=4.3, 95%CI: 1.33, 13.9), family history of hypertension (aOR=7.19, 95%CI: 3.24, 15.2), family history of diabetes mellitus (aOR=2.4, 95%CI: 1.09, 5.6) and being unmarried (aOR=3.03, 95%CI 1.12, 8.2) respectively.
(Cho et al., 2015) South Korea Retrospective cohort study	N=222,137 pregnant women	Previous caesarian section	PE	-Preeclampsia risk in any pregnancy was 2.17%; 2.76% in first pregnancy, and 1.15% in second pregnancy. -During the second pregnancy of women with preeclampsia history in their first pregnancy, Preeclampsia risks were 13.30% and, 0.85% for those who had not. -Prior cesarean section in women was found to be associated with preeclampsia risk in their subsequent pregnancy at OR=1.26, 95%CI: 1.13, 1.41 in the entire population analysis. -A previous cesarean section was associated with preeclampsia risk in the second pregnancy among

First author, Location, study design	Population	Study factor	Outcome factor	Results
				women with first preeclampsia history at OR=1.35; 95%CI: 1.09, 1.67; and among women without first pregnancy preeclampsia at OR=1.23; 95%CI: 1.08, 1.40.
(Pereira et al., 2012) Perth, Australia Retrospective cohort study	N=23452 pregnant women	Air pollution	PE risk	-Increase in each IQR of traffic-related air pollution in the entire pregnancy period and in the third trimester was found to be associated with a (12%; 95%CI: 1%, 25%) and (30%; 95%CI: 7%, 58%) increased risk of pre-eclampsia. -The effect of risk of preeclampsia was larger in women less than 20 years or 40 years or above (34%; 95%CI: 5%, 72%), aboriginal women (35%; 95%CI; 0%, 82%) and women having prior diabetes 53%; 95%CI: 7%, 219%) in relation to each IQR increase of traffic-related air pollution in the entire pregnancy.
(Dadvand et al., 2013) Retrospective cohort study	N= 8,398 pregnant women	Exposure to pollutants of NO_2, NO_x, $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, $PM_{2.5}$ absorbance	Overall PE, Early-onset PE Late-onset PE	-Overall preeclampsia and late-onset preeclampsia had strongest association with the third-trimester exposure to fine particulate pollutants. -Early-onset preeclampsia had positive association with the first-trimester exposure to fine particulate pollutants. -Women of first- and third-trimester exposures to $PM_{2.5}$ and third-trimester exposure to $PM_{2.5}$ absorbance were

First author, Location, study design	Population	Study factor	Outcome factor	Results
				significantly related to overall preeclampsia. -Women of third-trimester exposure to $PM_{2.5}$ were statistically significant for late-onset preeclampsia.
(Agrawal and Yamamoto, 2015) India Cross-sectional	N= 39657 (15-49 years) having had a live birth 5 years ago	Indoor air pollution related to biomass fuel use	Preeclampsia symptoms	-Women in households of using biomass fuels and solid fuels were found to have two times more likelihood (OR=2.21; 95%CI: 1.26–3.87; P =0.006) of reporting symptoms of preeclampsia or eclampsia than women in households of using cleaner fuels types following adjustments for potential confounders.
(Milic et al., 2017) Systematic reviews; meta-analysis	N =14 Studies	Women with PE and without PE	CIMT in PE and without PE	-Regarding CIMT measurements, 7/14 were carried out during pregnancy complicated by PE, 10/17 were carried out up to 10-years postpartum and 3/17 included measurements obtained at both time points. -Compared to CIMT in women with PE and non-PE, significantly higher CIMT in PE women than those who without PE was found. -Levels were (Standard Mean Difference=1.10, 95%CI: 0.73, 1.48); P<0.001) at the time of diagnosis and (Standard Mean Difference=0.58, 95%CI: 0.36, 0.79; P<0.001) in the first decade postpartum.
(Garovic et al., 2017)	N= 40 PE pregnancy	Post-menopausal	CIMT in women after	-Higher CMIT in median and interquartile range, was found

First author, Location, study design	Population	Study factor	Outcome factor	Results
Minnesota, USA Retrospective cohort Meta-analysis	N= 40 normotensive pregnancy	women with histories of PE and normotension	10 years of PE and without PE	in the preeclampsia group (0.80mm, 95%CI: 0.75, 0.85mm) than in normotensive group (0.73mm, 95%CI: 0.70, 0.78mm; P=004). -At CIMT level threshold set at (0.77mm), an odd of having CIMT higher than threshold was (OR=3.17; 95%CI: 1.10, 9.14) with statistically significance confounding factors adjustments. - CIMT was greater among women with prior preeclampsia, with a standardized mean difference=0.18mm, 95%CI: 0.05, 0.30; P=004 in the meta-analysis of 10 studies conducted 10 or more years post-partum including 813 women with and 2874 without preeclampsia histories,
(Brückmann et al., 2016b) Cross-sectional study	Total N= 700 with N=347 (first trimester) N=543 (second trimester)	CIMT at first and second trimesters	Preeclampsia	347 pregnant women at first trimester (11.4±1.9 weeks) 543 pregnant women at first trimester (21.5±2.3 weeks) Ages of PE women (32±5 years) - 82 women with any of 4 types PE (early onset, late onset, superimposed early onset, superimposed late onset) had higher CIMT compared to non-PE (p<0.010). -Early onset PE and superimposed early onset PE can be predicted with sensitivity of 64.3% and

First author, Location, study design	Population	Study factor	Outcome factor	Results
				68.6% if cut-off CIMT is set at ≥0.5mm at 1st trimester and >0.4mm at 2nd trimester. -No difference of CIMT found between non PE and women with chronic hypertension during trimesters.
(Brückmann et al., 2016a) Longitudinal cohort	Total N= 678	CIMT at 1st trimester (11.4±1.9 weeks); 2nd trimester (21.5±2.3 weeks); 3rd trimester (32.5.4±2.9 weeks)	Preeclampsia	-Among women, 417 women (31±5 years) underwent CIMT measurement at 1st trimester (11.4±1.9 weeks); 2nd trimester (21.5±2.5 weeks); (32.5±2.9 weeks); and (21.6±23.6 weeks). -Significantly different CIMT in mm in 56 PE women (31±5 years) had (0.47±0.16 at 1st trimester); (0.45±0.14 at 2nd trimester); (0.43±0.12 at 3rd trimester) at ($p<0.01$) compared to women developed non-PE (n=618)- (0.32±0.09 at 1st trimester); (0.33±0.10 at 2nd trimester); (0.33±0.09 at 3rd trimester). -Difference in CIMT between postpartum (0.55±0.11) and 0.36±0.10) at ($p<0.01$).
Niemczyk, N.A., et al., 2018, Pittsburgh Pregnancy cohort	N=37 first time pregnant women	Pregnancy	-Inter-adventitial diameter (IAD) changes -CIMT changes in 1st, 2nd and 3rd	-Adjusting for age, BMI before pregnancy, progression of inter-adventitial diameter (IAD) started its increment at first trimester (6.38mm, SD=0.08) through third trimester (6.92mm, SD=0.09), which returned to first trimester level after postpartum.

First author, Location, study design	Population	Study factor	Outcome factor	Results
			trimesters; post-partum	-For common carotid IMT, thickness was found to begin at second trimester (0.456mm, SD=0.01) along the course of pregnancy, which stays at the higher level (0.581mm, SD=0.02) till 2.7 years after delivery.

CHAPTER 3

METHODOLOGY

3.1 Study design

A community-based, prospective cohort study was conducted on self-cooking pregnant women in Nay Pyi Taw Area in Myanmar where cooking fuels use are widespread, to investigate associations between type of cooking fuels use and increased maternal CIMT and preeclampsia. Pregnant women were recruited from 15 rural health centers (RHC) where pregnant women take antenatal care services by registrations. A purposive sampling was used to recruit participants; and cooking fuels use (firewood, charcoal, coal, gas, LPG, electricity) at households was ascertained by field inspection (Bartington et al., 2017) to assure fuel use status at participants' home. The duration of recruitment was from September 2019 to November 2019. Selected participants were interviewed for sociodemographic characteristics, residential characteristics and cooking fuels use characteristics by face-to-face manner with semi-structured questionnaires. Furthermore, the participants were undergone clinical assessments on hemodynamic parameters, blood chemistries, urinary proteins and CIMT levels. Utilization of four trained research assistants, validated questionnaires, calibrated apparatus and standardized procedures were applied in the entire study. The study duration was from January, 2019 to June, 2020. The study protocol was approved by the Ethical Committee, Chulalongkorn University (COA; No.133/2019) and the Institutional Review Board, University of Public Health, UPH-IRB (2019/Research/34). After eligibility screening employed on 211 pregnant women, a total sample of 192 eligible women required for this cohort were selected at baseline, where 19 were excluded for ineligibility (gestation>18 weeks). All participants were then followed-up to investigate associations between increased maternal CIMT and preeclampsia.

One hundred and seventy six participants completed the follow-up data collections which occurred in the third trimester (>27 weeks). Participants who were lost to follow-up were 8%.

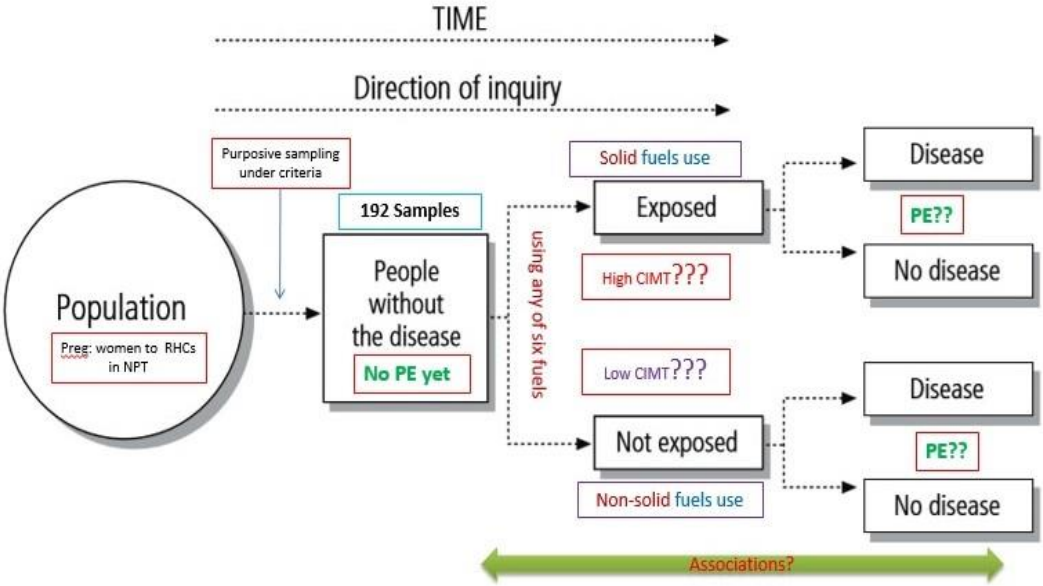


Figure 5 Schematic diagram of cohort study design

3.2 Study setting

Rural health centers (RHC) in Nay Pyi Taw Area were defined as the study setting. According to unpublished health statistics 2018 of Nay Pyi Taw Council Health Department, there are 156 functioning RHC. The following 15 RHCs were selected depending on the availability of eligible participants and favorable distances: 1) Pyi san aung, 2) Nyaung bingyisu, 3) Aung zabu, 4) Thaedaw, 5) Tabyae gone, 6) Koeywar tabyae gone, 7) Ayemyint tharyar, 8) Ottrathiri, 8) Mingone, 10) Kwum chansu, 11) Ywar thit, 12) Medee, 13) Alar, 14) Tayet kone, and 15) Thit poke pin. RHC are the basic health units providing promotive and preventive health services to the grass-roots people. Among health services of RHC, providing antenatal care services is one prime function. Therefore, RHC are essentially the immediate points to register pregnancy from the early gestational weeks till delivery. There is an antenatal coverage of over 81% among pregnant women although both government and private health facilities dominate this area according to unpublished source.

Nay Pyi Taw is a new capital city of Myanmar established over 10 years ago, and it occupies a total population of 1,160,242 with 32% urban dwellers. The area 70,572 sq-km composed of 8 townships in 2 districts (Department of Population, 2015a) bears no industrial complexes, holds bigger coverage of green spaces and has relatively lower number of vehicles. Some ambient pollutants concentration in $\mu g/m^3$ measurement reported weekly are for total suspended PM=174.4 and slightly elevated 24-hour PM_{10}=74.25 measured by high volume sampler; 24-hour mean SO_2=0.04 measured by Modified West and Gaeke method; annual mean NO_2=0.7, 1-hour mean NO_2=1.18 measured by Indian Standard with Sodium Arsenite Method at a monitoring station according to unpublished source. Accordingly, widespread use of different fuels in this area presented elsewhere.

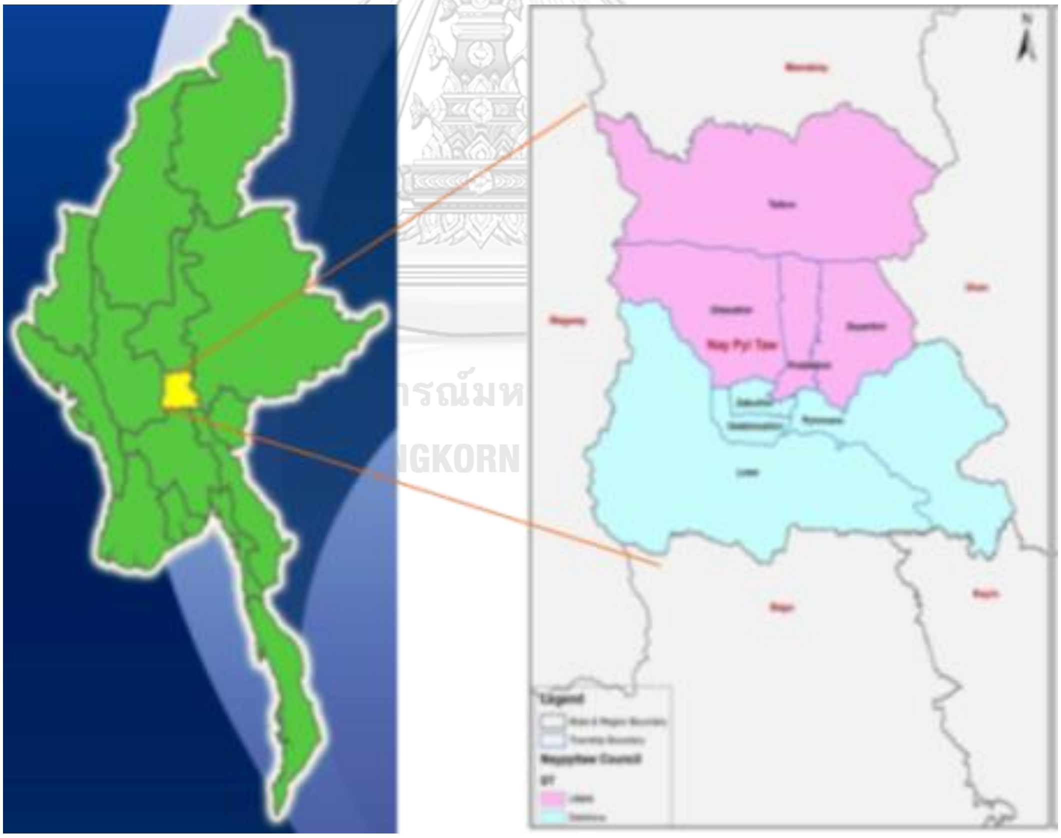


Figure 6 Study area of Nay Pyi Taw

3.3 Study population

Pregnant women in Nay Pyi Taw Area of Myanmar were the study population of this study. Women at reproductive age 15-49 years were 307,391(Department of Population, 2015a), and total number of deliveries in each year accounted for 6,261 in 2014, 7,078 in 2015 and 9,287 in 2016 respectively (MoHS, 2018). The antenatal target of 2018 was 19,731 in the whole Nay Pyi Taw Area.

3.4 Samples

Pregnant women registered at RHCs for antenatal care were samples in the study. From potentially eligible pregnant women, eligibilities were examined by screening with inclusion and exclusion criteria. Participants' fuels use at residences was also ascertained by field inspection checklists. Those participants meeting all criteria were asked for verbal and written consents to include in this study.

3.5 Sample size calculations

In this cohort study, in order to investigate preeclampsia among pregnant women, required sample size was estimated based on 6-8% of preeclampsia was estimated in Myanmar (Tin Tin Thein, 2008) while the global preeclampsia proportion of 3-5% (Duley, 2009; Hutcheon et al., 2011; Mol et al., 2016) was reported. The study in India has reported that women in the households of using biomass fuels and solid fuels are more likely to report preeclamptic symptoms (OR=2.21, 95%CI: 1.26-3.87; p=0.006) than those living in the households of using clean fuels (Agrawal & Yamamoto, 2015). Accordingly, when preeclampsia was expected as 8% among the clean fuels user, and odds ratio of preeclampsia in unclean fuels user was 3.87, the sample from calculation was resulted as 174 pregnant women setting (α =0.05) and power of 80%. epiinfo software version 7.2.2.16 was used. Addition of 10 % drop-out produced a final sample of 192 pregnant women altogether for the cohort.

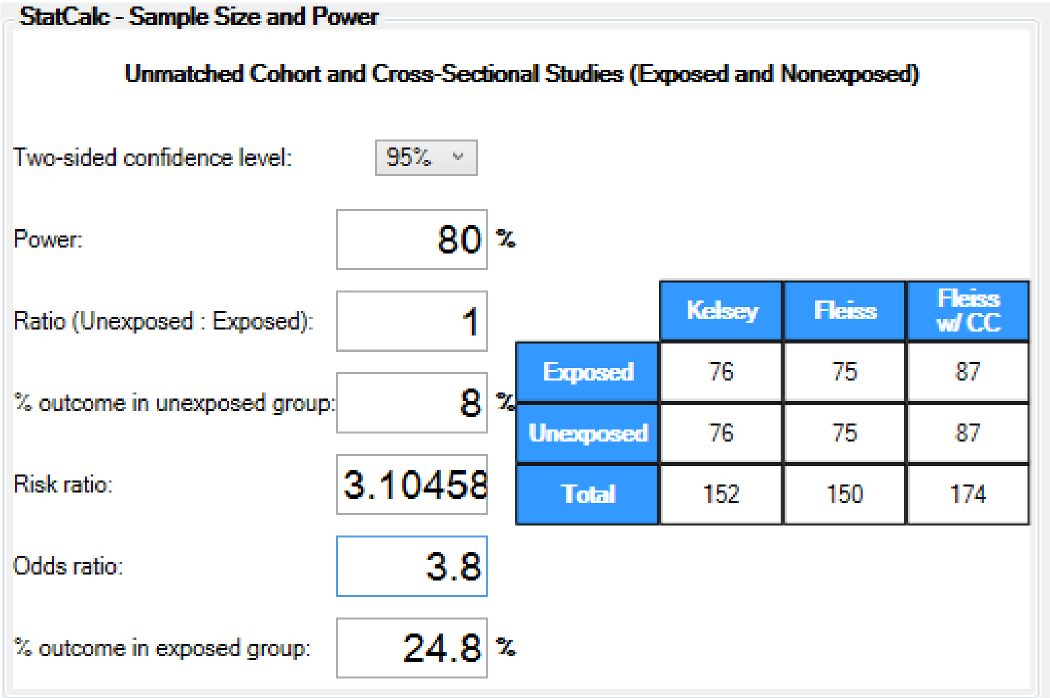


Figure 7 Sample size calculations for preeclampsia by epiinfo software version 7.2.2.16

Furthermore, to estimate if enough samples was in the cohort investigating difference of CIMT between clean fuels use group and unclean fuels use group, in the unavailability of previously published literature on CMIT values in any area of Myanmar, current computation was based on the findings of a cross-sectional study in Peru conducted to investigate chronic exposure to biomass fuel use and increased CIMT (Painschab et al., 2013), which indicated a mean difference of CIMT (0.06mm) between groups of different cooking fuel users (mean CIMT=0.60mm, SD=0.12 for clean fuels group), (mean CIMT=0.66mm, SD=0.13 for unclean fuels group). Study power of 80% with (α=0.05) produced a required total samples of 128, which reached to the final sample of 142 following addition of 10% drop-out expectations. The PS software version 3.1.2 was used to calculate the sample size. Finally, therefore, samples of 192 pregnant women in total were recruited for the whole cohort.

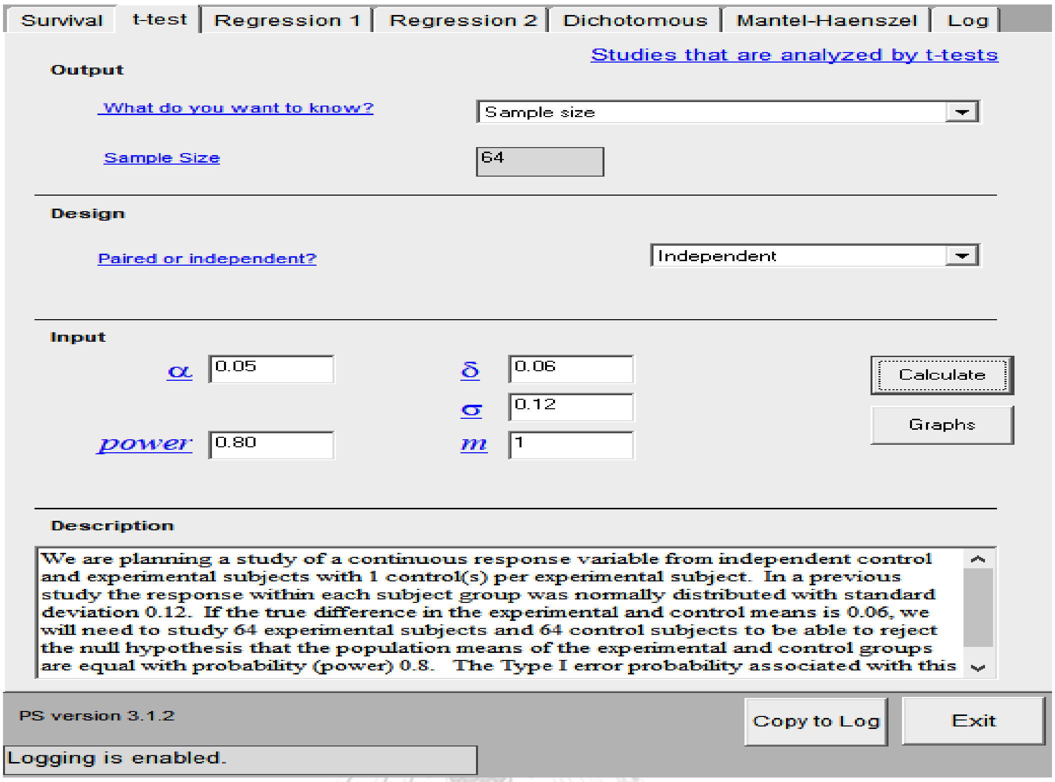


Figure 8 Sample size calculations for CIMT differences by PS software version 3.1.2

3.6 Sampling procedure

The purposive sampling method was used to recruit a total sample of 192 pregnant women from the 15 selected RHCs. Pregnant women are registered in RHC by midwifes who confirms pregnancy status based on women's last menstrual period (LMP) and/or other methods. All Pregnant women who met eligibility criteria (Appendix A) were enumerated by midwife of respective RHC.

Then, enumerated pregnant women were followed by inspection of residences to ensure fuels use which was ascertained by checklists (Appendix B). Beginning with the item of 'Is cooking done at home and how often is self-cooking at household?; and 'what type of fuel does household mainly use for cooking?', checklists will also focus on checking cooking fuels types, cook stoves types, recent cooking activity, kitchen characteristics.

Kitchen characteristics were examined by looking for kitchen attached or separated from home, chimney presence or absence. Evidence of cooking activity is reflected by fresh ash, presence of active cook stoves, evidence of ready-to-use fuels in the vicinity and installed sockets (Bartington et al., 2017), all these facts were observed and recorded for verification of cooking evidence.

Then confirmed pregnant women meeting all criteria were approached until the sample size of 192 was saturated, and both written and verbal consents were taken. Pregnant women were questioned by semi-structured questionnaire (Appendix C) for respective characteristics, and clinical assessments were performed accordingly.

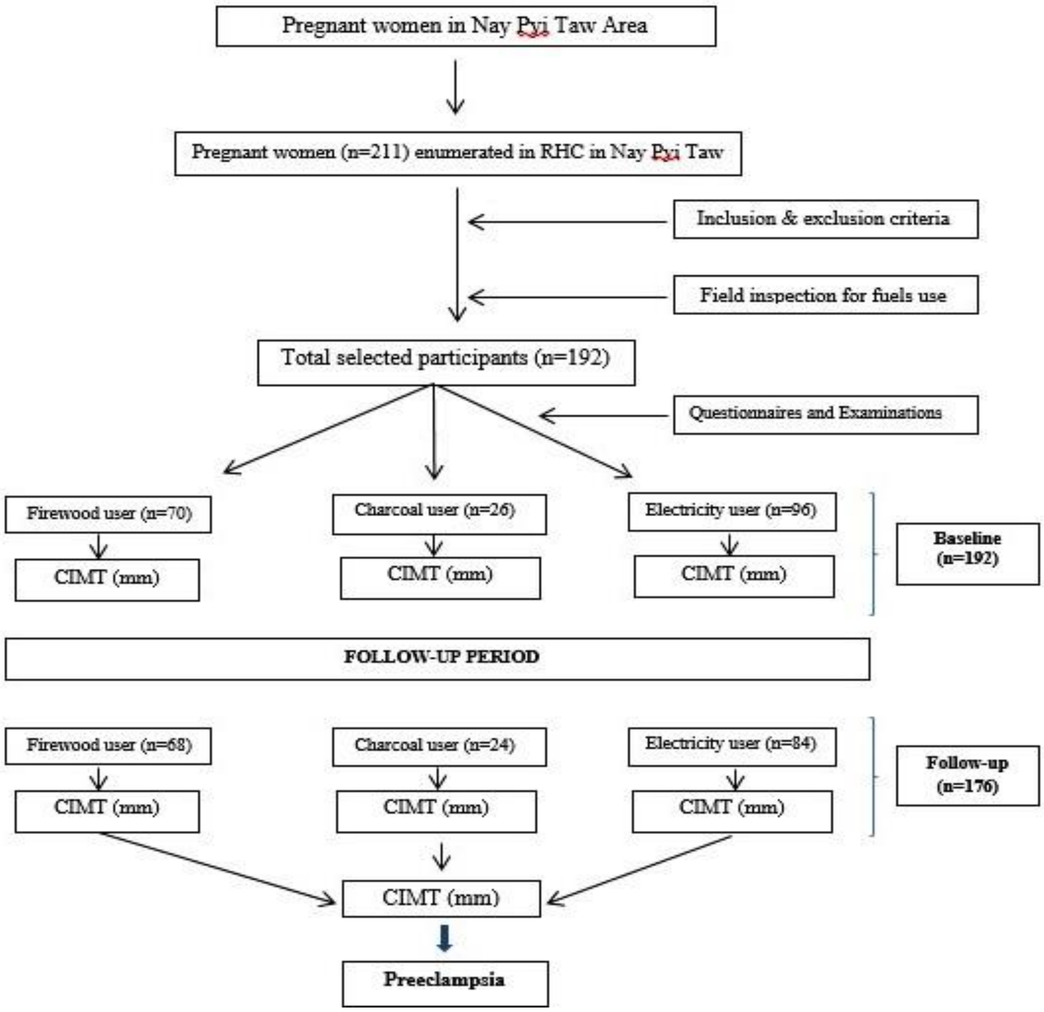


Figure 9 Participants selection flow chart

Table 4 Inclusion and exclusion criteria of participants

Inclusion	Exclusion
-Pregnant women in early trimester (<18 weeks of gestation) (Niemczyk et al., 2018; Olopade et al., 2017) -Age between 18-45 years -Self-cooking at household at least once a week -Use any type of fuels (firewood, coal, charcoal, gas, LPG, electricity) in cook stoves for cooking purposes at least 6 months (Peña et al., 2016) -Currently living in a household in NPT and confirmed to continue living in NPT until delivery -Who expressed willingness and gave consent	-Hypertension (≥140/90 mmHg) (Garovic & August, 2013) -Proteinuria ≥1+ (American College of Obstetricians and Gynecologists, 2013) -Urinary tract infections -Known renal and liver diseases

3.7 Measurement tools

In addition to field inspection checklists (Appendix B) for ascertaining cooking fuels use status, tools for data collection in this study included questionnaires; ultrasound for CIMT measurements; laboratory tests for blood (blood sugar, complete blood count, urinary protein) and OMRON digital blood pressure monitors for hemodynamic measurements.

3.7.1. Semi-structured questionnaires

Semi-structured questionnaires based on information on MCH handbook were developed by researcher addressing on sociodemographic characteristics, residential characteristics and cooking fuels use characteristics. The questionnaires were in Myanmar (Burmese) (Appendix C-Myanmar) to investigate risks factors or associated factors for increased maternal CIMT and preeclampsia. Three parts of questionnaires with items that were included (Appendix C) were as follows:

Part-1. Sociodemographic characteristics: This part contained (7) items to assess socio-demographic status of participants.

Part-2. Residential characteristics: This part was composed of (5) items so as to focus on household factors related to pollution.

Part-3. Cooking fuels use characteristics: This part was formed with (5) questions to address cooking fuels use of participants.

Validation of questionnaire's content was conducted with 3 experts in environmental health and public health fields. Item-Objective Congruence (IOC) index was used to evaluate whether content of questionnaires could measure the set objectives of the study. Items for each objectives were rated as (+1 for clearly measured items, -1 for not clearly measured item, 0 for ambiguously measured item) by experts. Item-Objective Congruence (IOC) score of over 0.5 was accepted. Item-Objective Congruence (IOC) index of questionnaires for this study was 0.92.

3.7.2 Clinical assessments

Carotid intima-media thickness of women were scanned at RHCs and all blood and urine analysis were undergone at a hospital (Zabuthiri Specialists Hospital) locating at the center of Nay Pyi Taw Area.

Figure 10 Laboratory of Zabuthiri Specialist Hospital

Ultrasound for CIMT: For CIMT measurement, high resolution portable ultrasound machine (SAMSUNG MEDISON CO., LTD, KOREA) was used. This brand of ultrasound machine is a versatile, mobile unit designed for visualizing body parts - abdomen, heart, vessels, and internal organs with proved reliability. Appropriate linear transducer (B-mode) within the frequency range of 3.1-15 MHz was applied. Moreover, this ultrasound is applicable to well viewing vascular walls of common carotid arteries which are of interest portions in this study. The machine was ensured to be validated within 6 months (Simova, 2015). The final images produced by this ultrasound was instantly read by radiologists masked the patients' exposure condition.

Figure 11 Ultrasound Machine for CIMT assessments

Laboratory tests: Laboratory tests were included in the study for analysis of blood and urine, all of which were checked by Cobas c311 Analyzer (Roche, HITACHI, Germany). This analyzer is used to objectively analyze clinical chemistries of substrates, enzymes, electrolytes, proteins and many others.

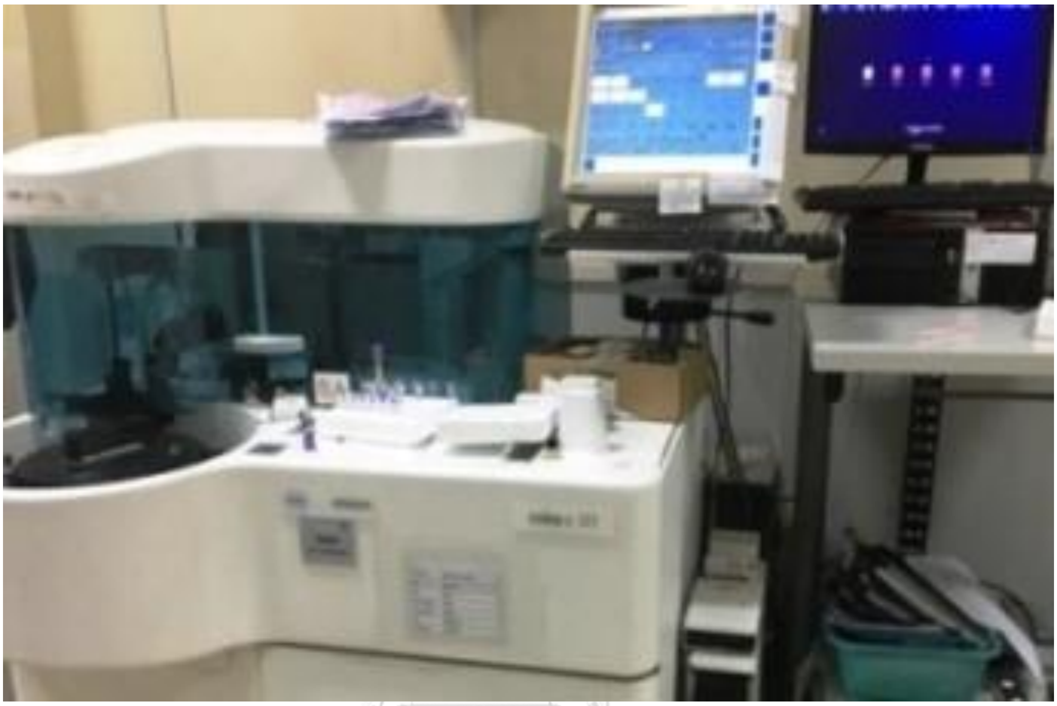


Figure 12 c311 analyzer

Blood: In blood taken in single use sterile syringe, Complete Blood Count (CBC), blood sugar level and non-fasting lipids were mainly analyzed.

Figure 13 Blood collection for lipids and complete blood pictures

Urine: Urinary protein from urine samples was analyzed for protein content which is an important marker to monitor the development of preeclampsia among pregnant women. To obtain reliable urinary protein, participants' urine was collected in urine collection bottle following the standard protocols. Protein in urine was then quantitatively analyzed.

Figure 14 Urine samples in urine collecting bottles

Hemodynamic measurements: Hemodynamic parameters such as blood pressure and heart rate were taken. All apparatus were standardized in each measurement. Appropriate battery changes were done after 100 times use to minimize errors of low power of batteries. Health staff and research assistants took measurements. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were reported in the reporting format.

Blood pressure machine: For blood pressure, validated OMRON automatic blood pressure monitor (HEM-7130) was used. OMRON blood pressure monitor is widely used with high reliability.

Figure 15 A participant assessed for blood pressure by OMRON BP cuff

Weighing machine, height board: For weight and height measures, standardized digital weighing machine and measuring board fitted with measuring units were used. Body weight in kilograms and height in meters were taken for body mass index calculation.

Figure 16 A participant on digital bathroom scale

3.8 Data collection

Collection of sociodemographic, residential and fuels use characteristics and clinical assessments on all selected participants were undertaken with first assessment occurred at (<18 weeks) and follow-up clinical assessments happened at third trimester (>27 weeks) so that clinical parameters changes (urine sugar, urine protein, CBC, lipids, CIMT, BP, HR) could be recognized to monitor development of preeclampsia. Required data including CIMT scans were collected at RHCs at each appointed visits and analysis of blood and urine samples were performed at the laboratory of Zabuthiri Specialist Hospital. Information form MCH handbook was also reviewed for completeness of data about pregnancy and related information.

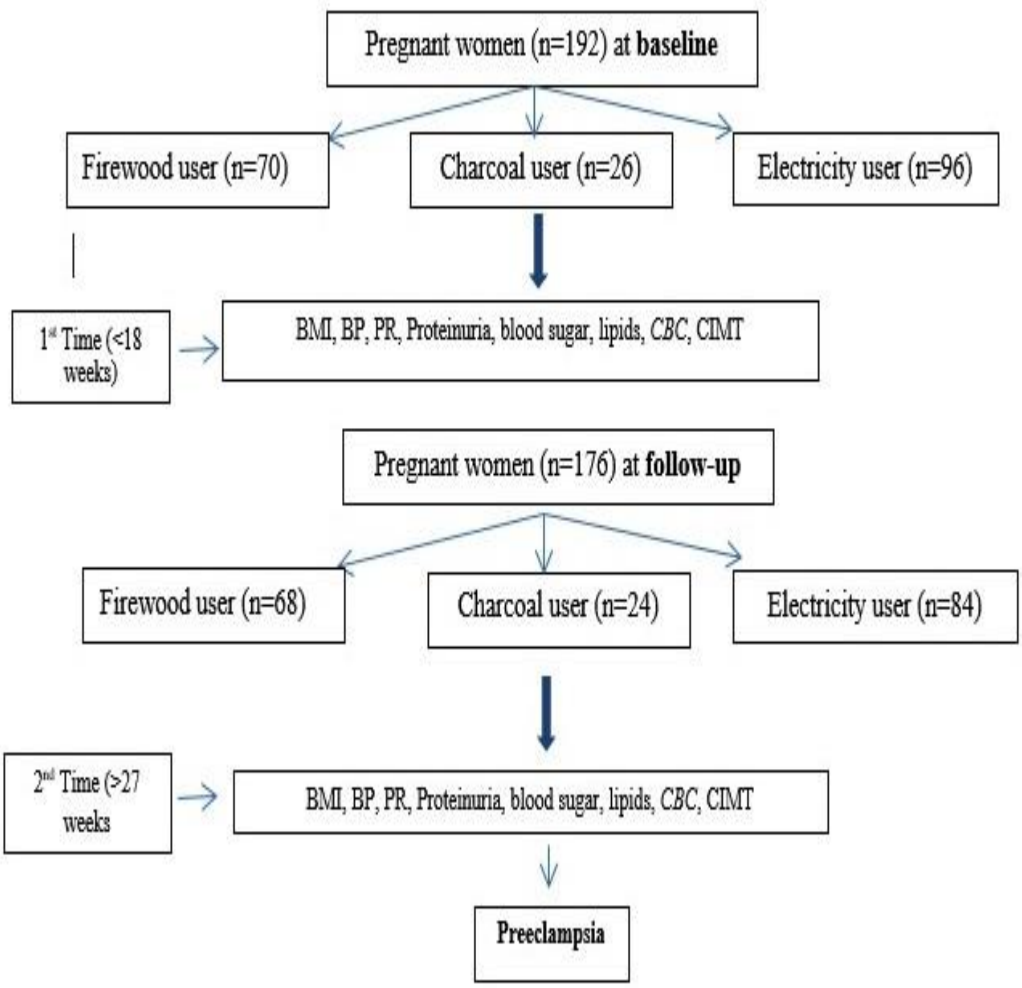


Figure 17 Data collection flow chart

Data collection was conducted during the study period of January 2019 to June 2020 including the following phases-

Preparation phase: Beginning from approvals of authorities concerned and readiness of instruments, training (orientation) of four research assistants with graduate education level was done to run the study smoothly and to minimize the effect of interviewer. These four trained research assistants conducted data collection, go field-visits to residences for ascertainment of cooking fuels use.

Monitoring and follow-up phase: In order to perform clinical assessments at the scheduled time points, participants were maintained contacted for monitoring and follow-up purposes through multiple common channels in Myanmar - phone contacts or message contacts or messenger contacts, all participants were notified in due time for follow-up visits mediated by midwifes. Data were collected accordingly.

3.8.1 Field visits

By using validated semi-structured questionnaires, data on sociodemographic characteristics, residential characteristics and cooking fuel use characteristics were collected in 3 parts questionnaire at recruitment of participants for baseline data after consent obtained. All were performed by 4 trained research assistants in face-to-face manner. Weight and height measurement, hemodynamic measurement, urine sample collection and blood collection were done at altogether with the help of health staff (midwifes) as well.

3.8.2 Carotid intima-media thickness (CIMT) values

The CIMT was measured on both RCCA and LCCA in centimeters (cm). Offline images captured with linear probes (7.5 MHz) of high resolution of a portable ultrasound (SAMSUNG MEDISON CO., LTD, Korea) were taken by a radiologist blinded to exposure status of participants at recruitment and follow-up visits. Acknowledging possible changes of CIMT during cardiac cycle (Polak et al., 2012) and substantial dependency on technician skills in its imaging (Darabian et al., 2013), standard protocol (Bauer et al., 2012; Simova, 2015; Stein et al., 2008) was followed by the radiologist at all times. Procedurally, participants were comfortably and properly positioned in supine position with their heads rotated 45 degree to the right then to the left in alternative turns for clear visualization of the CIMT of both arteries (Darabian et al., 2013). The far-wall thickness of both arteries viewed at a 10-mm distance proximal to the bulk of common carotid arteries (Simova, 2015) were taken from anterior, lateral and posterior views because of its true thickness on histological validation. Furthermore, as reported by Naqvi and Lee, this measurement has good inter- and intra-observer reproducibility with ICC>0.90 if performed by satisfactorily trained technicians maintaining strict protocol adherence (Naqvi & Lee, 2014). The thickness of the layer between medial-adventitial and intimal-luminal interfaces that was shown in color-coded double line density were the CIMT values. Finally, CIMT values of each participant were calculated. The combined mean CIMT, mean CIMT of the LCCA, mean CIMT of the RCCA and overall means of CIMT were reported in millimeters (mm) and analysis was preformed accordingly (Painschab et al., 2013).

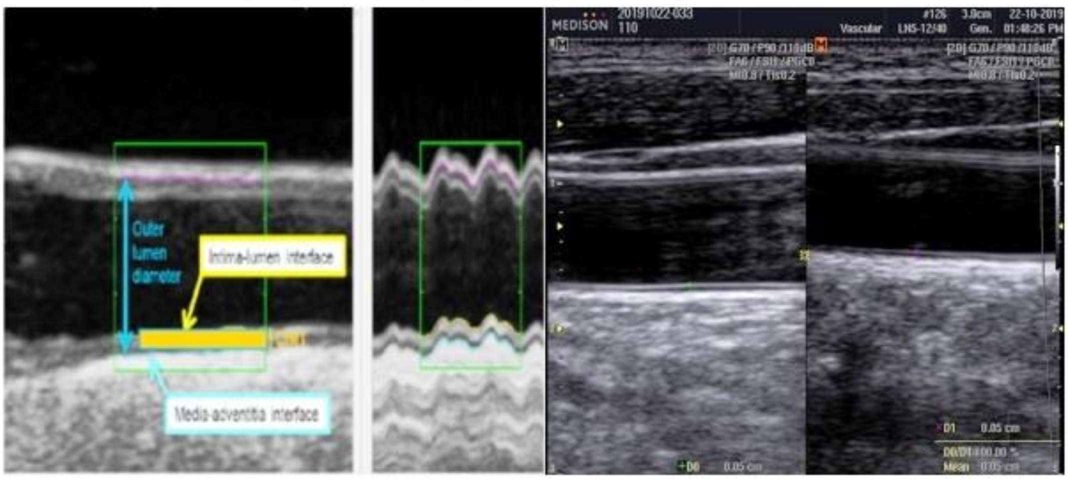


Figure 18 Captured part of carotid intima-media thickness (CIMT)

3.8.3 Blood and urine results

Blood of all participants without overnight fasting was collected at baseline and follow-up visits for CBC analysis in line with standard protocol because thrombocytopenia platelet count less than100,000/microliter is informative about preeclampsia (American College of Obstetricians and Gynecologists, 2013). Participants were well informed and explained about procedures, not the outcome of interests which were discussed with attending physicians if necessary. Following universal precaution at all time during samples collection was ensured. Collected blood of 5 milliliters in collection tubes was sent to Department of laboratory at Zabuthiri Specialist Hospital, and samples were stored at recommended temperature if immediate analysis was impossible and, all analysis was done on Cobas c311 analyzer (Roche, HITACHI, Germany). Results were recorded, reported and utilized for study purposes and for attending physician's reference if required. Milligram per 24 hour (mg/24h) of protein content in urine sample of participants was reported in the reporting format.

3.8.4 Blood pressure, heart rate, body weight and height

All participants were allowed 15-minutes complete rest before taking blood pressure by health staff and research assistants. Systolic and diastolic blood pressures of each participant at baseline and follow-up visits were taken thrice from the right arm at sitting position with proper deflation and inflation, and then 3-times measurements were averaged to calculate mean blood pressure. The same procedure applies to heart rate. Blood pressure was reported in millimeters of mercury (mmHg). Body weight and height were taken as per the protocol, and calculated body mass index (BMI) was reported. The clinical assessments were reported in the format as shown in Table 5.

Table 5 Report form for clinical assessments at time points

Variables	1st time (<18 weeks gestation)			2nd time (> 27 weeks onwards)			Average Total
	1st time	2nd time	3rd time	1st time	2nd time	3rd time	
HR per min							
BP (mmHg)							
Height (m)							
Weight (kg)							
Urinary protein (mg/24h)							
Random blood sugar (mg/dl)							
CBC values							
CIMT (mm)							

3.9 Statistical analysis

The main outcomes of the cohort were the CIMT levels and preeclampsia in relation to types of cooking fuels use. Continuous variables were presented in mean±standard deviation and, median and interquartile range (IQR) depending on data distributions. Categorical variables were reported in number and percentage.

One-way analysis of variances (ANOVA) was applied for comparing CIMT differences among 3 fuels use groups. If overall significance was detected, post-hoc test was follwed to report which specific groups differ in the cohort. Significant level was set 0.05. Paired t-test was used for comparing CIMT of each group baseline and at the follow up. Chi-square test or Fisher's exact test was applied as appropriate for analyzing categorical data.

Dummy variables coding was created for firewood use and charcoal use with electricity use as a reference. For firewood use, firewood use was coded as ‘1’ while charcoal and electricity use were coded as ‘0’. Similarly for charcoal use, charcoal use was coded as ‘1’ and ‘0’ for firewood and electricity use. Multivariable linear regression was applied for examining association between type of cooking fuels use and CIMT by adjusting for pregnancy related factors (parity, gestational weeks, BMI) and factors associated with CIMT (age, diastolic pressure, heart rate, incense stick burning (Yes/No), random glucose, LDL). Covariates in the model were selected and included according to evidences in previous literatures (Kammoolkon et al., 2018; B. Liu et al., 2017; Ren, Cai, Liang, Li, & Sun, 2015). Multiple logistic regression was for examining association between CIMT and preeclampsia. Covariates in the model were selected and included (Kammoolkon et al., 2018; B. Liu et al., 2017; Ren et al., 2015).

Table 6 Main variables and statistics

Objectives	Main variables	Statistics
Objective 1: To find association between type of cooking fuels use and maternal CIMT at early trimester (baseline)	-Types of cooking fuels use -CIMT levels	-Multivariable Linear Regression
Objective 2: To examine changes of carotid intima-media thickness from the baseline to the follow-up among self-cooking pregnant women in Nay Pyi Taw area, Myanmar	CIMT levels within each group	-Paired t-test
Objective 3: To find association between type of cooking fuels use and increase of maternal CIMT at third trimester (follow-up)	-Types of cooking fuels use -CIMT levels at follow-up	-Multivariable Linear Regression
Objective 4: To find association between type cooking fuels use and preeclampsia among self-cooking pregnant women in Nay Pyi Taw area, Myanmar	-Types of cooking fuels use -Preeclampsia	-Multiple Logistic Regression
Objective 5: To find an association between maternal CIMT in early and third trimesters and preeclampsia among self-cooking pregnant women in Nay Pyi Taw area, Myanmar.	-CIMT levels combined in early and third trimesters -Preeclampsia	-Multiple Logistic Regression -Multiple Logistic Regression

Variables	**Statistics**
BMI (kg/m²)	Descriptive statistics -Frequency (%) for categorical data -Chi-square test or Fisher's exact test for categorical data -Mean (SD) for continuous data -One-way ANOVA for difference among 3 groups
HR (per minute)	
BP mmHg	
Urinary protein (mg/day)	
Random blood sugar level (g/dl)	
CBC values	
CIMT (mm)	

3.10 Ethical considerations

Ethical approval was taken from the Ethical Committee, Chulalongkorn University, Thailand (COA; No.133/2019) and the Ethical Review Board, University of Public Health, Yangon, Myanmar (UPH-IRB; 2019/Research/34). In case of complications of pregnancy e.g. miscarriage, preeclampsia, eclampsia and/or severe proteinuria, guidelines in 'a manual for basic health staff' were followed (MOH, 2016), and such condition were prepared to report to respective ethical boards. The study time was until 36 weeks of pregnancy. Overall time for interview, weight and height measurement, hemodynamic measurement, urine sample and blood sample collection were 15 minutes, and ultrasound examination for CIMT and abdomen were 15 minutes maximum. Cash in the amount of 50 baht was given to participants as compensations. All information were explained in the participant information sheet.

CHAPTER 4

RESULTS

A community-based cohort study, to investigate the effect of cooking fuels use on maternal carotid intima-media thickness and preeclampsia, was conducted in Nay Pyi Taw Area, Myanmar. Participants were women meeting all criteria of pregnancy under 18 weeks gestation, age 18-45 years, using fuels (firewood, charcoal, coal, gas, LPG, electricity) at least 6 months, living in Nay Pyi Taw Area. From 211 screened participants from 15 selected RHCs in Nay Pyi Taw, 192 eligible pregnant women were recruited by the purposive sampling method. Nineteen participants (n=19) were excluded for ultrasound gestational weeks that was larger than 18 weeks. Based on fuels use, participants were stratified into firewood, charcoal and electricity users. There was no coal, gas and LPG user. Socio-demographic information, residential characteristics, fuels use data were collected with validated questionnaires by four trained research assistants in face-to-face interviews. Fuels use status of participant was assured with inspection checklists in field inspections by research assistants. Anthropometric measurements for body weight and height were done. Hemodynamic measurements for (systolic and diastolic) blood pressure were taken. Clinical assessments on blood for complete blood count (CBC) and non-fasting lipid profiles; and on urine for proteinuria were performed. Carotid intima media thickness (CIMT) was assessed with a portable ultrasound machine. In the follow-up data collection, 176 out of 192 participants completed the study. Sixteen participants (8%) were lost to follow-up who were (delivery=4, contact lost=6, return to native village=3 and abortion=3) respectively. Anthropometric, hemodynamic and clinical assessments were performed as was in the baseline procedure. The results of the study were presented as follows;

4.1 Baseline characteristics

4.1.1 General characteristics

4.1.1.1 Sociodemographic, residential and cooking fuels use information at baseline

Basic characteristics of 192 participants included at baseline of this study are summarized in Table 7. Of 192 pregnant women included, solid fuels (SF) user (n=96; 50%) group was subdivided into firewood user (n=70; 36.46%) and charcoal user (n=26; 13.54%). Non-solid fuels (NSF) user (n=96; 50%) group had electricity user (n=96; 50%).

Regarding with sociodemographic characteristic, mean age (±SD; years) of pregnant women were 26.94±6.35 overall. Although firewood group (27.57±6.37) and charcoal group (27.92±7.80) had older age than electricity group (26.22±5.87), it showed no significance difference between the groups (P=0.280). Mean gestational weeks (±SD; weeks) on ultrasound examination was (14.38±3.32), and firewood user had the greatest gestational weeks (15.26±2.58) than charcoal user (14.42±3.42) and electricity user (13.72±3.62) which was significantly different (P=0.012). First time pregnancy (parity=0) was 117 (60.9%) of all women with significant difference (P=0.019) among fuels use groups. Most participant were house wives 107 (55.7%) who included in the electricity users with the highest number 52 (54.2%) and it achieved no significant difference (P=0.798). Most participants finished primary level education 104 (54.2%); and earned average income (kyats) above 200,001 per month 101 (52.6%), which were however significantly different (P<0.05) among fuels user groups.

With respect to residential characteristics, 148 (77.1%) of households had kitchens attached home which was higher in electricity user 70 (72.9%). Most women 140 (72.9%) reported that they burned incense sticks inside home and it was higher in electricity user 64 (66.7%). However, more participants 150 (78.1%) did not do mosquito coils burning inside home which was also higher in electricity users 70 (72.9%). Participants with no smokers at home was 104 (54.2%) and such condition was higher in electricity users 50 (52.1%). All of these three residential characteristics were not statistically different (P>0.05).

In fuels use characteristics, all participants had been using respective fuels over 10 years. Mean firewood use duration (±SD; years) in firewood user (11.71±7.04) was higher than charcoal user (9.35±7.44) and electricity user (10.67±3.78) (P=0.178). Mean cooking frequency per week (±SD; weeks) was (12.04±3.45) in charcoal user when firewood users and electricity user did cooking (11.97±4.20) and (10.29±5.16) per week (P=0.041). All participants spent over 60 minutes (1-hour) for each cooking with mean duration of (±SD; minutes) (67.63±38.58). Firewood users cooked longer (71.93±36.94) than charcoal user (62.31±35.17) and electricity user (65.94±40.65) which was not significantly different (P=0.463).

Table 7 Basic sociodemographic, residential and fuels use characteristics of pregnant women using cooking fuels (n=192)

Variables	Total (n=192)	Solid fuel user (n=96)		Non-solid fuel user (n=96)	P value
		Firewood (n=70)	Charcoal (n=26)	Electricity (n=96)	
Socio-demographic characteristics					
Age years (mean ±SD)	26.94±6.35	27.57±6.37	27.92±7.80	26.22 ±5.87	0.280[a]
Gestational weeks by USG(mean ±SD)	14.38±3.32	15.26±2.58	14.42±3.42	13.72 ±3.62	0.012[a]
Parity, n (%)					0.019[b]
Parity=0	117 (60.9)	36 (51.4)	13 (50.0)	68 (70.8)	
Parity≥ 1	75 (39.1)	34 (48.6)	13 (50.0)	28 (29.2)	
Education level, n (%)					<0.001[b]
> Primary	104 (54.2)	25 (35.7)	15 (57.7)	64 (66.7)	
≤ Primary	88 (45.8)	45 (64.3)	11 (42.3)	32 (33.3)	
Occupation, n (%)					0.798[b]
House-wife	107 (55.7)	39 (55.7)	16 (61.5)	52 (54.2)	
Others	85 (44.3)	31 (44.3)	10 (38.5)	44 (45.8)	
Monthly family income (Kyats), n (%)					0.021[b]
> 200,001	91 (47.4))	24 (34.3)	15 (57.7)	52 (54.2)	
≤ 200,000	101 (52.6)	46 (65.7)	11 (42.3)	44 (45.8)	
Residential characteristics					
Kitchen Type, n (%)					0.115[c]
Home attached	148 (77.1)	54 (77.1)	24 (92.3)	70 (72.9)	
Separated	44 (22.9)	16 (22.9)	2 (7.7)	26 (27.1)	
Daily incense sticks burning, n (%)					0.061[b]
Yes	140 (72.9)	58 (82.9)	18 (69.2)	64 (66.7)	
No	52 (27.1)	12 (17.1)	8 (30.8)	32 (33.3)	

Daily mosquito coils burning, n (%)					0.142[b]
Yes	42 (21.9)	10 (14.3)	6 (23.1)	26 (27.1)	
No	150 (78.1)	60 (85.7)	20 (76.9)	70 (72.9)	
Smokers at home, n (%)					0.833[b]
Yes	88 (45.8)	31 (44.3)	11 (42.3)	46 (47.9)	
No	104 (54.2)	39 (55.7)	15 (57.7)	50 (52.1)	
Fuels use					
Cooking frequency at household per week	11.14±4.68	11.97±4.20	12.04±3.45	10.29±5.16	0.041[a]
Cooking duration per time (min) (mean ±SD)	67.63±38.58	71.93±36.94	62.31±35.17	65.94±40.65	0.463[a]
Fuels use duration years (mean ±SD)	10.87± 5.73	11.71±7.04	9.35 ±7.44	10.67± 3.78	0.178[a]

[a] = One-way analysis of variance; [b] = Chi-square test; [c] = Fisher's exact test

4.1.1.2 Characteristics of clinical parameters assessed at baseline

Table 8 describes characteristics of clinical assessments by type of cooking fuels use. Mean Body Mass Index (±SD; kg/m^2) was (22.62±4.81). BMI was higher in charcoal user (24.22±7.29) than firewood (22.61±4.24) and electricity (22.18±4.32) users where it was not statistically different (P=0.163). Mean heart rate per minute (±SD; rate) was (90.73 ±11.91) and charcoal users had highest heart rate (96.31±12.33) with significant difference among the groups (P=0.019). Mean systolic blood pressure (SBP) (±SD; mmHg) was (105.55±11.73) without significantly difference (P=0.129) among fuels users of firewood (103.91±11.35), charcoal (103.62±16.07) and electricity (107.26±10.45). Similarly, mean diastolic blood pressure (DBP) was (67.82±7.99) and they did not differ among fuels user groups (P=0.110). Moreover, means of other blood chemistries such as random blood sugar (89.09±17.09), total cholesterol (190.95±33.64, HDL (55.39±14.69), LDL (108.42±27.36), triglycerides (136.24±66.87) and cholesterol and HDL ratio (3.91±2.67) were not significantly different among groups (P>0.05).

Table 8 Basic clinical characteristics of pregnant women by cooking fuels (n=192)

Characteristics of clinical assessments	Total (n=192)	Solid fuel user (n=96)		Non-solid fuel user (n=96)	P value
		Firewood (n=70)	Charcoal (n=26)	Electricity (n=96)	
Body Mass Index (kg/m²) (mean ±SD)	22.62±4.81	22.61±4.24	24.22±7.29	22.18±4.32	0.163[a]
Heart rate per minute (mean ±SD)	90.73±11.91	88.67±10.85	96.31±12.33	90.72±12.16	0.019[a]
BP (mmHg) (mean ±SD)					
Systolic Blood Pressure	105.55±11.73	103.91±11.35	103.62±16.07	107.26±10.45	0.129[a]
Diastolic Blood Pressure	67.82±7.99	66.49±7.61	70.19±9.47	68.16±7.74	0.110[a]
Random blood sugar (60-180mg/dl) (mean ±SD)	89.09±17.09	88.53±17.66	89.94 ±15.22	89.28 ±17.29	0.928[a]
Random blood cholesterol (mg/dl) (mean ±SD)					
Total cholesterol (up to 220)	190.95±33.64	187.79±29.89	191.82±33.09	193.02±36.42	0.610[a]
HDL cholesterol (35-45)	55.39±14.69	57.29±15.39	50.81±11.86	55.24±14.72	0.156[a]
LDL cholesterol (<150)	108.42±27.36	103.31±24.47	111.16±28.12	111.41±28.84	0.146[a]
Triglycerides cholesterol (<200)	136.24±66.87	133.77±66.94	151.24±80.75	133.98±62.84	0.472[a]
Cholesterol and HDL ratio	3.91±2.67	4.15±4.17	3.95±1.12	3.73±1.13	0.602[a]

[a] = One-way analysis of variance; [b] = Chi-square test; [c] = Fisher's Exact test

4.1.1.3 Carotid intima-media thickness (CIMT) characteristics at baseline

Comparing combined mean CIMT of CCA, firewood users had the highest levels of combined mean CIMT (0.424±0.051mm). Combined mean CIMT (0.421±0.043mm) in charcoal users was higher than electricity users (0.394±0.04mm). Statistically significant difference in the mean values among three groups were observed (P<0.001). For mean CIMT of LCCA, the thickness in firewood users (0.415±0.048mm) was higher than that of charcoal users (0.408±0.042mm) and electricity users (0.389±0.046mm), which were significantly different (P=0.001). Similar finding was found in mean CIMT of RCCA where CIMT level in firewood user (0.432±0.064mm) and in charcoal users (0.435±0.054mm) were greater than levels in electricity users (0.400±0.057mm). The differences were statistically significant (P=0.001) (Table 9).

Table 9 CIMT of Common Carotid Arteries of pregnant women by fuels use (n=192)

CIMT (mm) (mean ±SD)	Total (n=192)	Solid Fuels (n=96)		Non-solid fuels	P value
		Firewood (n=70)	Charcoal (n=26)	Electricity (n=96)	
Combined mean CIMT	0.409 ±0.049	0.424 ±0.051	0.421 ±0.043	0.394 ±0.046	< 0.001[a]
Mean CIMT of the LCCA	0.400 ±0.048	0.415 ±0.048	0.408 ±0.042	0.389 ±0.046	0.001[a]
Mean CIMT of the RCCA	0.416 ±0.061	0.432 ±0.064	0.435 ±0.054	0.400 ±0.057	0.001[a]

[a] = One-way analysis of variance

Differences among fuels user groups are shown in Table 10. Bonferroni correction was used to compare difference of respective thickness of carotid arteries. In combined mean CIMT (both means CIMT of LCCA and RCCA combined), CIMT was found significantly difference in which CIMT of electricity users were different to these of firewood users and charcoal users ($p<0.05$). However, difference was not significant between firewood users and charcoal users ($P>0.05$). In mean CIMT of LCCA, significant difference was found between electricity users and firewood users only ($P<0.05$). In mean CIMT of RCCA, CIMT difference was significant between users of electricity and firewood ($P=0.002$); electricity and charcoal ($P=0.028$), but significant difference was not achieved between firewood users and charcoal users ($P=0.999$).

Table 10 Pairwise comparison of CIMT difference by fuels use among pregnant women at baseline (n=192)

CIMT	Fuels use (I)	Fuels use (J)	Mean difference (I-J)	SE	P value	95% CI of mean difference	
						Upper	Lower
Combined mean CIMT	FW	CC	.00242	.01098	0.999	-.0241	.0289
	FW	E	.02930*	.00752	0.000	.0111	.0475
	CC	E	.02688*	.01057	0.035	.0013	.0524
Mean CIMT of the LCCA	FW	CC	.00755	.01071	0.999	-.0183	.0334
	FW	E	.02670*	.00733	0.001	.0090	.0444
	CC	E	.01915	.01031	0.194	-.0057	.0440
Mean CIMT of the RCCA	FW	E	.03190*	.00935	0.002	.0093	.0545
	CC	FW	.00271	.01366	0.999	-.0303	.0357
	CC	E	.03462*	.01315	0.028	.0029	.0664

Note: FW = firewood, CC=Charcoal, E= electricity

Bonferroni correction; *The mean difference is significant at the 0.05 level.

4.1.1.4 Association of fuels use type and carotid intima-media thickness (CIMT) at baseline

Table 11 is multivariate regression analysis which shows the analysis for association between fuels use type and CIMT. Firewood use had significant associations with increase of all CIMT analyzed. After adjusting for pregnancy related factors and factors related with CIMT, mean CIMT of RCCA consistently showed significant association with firewood and charcoal use in all models. More specifically, charcoal use was independently associated with 0.033 mm increase in mean CIMT of the RCCA while firewood use was associated with 0.026 mm increase in mean CIMT of the RCCA, which were statistically significant ($p<0.05$) (Fig 19).

Table 11 Multivariable linear regression model for combined mean CIMT, mean CIMT of the LCCA and mean CIMT of the RCCA

CIMT (mm)	Electricity		Firewood		Charcoal	
	Coefficient	95% CI	Coefficient	95% CI	Coefficient	95% CI
Unadjusted Model						
Combined mean CIMT	Ref. category		0.029	0.014, 0.044**	0.027	0.006, 0.048*
Mean CIMT of the LCCA	Ref. category		0.027	0.012, 0.041**	0.019	- 0.001, 0.039
Mean CIMT of the RCCA	Ref. category		0.032	0.013, 0.050*	0.035	0.009, 0.061*
Adjusted Model [a]						
Combined mean CIMT	Ref. category		0.025	0.010, 0.040*	0.021	0.001, 0.042*
Mean CIMT of the LCCA	Ref. category		0.020	0.005, 0.053*	0.013	- 0.007, 0.033
Mean CIMT of the RCCA	Ref. category		0.029	0.010, 0.048*	0.030	0.004, 0.056*
Adjusted Model [b]						
Combined mean CIMT	Ref. category		0.027	0.012, 0.042**	0.025	0.004, 0.045**
Mean CIMT of the LCCA	Ref. category		0.024	0.010, 0.039*	0.017	- 0.003, 0.037
Mean CIMT of the RCCA	Ref. category		0.029	0.010, 0.048*	0.033	0.007, 0.059*
Adjusted Model [c]						
Combined mean CIMT	Ref. category		0.025	0.010,0.041*	0.023	0.002, 0.044*
Mean CIMT of the LCCA	Ref. category		0.022	0.006, 0.036*	0.014	- 0.006, 0.034
Mean CIMT of the RCCA	Ref. category		0.029	0.010, 0.049*	0.033	0.006, 0.058*

* P < .05; ** P < .001, CI confidence interval
[a]= Adjusted for pregnancy related factors (parity, gestational weeks, BMI)
[b]= Adjusted for factors associated with CIMT: age, diastolic blood pressure, heart rate, daily incense sticks burning (yes/no), random blood glucose, low density lipoprotein cholesterol
[c]= Adjusted for factors in Model [a] and Model [b]

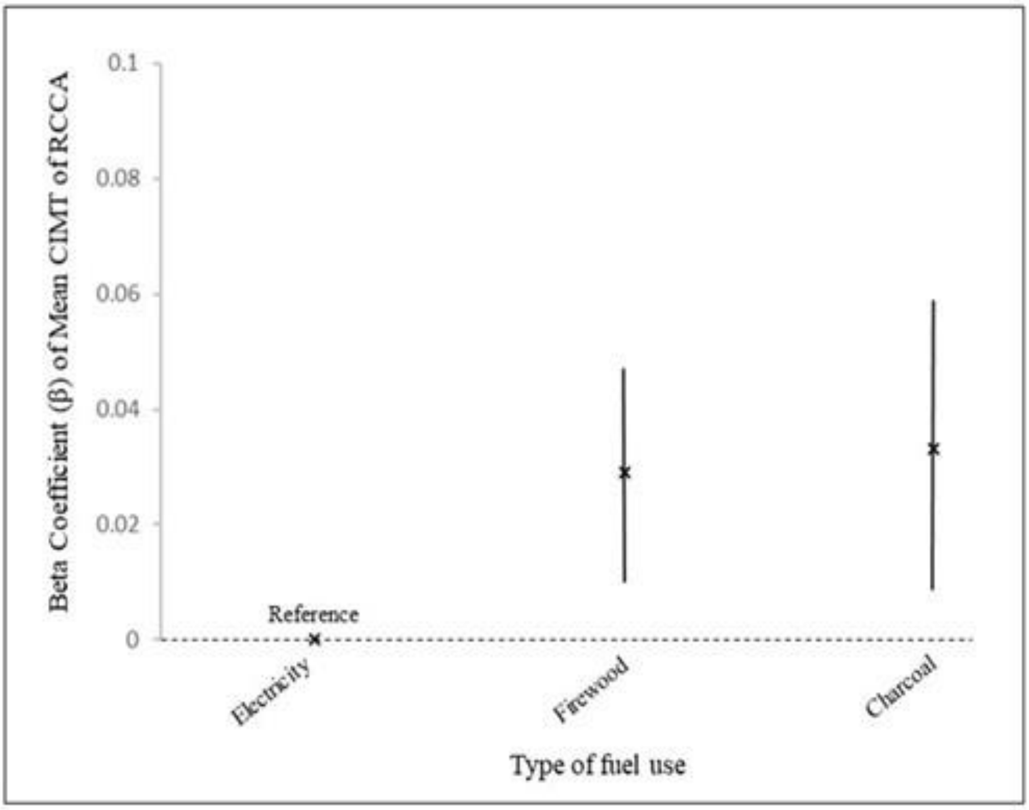


Figure 19 Beta coefficient of mean CIMT of the RCCA by type of fuels use

4.2 Follow–up characteristics

4.2.1 General characteristics

4.2.1.1 Sociodemographic, residential and cooking fuels use information at follow-up

At follow-up, 176 out of 192 participants at baseline completed follow-up data collection. Characteristics of participants at follow-up were presented in (Table 12). Most characteristics among fuels use groups did not differ (P>0.05) except for education level, family income, kitchen type and cooking frequency P<0.05. Sixteen participants (8%) were lost to follow-up who were (delivery=4, contact lost=6, return to native village=3 and abortion=3) respectively. No difference in characteristics of lost to follow-up was found and it was presented in (Appendix D).

Table 12 Sociodemographic, residential and cooking fuels use information at follow-up (n=176)

Variables	Total (n=176)	Solid fuel user (n=92)		Non-solid fuel user (n=84)	P value
		Firewood (n=68)	Charcoal (n=24)	Electricity (n=84)	
Sociodemographic characteristics					
Age years (mean ±SD)	26.99±6.29	27.69±6.41	27.71±7.48	26.23±5.81	0.304[a]
Gestational weeks by USG (mean ±SD)	32.81±3.41	33.03±3.42	33.49±3.52	32.45±3.36	0.332[a]
Gestational weeks by USG, n (%)					0.219
≤ 34 weeks	106 (60.2)	38 (55.9)	12 (50.0)	56 (66.7)	
> 34 weeks	70 (39.8)	30 (44.1)	12 (50.0)	28 (33.3)	
Parity, n (%)					0.056[b]
Parity=0	103 (58.5)	34 (50.0)	12 (50.0)	57 (67.9)	
Parity ≥ 1	73 (41.5)	34 (50.0)	12 (50.0)	27 (32.1)	
Education level, n (%)					0.001[b]
> Primary	93 (52.8)	24 (35.3)	13 (54.2)	56 (66.7)	
≤ Primary	83 (47.2)	44 (64.7)	11 (45.8)	29 (33.3)	
Occupation, n (%)					0.552[b]
House-wife	97 (55.1)	39 (57.4)	15 (62.5)	43 (51.2)	
Others	79 (44.9)	29 (42.6)	9 (37.5)	41 (48.8)	
Monthly family income (Kyats), n (%)					0.004[b]
> 200,001	85 (48.3)	22 (32.4)	14 (58.3)	49 (58.3)	
≤ 200,000	91 (51.7)	46 (67.6)	10 (41.7)	35 (41.7)	
Residential characteristics					
Kitchen Type (n, %)					0.038[c]
Home attached	137 (77.1)	53 (77.9)	23 (95.8)	61 (72.6)	
Separated	39 (22.9)	15 (22.1)	1 (4.2)	23 (27.4)	
Daily incense sticks burning inside home, n (%)					0.202[b]
Yes	132 (75.0)	56 (82.4)	17 (70.8)	59 (70.2)	
No	44 (25.0)	12 (17.6)	7 (29.2)	25 (29.8)	
Daily mosquito coils burning, inside home, n (%)					0.099[b]
Yes	38 (21.6)	9 (12.2)	6 (25.0)	23 (27.4)	
No	138 (78.4)	59 (86.8)	18 (75.0)	61 (72.6)	
Smokers at home, n (%)					0.816[b]
Yes	82 (46.6)	31 (45.6)	10 (41.7)	41 (48.8)	
No	94 (53.4)	37 (54.4)	14 (58.3)	43 (51.2)	
Fuels use (mean ±SD)					
Cooking frequency at household per week (times)	11.27±4.59	12.28 ±3.84	12.17±3.41	10.21±5.21	0.012[a]
Cooking duration per time (min)	67.73±38.65	72.28±37.43	62.50±36.65	65.54±40.20	0.440[a]
Fuels use duration years	10.80±5.78	11.72±7.12	9.09±7.37	10.55± 3.61	0.137[a]

[a] = One-way analysis of variance [b] = Chi-square test [c] = Fisher's exact test

4.2.1.2 Characteristics of anthropometric, hemodynamic and blood lipid parameters of participants at follow-up

Clinical assessments among firewood, charcoal and electricity fuels users were analyzed. Mean BMI (±SD) is the highest in charcoal user 27.32±7.57 and, it was 25.11±5.19 and 25.39±4.56 in firewood and electricity users. Mean diastolic blood pressure (±SD) were

67.44±8.46, 69.74±8.99 and 68.62±7.87 mmHg. Mean urine protein (±SD) were 53.7±99.0, 59.4±65.8 and 36.7±34.8mg/24H. Mean LDL (±SD) were 135.63±39.04, 133.25±37.47 and 134.98±36.21mg/dl. All characteristics of clinical assessments were not different significantly among three groups (Table 13).

Table 13 Clinical characteristics of pregnant women by cooking fuels use at follow-up (n=176)

Characteristics of clinical assessments	Total (n=176)	Solid fuel user (n=92)		Non-solid fuel user (n=84)	P value
		Firewood (n=68)	Charcoal (n=24)	Electricity (n=84)	
Clinical assessments					
Body Mass Index (kg/m^2) (mean ±SD)	25.70±5.30	25.11±5.19	27.32±7.57	25.39±4.56	0.272[a]
Heart rate per minute (mean ±SD)	95.29±12.67	95.75±15.07	96.33±14.06	94.62±9.97	0.784[a]
BP (mmHg) (mean ±SD)					
Systolic Blood Pressure	108.73±10.07	108.49±10.34	111.94±11.88	107.99±9.22	0.231[a]
Diastolic Blood Pressure	68.32±8.25	67.44±8.46	69.74±8.99	68.62±7.87	0.453[a]
Urine protein (mg/24h), (mean ±SD)	46.4±70.6	53.7±99.0	59.4±65.8	36.7±34.8	0.212
Random blood sugar (60-180mg/dl) (mean ±SD)	87.85±16.68	85.33±14.67	84.46±16.58	90.86±17.86	0.071[a]
Random blood cholesterol (mg/dl) (mean ±SD)					
Total cholesterol (up to 220)	234.09±134.02	222.33±41.80	223.15±45.72	246.74±188.61	0.491[a]
HDL cholesterol (35-45)	45.46±9.87	44.61±9.19	48.39±14.01	45.31±8.93	0.270[a]
LDL cholesterol (<150)	134.99±37.29	135.63±39.04	133.25±37.47	134.98±36.21	0.965[a]
Triglycerides cholesterol (<200)	224.87±94.86	217.37±91.54	226.51±92.37	230.48±98.07	0.698[a]
Cholesterol and HDL ratio	5.06±1.03	5.12±1.13	4.92±1.04	5.06±0.94	0.719[a]

[a] = One-way analysis of variance; [b] = Chi-square test; [c] = Fisher's exact test

4.2.1.3 Characteristics of Complete Blood Count (CBC) parameters of participants at follow-up

Regarding with complete blood count (CBC) values, over half of participants105 (59.7%) had hemoglobin below normal level (11-18g/dl). Participants with hemoglobin below normal range were 46 (67.6%) in firewood, 14 (53.7%) in charcoal and 45 (53.6%) in electricity users respectively. All of CBC parameters were not different significantly among fuels user groups P>0.05 (Table 14).

Table 14 Characteristics of Complete Blood Count (CBC) parameters of participants at follow-up (n=176)

Complete Blood Count (CBC) values	Total (n=176)	Solid fuels user (n=92)		Non-solid fuels user (n=84)	P value
		Firewood (n=68)	Charcoal (n=24)	Electricity (n=84)	
Hemoglobin level (g/dl), n (%)					0.221 [a]
Below normal (≤10.9 g/dl)	105 (59.7)	46 (67.6))	14 (58.3)	45 (53.6)	
Normal (11-18 g/dl)	71 (40.3)	22 (32.4)	10 (41.7)	39 (46.4)	
White Blood Cell (4.0-11.0×10^^{9} /L)	10.27±2.30	9.84±1.86	10.57±2.72	10.53±2.46	0.148 [b]
Lymphocytes (1.0-5.0×10^^{9} /L)	2.05±0.50	1.94±0.43	2.09±0.53	2.12±0.53	0.070 [b]
Mid (0.2-1.6×10^^{9} /L)	0.88±0.31	0.88±0.25	0.89±0.29	0.87±0.36	0.962 [b]
Granulocytes (2.0-7.0×10^^{9} /L)	7.32±1.77	7.01±1.40	7.45±2.21	7.52±1.92	0.192 [b]
Lymphocyte % (20.0-45.0)	20.14±3.40	19.71±2.91	20.29±3.18	20.44±3.81	0.412 [b]
Mid % (2.0-16.0)	8.71±2.17	9.12±1.83	8.77±1.84	8.36±2.45	0.098 [b]
Granulocyte % (40.0-75.0)	71.14±4.32	71.15±3.79	70.91±4.25	71.19±4.79	0.963 [b]
Red Blood Cell (4.0-6.2×10^^{12} /L)	4.25±0.57	4.21±0.49	4.35±0.45	4.26±0.66	0.226 [b]
HCT (35.0-54.0)	33.46±3.99	32.81±3.30	33.85±3.25	33.88±4.62	0.548 [b]
MCV (fL) (76.0-100 fL)	79.25±7.42	78.57±7.94	78.25±7.06	80.09±7.08	0.228 [b]
MCH (pg) (26.0-34.0)	25.23±2.75	24.97±2.94	24.84±2.34	25.56±2.69	0.359 [b]
MCHC (g/dl) (30.0-35.0)	31.87±0.87	31.78±0.89	31.87±0.78	31.94±0.89	0.313 [b]
RDW-CV % (11.0-16.0)	14.63±1.44	14.60±1.70	14.62±0.90	14.66±1.34	0.568 [b]
RDW-SD (35.0-56.0 fL)	42.07±4.17	41.52±3.85	41.62±4.73	42.65±4.22	0.966 [b]
Platelets (150-400×10^^{9} /L)	279.68±69.56	283.79±73.63	287.12±61.89	274.67±68.78	0.215 [b]
MPV (6.0-15.0 fL)	8.80±0.86	8.82±0.93	8.96±1.12	8.75±0.71	0.167 [b]
PDW (9.0-14.0)	15.90±0.36	15.86±0.28	15.98±0.44	15.90±0.38	0.375 [b]
PCT % (0.108-0.282)	0.23±0.05	0.23±0.05	0.25±0.07	0.22±0.05	0.038 [b]

[a] = Chi-square test; [b]= One-way analysis of variance

4.2.1.4 Carotid intima-media thickness (CIMT) characteristics at follow-up

At follow-up, charcoal users had the greatest combined mean CIMT (±SD) 0.429±0.049mm, mean CIMT of the LCCA 0.427±0.064mm, mean CIMT of the RCCA 0.431±0.047mm. Combined mean CIMT, mean CIMT of the LCCA and mean CIMT of the RCCA were also higher in firewood users than those in electricity users. CIMT difference was observed among fuels use groups (p<0.05) (Table 15).

Table 15 Carotid intima-media thickness (CIMT) levels by fuels use at follow-up (n=176)

CIMT (mm) (mean ±SD)	Total (n=176)	Solid Fuels (n=92)		Non-solid fuels (84)	P value
		Firewood (n=68)	Charcoal (n=24)	Electricity (n=84)	
Combined mean CIMT	0.405±0.055	0.409±0.059	0.429±0.049	0.393±0.051	0.011 [a]
Mean CIMT of the LCCA	0.405±0.056	0.409±0.007	0.427±0.064	0.396±0.048	0.039 [a]
Mean CIMT of the RCCA	0.403±0.064	0.408±0.068	0.431±0.047	0.390±0.061	0.014 [a]

[a] = One-way analysis of variance

In pairwise comparison of CIMT by Bonforroni correction, the statistically significance difference in all CIMT was observed between charcoal and electricity users; and the difference between firewood users and charcoal users, firewood and electricity users did not reach to the significant level. Combined mean CIMT (mean difference±SE) between charcoal and electricity user was (0.03641±0.01251mm; P=0.012). Mean CIMT of the LCCA (mean difference±SE) between charcoal and electricity user was (0.03175±0.01288mm; P=0.044). Mean CIMT of the RCCA (mean difference±SE) between charcoal and electricity user was (0.04107±0.01452mm; P=0.016) (Table 16).

Table 16 Pairwise comparison of CIMT difference by fuels use among pregnant women at follow-up (n=176)

CIMT	Fuels use (I)	Fuels use (J)	Mean difference (I-J)	SE	P value	95% CI of mean difference	
						Upper	Lower
Combined mean CIMT	Firewood	Electricity	.01562	.00882	.235	-.0057	.0369
	Charcoal	Firewood	.02079	.01284	.321	-.0102	.0518
	Charcoal	Electricity	.03641*	.01251	.012	.0062	.0667
Mean CIMT of the LCCA	Firewood	Electricity	.01328	.00907	.435	-.0087	.0352
	Charcoal	Firewood	.01846	.01321	.492	-.0135	.0504
	Charcoal	Electricity	.03175*	.01288	.044	.0006	.0629
Mean CIMT of the RCCA	Firewood	Electricity	.01795	.01023	.244	-.0068	.0427
	Charcoal	Firewood	.02312	.01490	.367	-.0129	.0591
	Charcoal	Electricity	.04107*	.01452	.016	.0060	.0762

*The mean difference is significant at the 0.05 level.

Bonferroni correction; *The mean difference is significant at the 0.05 level.

4.2.1.5 Association of fuels use with CIMT at follow-up

In exploring associations between fuels use and increase of CIMT, increase of all CIMT was found to be associated with charcoal use only in all models. After adjusting for pregnancy-related factors and factors associated with CIMT, charcoal fuels use was significantly associated with increase of combined mean CIMT (β=0.036mm, 95%CI: 0.010, 0.060), mean CIMT of the LCCA (β=0.029mm, 95%CI: 0.004, 0.054), and mean CIMT of the RCCA (β=0.041mm, 95%CI: 0.012, 0.071); all of these associations were significant (P<0.05). There was no significant association between firewood use and increase of all CIMT (Table 17).

Table 17 Multivariable linear regression Model for combined mean CIMT, mean CIMT of the LCCA and mean CIMT of the RCCA at follow-up (n=176)

CIMT (mm)	Electricity		Firewood		Charcoal	
	Coefficient	95% CI	Coefficient	95% CI	Coefficient	95% CI
Unadjusted model						
Combined mean CIMT	Ref. category		0.016	- 0.002, 0.033	0.036	0.012, 0.061*
Mean CIMT of the LCCA	Ref. category		0.013	- 0.005, 0.031	0.032	0.006, 0.057*
Mean CIMT of the RCCA	Ref. category		0.018	- 0.002, 0.038	0.041	0.012, 0.070*
Adjusted model[a]						
Combined mean CIMT	Ref. category		0.013	- 0.005, 0.030	0.034	0.009, 0.059*
Mean CIMT of the LCCA	Ref. category		0.010	- 0.008, 0.028	0.028	0.002, 0.053*
Mean CIMT of the RCCA	Ref. category		0.016	- 0.005, 0.036	0.040	0.011, 0.069*
Adjusted model[b]						
Combined mean CIMT	Ref. category		0.015	- 0.002, 0.033	0.036	0.011, 0.060*
Mean CIMT of the LCCA	Ref. category		0.012	- 0.006, 0.029	0.029	0.005, 0.054*
Mean CIMT of the RCCA	Ref. category		0.019	- 0.002, 0.039	0.042	0.013, 0.071*
Fully adjusted model[c]						
Combined mean CIMT	Ref. category		0.015	- 0.003, 0.033	0.035	0.010, 0.060*
Mean CIMT of the LCCA	Ref. category		0.012	- 0.006, 0.030	0.029	0.004, 0.054*
Mean CIMT of the RCCA	Ref. category		0.018	- 0.004, 0.039	0.041	0.012, 0.071*

* P < .05 ; ** P < .001 CI: confidence interval

[a]= Adjusted for pregnancy related factors (parity, gestational weeks, BMI)

[b]= Adjusted for factors associated with CIMT: age, diastolic blood pressure, heart rate, daily incense sticks burning (yes/no), low density lipoprotein cholesterol

[c]= Adjusted for factors in Model [a] and Model [b]

4.2.1.6 Comparison of CIMT at baseline and at follow-up among fuels use groups

Comparing CIMT at baseline and at follow-up among firewood, charcoal and electricity fuels users, no increase of each CIMT was noted (P>0.05). However, reduction of CIMT in combined mean CIMT (0.42±0.05mm vs 0.41±0.06mm); and in mean CIMT of the RCCA (0.43±0.06mm vs 0.41±0.07mm) in firewood users was observed that have achieved statistically significant difference (P<0.05) (Table 18).

Table 18 Comparison of respective CIMT within groups at baseline and at follow-up by fuels use (n=176)

Fuels use	Combined mean CIMT (mm)		P value	Mean CIMT of the LCCA (mm)		P value	Mean CIMT of the RCCA (mm)		P value
	Baseline	Follow-up		Baseline	Follow-up		Baseline	Follow-up	
Firewood	0.42±0.05	0.41±0.06	0.039	0.42±0.05	0.41±0.06	0.378	0.43±0.06	0.41±0.07	0.008
Charcoal	0.43±0.04	0.43±0.05	0.758	0.41±0.04	0.43±0.06	0.257	0.44±0.05	0.43±0.05	0.347
Electricity	0.39±0.05	0.39±0.05	0.778	0.39±0.05	0.40±0.05	0.260	0.40±0.06	0.39±0.06	0.185

Paired t-test was used to calculate P value.

4.3 Fuels use and preeclampsia

4.3.1 Association between fuels use type and preeclampsia

Table 19 describes the number of pregnant women who meet the criteria for preeclampsia defined by systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg and proteinuria >300mg/24h. There was no woman who developed preeclampsia in this cohort.

Table 19 Number of pregnant women meeting criteria for preeclampsia by fuels use type (n=176)

Variables	Total n=176	Criteria for preeclampsia			Preeclampsia
		Blood pressure		Urine protein	
		SBP≥140mmHg	DBP≥90 mmHg	>300mg/24h	
Firewood	68	-	-	1	-
Charcoal	24	-	-	-	-
Electricity	84	-	1	-	-

4.3.2 Association of systolic blood pressure, diastolic blood pressure and urine protein with fuels use at follow-up

No significant association between fuels use and systolic blood pressure, diastolic blood pressure, and urine protein was observed in unadjusted model. In charcoal use, 3 mmHg increase in SBP and 1 mmHg increase in DBP were found; but, they all did not achieve statistical significance (P>0.05) (Table 20). Such changes have contributed to a little clinical importance.

Table 20 Multivariable linear regression model for systolic blood pressure, diastolic blood pressure and urine protein at follow-up (n=176)

SBP, DBP& urine protein	Electricity		Firewood		Charcoal	
	Coefficient	95% CI	Coefficient	95% CI	Coefficient	95% CI
Unadjusted model						
Systolic BP	Ref. category		0.497	- 2.239, 3.732	3.956	- 0.634, 8.546
Diastolic BP	Ref. category		-1.183	- 3.840, 1.476	1.113	- 2.659, 4.885
Urine protein (mg/24h)	Ref. category		16.94	- 5.72, 39.61	16.29	- 9.44, 54.86

* P <.05 ; CI: confidence interval

4.4 CIMT and preeclampsia

4.4.1 Association between CIMT and preeclampsia criteria

By categorizing CIMT by its mean value and criteria parameters for preeclampsia (systolic blood pressure, diastolic pressure and proteinuria), analysis by Fisher's exact test showed no association between respective CIMT and preeclampsia parameters (P>0.05) (Table 21).

Table 21 Association of CIMT with preeclampsia parameters

CIMT	SBP mmHg		P value	DBP mmHg		P value	Urine protein (mg/24h)		P value
	≥ 140	< 140		≥ 90	< 90		> 300	≤ 300	
Overall mean CIMT									
Low (≤ 0.40 mm)	-	67	0.999[a]	1	66	0.999[a]	-	67	0.999[a]
High (> 0.40 mm)	1	108		-	109		1	108	
Overall mean CIMT of the LCCA									
Low (≤ 0.40 mm)	-	73	0.999[a]	1	72	0.999[a]	-	73	0.999[a]
High (> 0.40 mm)	1	102		-	103		1	102	
Overall mean CIMT of the RCCA									
Low (≤ 0.41 mm)	-	74	0.999[a]	1	73	0.999[a]	-	74	0.999[a]
High (> 0.41 mm)	1	101		-	102		1	101	

Note: CIMT: combined all CIMT at baseline and at follow-up; [a] Fisher's exact test

4.4.2 Association of respective CIMT with systolic blood pressure, diastolic blood pressure and urine protein at follow-up

To investigate associations between CIMT and blood pressures and urine protein, these CIMT value was categorized by its mean value and blood pressures and urine protein values were categorized by their median values. Multiple logistic regression models was adjusted for age, parity, daily incense sticks burning, smokers at home; and there was no associations of respective CIMT with systolic pressure, diastolic blood pressure and urine protein which did not reach the significant level (Table 22-24).

Table 22 Multiple logistic regression models of CIMT and systolic blood pressure

CIMT group by mean	Systolic BP (mmHg) group by median value		OR	95% CI	aOR	95% CI
	High ≥ 108	Low < 108				
Overall mean CIMT						
Low (≤ 0.40 mm)			1	Reference	1	Reference
High (> 0.40 mm)			2.16	0.640, 7.286	2.26	0.650, 7.907
Overall mean CIMT of the LCCA						
Low (≤ 0.40 mm)			1	Reference	1	Reference
High (> 0.40 mm)			1.22	0.554, 2.723	1.26	0.555, 2.880
Overall mean CIMT of the RCCA						
Low (≤ 0.41 mm)			1	Reference	1	Reference
High (> 0.41 mm)			0.56	0.203, 1.588	0.55	0.193, 1.567

Adjusted for age, parity, daily incense sticks burning, smokers at home

OR= Crude Odds Ratio; aOR= Adjusted Odds Ratio; * P < .05

Table 23 Multiple logistic regression models of CIMT and diastolic blood pressure

CIMT group by mean	Diastolic BP (mmHg) group by median value		OR	95% CI	aOR	95% CI
	High ≥ 68	Low < 68				
Overall mean CIMT						
Low (≤ 0.40 mm)			1	Reference	1	Reference
High (> 0.40 mm)			3.127	0.887, 11.019	3.655	0.997, 13.405
Overall mean CIMT of the LCCA						
Low (≤ 0.40 mm)			1	Reference	1	Reference
High (> 0.40 mm)			1.073	0.483, 2.384	0.995	0.434,2.281
Overall mean CIMT of the RCCA						
Low (≤ 0.41 mm)			1	Reference	1	Reference
High (> 0.41 mm)			0.441	0.150, 1.299	0.338	0.497, 1.170

Adjusted for age, parity, daily incense sticks burning, smokers at home

OR= Crude Odds Ratio; aOR= Adjusted Odds Ratio; * P < .05

Table 24 Multiple logistic regression models of CIMT and urine protein

CIMT group by mean	Urine protein (mg/24h) group by median value		OR	95% CI	aOR	95% CI
	High ≥ 32	Low < 32				
Overall mean CIMT						
Low (≤ 0.40 mm)			1	Reference	1	Reference
High (> 0.40 mm)			2.204	0.667, 7.278	2.551	0.738, 8.816
Overall mean CIMT of the LCCA						
Low (≤ 0.40 mm)			1	Reference	1	Reference
High (> 0.40 mm)			0.805	0.357, 1.812	0.820	0.354, 1.900
Overall mean CIMT of the RCCA						
Low (≤ 0.41 mm)			1	Reference	1	Reference
High (> 0.41 mm)			0.723	0.270, 1.942	0.683	0.249, 1.874

Adjusted for age, parity, daily incense sticks burning, smokers at home

OR= Crude Odds Ratio; aOR= Adjusted Odds Ratio; * P < .05.

CHAPTER 5

DISCUSSION

Our study revealed that carotid intima media-thickness in early pregnancy is higher in firewood and charcoal use groups than in the electricity use group in this study population. Firewood use is associated with an increase of all CIMT analyzed. More importantly, greater increase of mean CIMT of the RCCA has significant association with charcoal use compared to firewood use among cooking pregnant women at baseline. In the follow-up assessments, charcoal use has remained significantly associated with increase of all CIMT whereas firewood use did not show a significant association. Therefore, charcoal use among other solid fuels is a considerable risk factor for increase of CIMT.

5.1 Factors associated with CIMT in the study

General characteristics of participants at baseline were not different from those at follow-up. Completed age of our participants' age was 26 years. Age is one of the important risk factors for not only thickened CIMT (Lim, Lim, Dwivedi, Kooner, & Senior, 2008; Ren et al., 2015) but also cardiovascular diseases such as strokes, myocardial infarctions, and ischemic heart diseases (Baroncini, de Castro Sylvestre, & Pecoits Filho, 2015). In our study, age has association with CIMT. A prior study mentioned that normal median CIMT levels in women at age <30 years are 0.39mm (25th percentile), 0.40mm (50th percentile), and 0.43mm (75th percentile) for both right and left arteries (Simova, 2015). In our study, the overall thickness of CIMT is 0.409mm (SD=0.049) for combined mean CIMT, 0.400mm (SD=0.048) for LCCA and 0.416mm (SD=0.061) for RCCA, which are comparatively in the normal ranges. However, setting and population differences to our study population should be taken into account, and the finding of increased CIMT in younger age (nearly 27 years) solid fuels users in our study underlines an important significance although CIMT level>0.90mm was considered to be high-risk for cardiovascular diseases (Simova, 2015).

Nearly 58.5% of our participants were women with zero parity. Regarding parity, in the findings of a study in Bangladesh, a number of children were positively associated with a CIMT increase of 4.5µm per one birth (95%CI: 0.8, 8.1; P=0.02) when analyzing 718 women (mean age 37.5 years) and 417 men (mean age 43.1 years). Again, their further analysis revealed that women with more children tend to have a higher thickness of CIMT, not men-following adjustments for BMI, blood pressure, betel use or age (Chat et al., 2018). Another study in Germany demonstrated U-shaped associations of nulliparity (adjusted mean CIMT=0.81mm (95%CI: 0.78, 0.84) and single parity (mean CIMT=0.73mm (95%CI: 0.72, 0.74) with increased CIMT when 1,195 women of 45 to 75 years of age were analyzed (Wolff et al., 2005). Since more pregnant women with zero parity are included in our study, it leaves cautious interpretation.

With respect to gestational weeks with CIMT, it was investigated in previous studies. According to a recent study in the US, CIMT is found to begin increasing from the second trimester throughout the course of pregnancy and postpartum (Niemczyk et al., 2018). In yet another study on pregnant women, CIMT in the first, second, and third trimesters were 0.47mm (SD=0.16), 0.45mm (SD=0.14), and 43.03mm (SD=0.12) in 56 women who later developed preeclampsia and 0.32mm (SD=0.09), 0.33mm (SD=0.10), 0.33mm (SD=0.09) in 618 women who developed non-preeclampsia (Brückmann, Seeliger, Lehmann, Schlembach, & Schleußner, 2016). Our study population with preeclampsia signs yet undetectable and 14.38 (3.32) weeks, one week after first trimester i.e., <13 weeks of gestation, have had thicker CIMT. Furthermore, blood pressure in pregnancy that remains lower until 18 weeks of pregnancy and a heart rate increase of 20% in early pregnancy (Enkhmaa et al., 2016) is in line with our study findings of low blood pressure and increased heart rates.

Education level, monthly income, gestational weeks, and parity were not found to have significant associations with CIMT in our study. A Chinese study, on the other hand, found that higher education is associated with decreased CIMT (B. Liu et al., 2017). Whatever the education level (>primary) among our participants, a true situation of unavailable electricity in some remote villages exists; therefore, they are to use only solid fuels without other choice. Also, women with lower income are more likely to use solid fuels rather than electricity simply because of inadequate funds for the costs of electricity and related appliances. All these conditions are met in our study, which may favor an increased risk of exposure to cooking smokes to possess increased CIMT.

5.2 Comparison of CIMT at baseline and follow-up

CIMT is increasingly measured not only because of the independent marker for cardiovascular diseases but also because of its usefulness for disorders in pregnancy and beyond (Garovic et al., 2017). A thickened carotid artery wall could be the result of structurally hypertrophic changes in response to metabolic insults from many factors, including pollutants exposed in a prolonged manner (Gill et al., 2011).

Comparing CIMT at baseline and follow-up among fuels user, CIMT values among three groups of fuels use remained almost unchanged, suggesting that the increased CIMT did not progress while we could not exclude whether pregnant women avoided the exposure to risks (solid fuels use). Also, duration of exposure (nearly seven months in our study) and even exposure-dose might matter in the increase of CIMT. Additionally, in firewood users, CIMT reduction in combined mean CIMT (0.42±0.05mm at baseline to 0.41±0.06mm at follow-up); and in mean CIMT of RCCA (0.43±0.06mm at baseline to 0.41±0.07mm at follow-up) were observed. According to a study to examine effect of clean stove intervention in Nigeria, inflammatory biomarkers following clean stove intervention were found to be decreased from the first trimester to the third trimester among pregnant women who initially used kerosene or firewood stoves (Olopade et al., 2017). Therefore, inflammatory biomarkers could have played a role in the reduction of CIMT among firewood users of our participants based on the fact that cooking practices tends to be reduced as the gestational weeks becomes larger. However, the information whether our participants who used firewood fuels stopped cooking or changed fuels type as gestation grew was lacking and inflammatory biomarkers analysis was also absent in our study.

In another study with a focus on examining the potential CIMT changes during pregnancy, measurements of common carotid IMT was conducted on 37 pregnant women experiencing no pregnancy complications. Following adjustments for age, BMI before pregnancy, the cohort demonstrated the progression of inter-adventitial diameter started its increment at first trimester (6.38mm, SD=0.08) through third trimester (6.92mm, SD=0.09), which returned to first trimester level after postpartum. For common carotid IMT, thickness was found to begin at second trimester (0.456mm, SD=0.01) along the course of pregnancy, which stays at the higher level (0.581mm, SD=0.02) till 2.7 years after delivery (Niemczyk et al., 2018).

5.3 Association between cooking fuels use and increased CIMT at baseline and follow-up

Our study also has demonstrated that firewood use is associated with the increase of all CIMT analyzed and, a greater increase of mean CIMT of the RCCA has significant association with charcoal use compared to firewood use at the baseline. Furthermore charcoal use remains significantly associated with increased of all CIMT analyzed while firewood showed no significant association at follow-up.

In our study, CIMT levels in the early stages of pregnancy in women who use different fuels in cooking were measured, and we found a significant association between cooking fuels used and increased CIMT. This finding is consistent with previous findings. Recent studies investigated the association of pollutants such as $PM_{2.5}$ with CIMT, and they found that there was higher $PM_{2.5}$ levels as well as a 0.04mm higher CIMT in biomass fuels users as compared with non-biomass fuels users (Ofori et al., 2018), which was reinforced by a meta-analysis in which it was concluded that each 5μg/m^3 higher in $PM_{2.5}$ exposure had a 1.04μm per year greater CIMT progression (Provost et al., 2015). Also, a study conducted in Peru showed that the biomass fuel user group had higher median $PM_{2.5}$ concentration compared with clean fuel group (280μg/m^3 vs 14μg/m^3; $P<0.001$). Moreover, they elucidated that there was greater CIMT (mean difference=0.03 mm) and a higher prevalence of carotid plague (OR=2.6; 95%CI: 1.1, 6.0; P=0.03) in biomass users compared to clean fuels users (Painschab et al., 2013).

Reasons could be firewood largely produces more particles (particulate matters of larger size) among hazardous pollutants emitted from solid fuels burning. When particles are inhaled, they induce oxidation of surfactants in the lungs' alveoli, which further activates the toll-like receptor 4. Again, that stimulates alveolar macrophages to produce pro-inflammatory cytokines. By passing alveolar epithelium, particles enter into circulation on a mechanism of transcytosis. Systemic inflammation then occurs by the interaction of particles with inflammatory mediators. Consequently, particles oxidize low density lipoprotein (LDLs) which is susceptibly up-taken by macrophages into the vessels' wall resulting in plaque growth and thickened artery wall (Von Bornstädt et al., 2014). Charcoal, on the other hand, produces more carbon monoxide (CO). One study examined the effect of CO on blood vessels and found that CO lowers calcium concentrations in the smooth muscles of arteries that result in relaxation and the dilatation of blood vessels (Lin & McGrath, 1988). Hence, the CIMT level taken on the relatively relaxed artery could be higher than the level measured on the calcified (constricted) artery. It is worth nothing that calcification occurred more often on the right carotid artery while plaque formation and thickness were more prone on the left carotid artery, according to a study on 1,414 stroke-free patients aged≥45 years (Selwaness et al., 2014). However, as CO concentrations measurements, calcium biomarkers, calcification levels, and plaque were not assessed in this study, effect of CO on calcium levels of arteries that may result in the increase of CIMT of the RCCA warrants additional clarifications.

5.4 Association between cooking fuels use type and preeclampsia

No association between cooking fuels use type and preeclampsia was revealed in our study. However, a study in India showed an association of indoor air pollution massively contributed by household combustion of biomass and solid fuel with preeclampsia. The research was conducted by obtaining related data from India's 3rd National Family Health Survey (2005-2006). The cross-sectional nature of the study analyzed data of 39,657 women (14-49 years). These women had live births last 5 years, and interrogated cooking smoke exposure ascertained by fuels use, symptoms of preeclampsia experienced during pregnancy. Main preeclampsia related symptoms were convulsions, legs, body or face puffiness, fatigue and daylight blurred vision used as a proxy measures for preeclampsia/eclampsia. Logistic regressions model by confounders adjustments depicted that women dwelling in households with biomass or solid fuel use (e.g. wood) are found to have (OR=2.21, 95%CI: 1.26, 3.81; P=0.006) of preeclampsia/eclampsia reported compared to those in households with clean fuels (e.g. gas). Major limitations include data lacking blood pressure and proteinuria of typical parameters for preeclampsia diagnosis, misclassification possibility and cross-sectional design. However, it possesses strengths of a larger data set of national health surveys and questionnaires in local languages to maximally gather desired information, which provide important insight to estimate the possible burden of preeclampsia posed by indoor air pollution. Based on the empirical evidences of this study, to be more robust findings still requires further research with emphasis on indoor smoke concentration, personal exposure level, ambient air pollution, and well-defined criteria for preeclampsia (Agrawal & Yamamoto, 2015).

Moreover, a great deal of studies has also demonstrated that air pollutants had associations with preeclampsia. In a retrospective study attempting to examine if traffic air pollution is related to increased risks of preeclampsia among urban mothers in Australia, it showed significant associations of pollutant NO_2 and preeclampsia. Based on 23452 women between 2000-2006, and exposure estimated by land use regression model, per IQR increase of NO_2 was significantly associated with increased risk (12%, 95%CI: 1%, 25%) of preeclampsia when assessed traffic-related air pollution exposure throughout entire pregnancy period. Further analysis gave clear evidence of associations (30%, 95%CI: 7%-58%) on the analysis of third trimester exposure. Then, association of traffic related NO_2 and preeclampsia at higher risks (34%, 95%CI: 5%, 72%) in women (<20 and >40 years) and (53%, 95%CI: 7%, 219%) in women with prior and gestational diabetes was revealed (Pereira et al., 2012). Field air pollution measurements, actual traffic counts and taking outdoor and indoor passive samples were some strengths of the study, while relying on the records for preeclampsia and failure of Land Use Regression model showing less performance in indoor air pollution perdition which can be link to preeclampsia were limited this study.

In the spatiotemporal analysis by obtaining geocoded addresses of 103 preeclampsia cases from 8398 pregnancies living in Barcelona, Spain from 2000 to 2005, the association of preeclampsia with exposure to NO_2, NO_x, $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, $PM_{2.5}$ absorbance was investigated. The study concluded that all pregnancy that developed preeclampsia had the strongest positive association with third trimester exposure to fine particulate matters among other under-study pollutants analyzed, and statistically significant associations of preeclampsia with third trimester exposure to $PM_{2.5}$ and $PM_{2.5}$ absorbance, and $PM_{2.5}$ exposure in the whole pregnancy were investigated. With regard to $PM_{2.5}$, per IQR increase of exposure to $PM_{2.5}$ at 5.1μg/m³ during whole pregnancy period had OR=1.32 (95%CI: 1.02, 1.71); and OR=1.51 (95%CI: 1.13, 2.01) in those with IQR increase exposing to $PM_{2.5}$ at 7.3μg/m³ in third trimester. Furthermore, late-onset preeclampsia was significantly associated with an IQR increase in $PM_{2.5}$ exposure of 7.3μg/m³ in third trimester (Dadvand et al., 2013). Acknowledging potential influence of exposure misclassifications on results from differences exposure to ambient and personal level, maternal use of cooking appliances and their activities time; lack of maternal diet and psychological stress, this study highlights the effect of particulate matters strongly associated with preeclampsia among women in Spain. In our study, however, the effect of ambient pollutants was not included.

5.5 Association between CIMT and preeclampsia

No association between CIMT and preeclampsia was found in our study. However, in an extended longitudinal study enrolling with 417 pregnant women to monitor CIMT status throughout pregnancy was conducted. The analysis of three trimester measurements of CIMT was done, and 56 preeclampsia women (31±5 years) had CIMT (mean=0.47±0.16 at 1^{st} trimester; mean=0.45±0.1 at 2^{nd} trimester; mean=0.43±0.12 at 3^{rd} trimester), which is significantly higher than CMIT of those (n=618) with no PE in the cohort (mean=0.32±0.09 at 1^{st} trimester; mean=0.33±0.1 at 2^{nd} trimester; mean=0.33±0.09 at 3^{rd} trimester). The CMIT measurements of PE and non-PE at postpartum also show significant difference (mean=0.55±0.1 vs mean=0.36±0.1; P<0.01). From this study, only the clues of increased CIMT preceded preeclampsia onset, which still remains increased postpartum among preeclampsia can be drawn (Brückmann, Seeliger, Lehmann, et al., 2016) while answers for causes still requires.

Another cross-sectional study stated that preeclampsia women exhibited significantly more increased femoral IMT level (mean femoral IMT=0.63mm, SD=0.14 vs mean femoral IMT=0.55mm, SD=0.06; P=0.005) than normal pregnant women. The study further observed that significant difference of CMIT between normal nulliparous pregnancy and preeclampsia pregnancy at (p<0.01). Given misclassification bias and small samples (n=22 in each 3 groups) for cross-sectional design, the differences stressed increased IMT in preeclampsia; requiring further prospective studies to establish which condition develop first (Blaauw et al., 2006).

Among very few studies which focus on measuring CIMT in the pregnancy period, a study measured CIMT (in mm) on total 700 pregnant women of 347 in first trimester (11.4±1.9 weeks) and 543 in second trimester (21.5±2.3 weeks) prospectively. Among 82 women (32±5 years) experiencing early onset PE, late onset PE, superimposed early onset PE, superimposed late onset PE and non-PE, thicker CMIT in PE groups than in non-PE was demonstrated at (P=0.01). Furthermore, more increased CIMT in trimesters in preeclampsia women than non-PE and even women who already have had chronic hypertension was found (p<0.010). The cohort also revealed that preeclampsia onsets such as early onset 64.3% and superimposed early onset 68.6% can be predicted if cut-off value of CIMT is set at ≥0.5mm at first trimester and >0.4mm at second trimester of pregnancy respectively (Brückmann, Seeliger, Schlembach, & Schleußner, 2016).

Recent systematic research and meta-analysis conducted by researchers at Mayo clinic was composed of 14 eligible studies with CIMT assessments during pregnancy or 10 years postpartum, which were retrieved from publications before 7 March 2016 on database (e.g. PubMed, Embase). Meta-analysis described that CIMT level at the time of preeclampsia is increased among preeclamptic patient compared to non-preeclamptic patient in terms of standard mean difference (SMD=1.10, 95%CI: 0.73, 1.48; P<0.001); and that difference remains significant until a decade postpartum (SMD=0.58, 95%CI: 0.36, 0.79; P<0.001). Their finding indicated that arthrosclerosis precedes preeclampsia and artery walls thickness remains different up to 10 years postpartum although the finding could be limited by data of different association due to designs matters (Milic et al., 2017).

In another study with 40 preeclamptic women and 40 normotensive women recruited based on medical records which were described to be covering all people's health information of the study area, Omlsted County, Minnesota. Participants were those whose records confirmed as having preeclampia and normotention between 1976 and 1982. These participants (median 59 years) were later recruited in 2014-2015, and their CIMT levels taken by high resolution ultrasound revealed more elevated CIMT in women with preeclamptic histories (median IQR=0.80mm, 95%CI: 0.75, 0.85) than those with normotention (medium IQR=0.73mm, 95%CI: 0.70, 0.78) at P=0.004. When the CIMT threshold level is at 0.77 mm, odds of having higher CIMT than that threshold in PE group is 3.17 times the risk of those in normotensive group (OR=3.17, 95%CI: 1.10, 9.14). The finding was further reinforced by concurrent meta-analysis on (n=813 preeclampsia history) and (n=2874 not preeclampsia history) from 10 eligible studies in which CIMT measurements were conducted at least 10 years and above. The CIMT in preeclamptic group had higher thickness than that of non-preeclamptic group with standardized mean difference of 0.18mm (95%CI: 0.05, 0.30; P=0.004). Small samples, possibility of bias across studies included, and different population characteristics between studies are to be addressed as limitations of this study. On the other hand, robust data source, meta-analysis of studies over 40 years-gap between preeclampsia and CIMT measurement serves as the strengths to draw an inference that CIMT tends to be ever increased in preeclampsia women (Garovic et al., 2017).

CHAPTER 6

CONCLUSION

This cohort study to investigate associations between type of cooking fuels use and increased maternal CIMT and preeclampsia among self-cooking pregnant women in Nay Pyi Taw area, Myanmar, showed that cooking fuels use was found to have association with increased CIMT. Solid fuels particularly charcoal use has significant association with greater increase in CIMT than firewood and electricity use. CIMT did not increase in thickness from the early pregnancy period to the third trimester among fuels users. Cooking fuels uses were not associated with preeclampsia across fuels users. Furthermore, CIMT did not show a significant association with preeclampsia parameters in this study.

Participants in our study were pregnant women aged 26 years who are primary cooks of the households. Majority of them were house-wives with education above primary level and with zero parity. Participants have been doing cooking nearly every day (11.14±4.68 times) for at least (67.63±38.58 minute) duration per cooking by using (firewood/charcoal/electricity) fuels more than (10.87±5.73) years.

At baseline, CIMT levels in firewood user and charcoal users were higher than that of electricity user. Also at follow-up, firewood user and charcoal user have thicker CIMT than that of electricity user. However, only CIMT value of charcoal user was significantly different from electricity user; CIMT of firewood user was not significantly different from the value of charcoal user and electricity user. By comparing the CIMT levels at baseline and at follow-up among three fuels use groups, CIMT values remained almost unchanged. In firewood use group, combined mean CIMT was even reduced to 0.41±0.06mm at follow-up from 0.42±0.05mm at baseline; and mean CIMT of the RCCA was decreased from 0.43±0.06mm at baseline to 0.41±0.07mm at follow-up. Age was found to be significantly associated with increase of CIMT.

With respect to associations of types of fuels use with CIMT at baseline, firewood use was significantly associated with the increase of all CIMT analyzed. After adjusting for confounding factors, mean CIMT of the RCCA consistently showed significant associations with firewood and charcoal use in all models. More specifically, charcoal use was independently associated with 0.033mm increase in mean CIMT of the RCCA while firewood use was associated with 0.026mm increase in mean CIMT of the RCCA, which were statistically significant ($P<0.05$). At follow-up, association between charcoal use and increase of combined mean CIMT; $\beta=0.035$mm; 95%CI: 0.010, 0.060; $P<0.05$), mean CIMT of the LCCA; $\beta=0.029$mm; 95%CI: 0.004, 0.054, $P<0.05$, mean CIMT of the RCCA; $\beta=0.041$mm; 95%CI: 0.012, 0.071, $P<0.05$) was found. No significant association between firewood use and all CIMT was observed.

Regarding with association between cooking fuels use and preeclampsia, no association between them was revealed. Additionally, there was also no significant association investigated between CIMT and preeclampsia in our study.

6.1 Expected benefits and applications

The results of the study may provide evidence of health effects from using different types of cooking fuels among pregnant women. These findings are valuable in Myanmar where the majority of people rely on solid fuels for cooking and measures to prevent health risks related to the use of such fuels should be instituted early on during pregnancy. The evidence would be beneficial in designing programs for these health consequences among vulnerable populations. The results may also provide facts for policy considerations relating to cooking fuels use in Myanmar. Despite carotid intima media thickness that may be useful in serving as a predictive factor for preeclampsia, we could not investigate it.

6.2 Limitations

Our study results might be affected by some limitations. Non-probability sampling method and the sample size sufficiently large for CIMT but insufficiently small for preeclampsia was recruited from the same area which might limit the generalizability of results to other population due to their similar general characteristics; it might lead to type II error due to insufficient power to detect preeclampsia at low prevalence in Myanmar (Tin Tin Thein, 2008). But, significant associations were investigated in the analysis. We did not measure specific pollutants to estimate their concentrations; however, cooking fuels use status of women in our study was confirmed by using inspection checklists by trained research assistants in addition to proper inclusion criteria for pollutants exposure. Regarding the kitchen characteristics, despite the information that the kitchen was attached home or separated was collected, specific information on the presence of windows, window area and their diameters were not included. However, previous studies worldwide to date rarely reported low emission of pollutants from solid fuels burnt inside households. Studies in Tanzania and Sri Lanka conducted indoor air pollutant measurements particularly at cook sites, and concentrations levels were CO geometric mean (SD)=4.8 (46) ppm and $PM_{2.5}$=40.5 (21.2)$\mu g/m^3$ in Tanzania (Wylie et al., 2017) and 48-hour CO concentrations (0.22ppm to 8.66ppm) and $PM_{2.5}$ (33$\mu g/m^3$ to 940$\mu g/m^3$) in Sri Lanka (Chartier et al., 2017). These studies provided the real-time pollutant concentrations to which women can be exposed during cooking. Thus, one can extrapolate that pollution exposure is inevitable in this study population. Another limitation was we could measure only mean CIMT in this study although some scholars performed measuring mean and maximal CIMT (Kammoolkon et al., 2018; Painschab et al., 2013). Moreover, fuels use data collection was done at a single time point, and CIMT scans was performed at two time points, which requires follow-ups measurements to explore CIMT levels throughout pregnancy and beyond. Other than fuels use factors (cooking frequency, cooking duration, and fuels use years), we could not include information regarding other risks factors such as genetics, lifestyles, some biomarkers (Qu & Qu, 2015), and ambient pollutants (Ranzani et al., 2019) in our study, which might impact on the CIMT levels. Further studies should include these factors. The mean lipids levels were within normal limits, and the analysis was conducted on non-fasting blood, which is encouraged and widely accepted (Nordestgaard, 2017). Our study results could be affected by the measurement errors; however, the CIMT was measured by only one experienced radiologist and gestational weeks which were confirmed by the same ultrasound machine already validated, strengthens validity of our findings. Regarding with urine protein, it was collected spot urine at the time of data collection and analysis was made and reported in g/L. In order to change to mg/24h urine protein, it was estimated the protein content based on the normal urine output of 2-4 litters a day. To obtain maximum urine protein (mg/24h), 2 L per day urine output was used instead of 4 litters.

6.3 Recommendations

In addition to our findings, according to several recent studies in Mexico that explored biomarkers related to biomass fuels use and their risks implications on human health, polycyclic aromatic hydrocarbons (PAHs), a chemical released from burning biomass fuels (woods), was investigated. Urinary 1-hydroxypyrene (1-OHP), an exposure biomarker for PAHs, was quantified and determined its associations with useful markers for cardiovascular diseases development. That 1-OHP has been found to be associated with serum adipocyte acid binding protein (FABP4), which is used in predicting metabolic diseases and CVDs (Ochoa-Martínez, Ruíz-Vera, Pruneda-Álvarez, et al., 2017). Vascular dysfunction was also significantly associated with 1-OHP levels higher than 0.24µmol/mol Cr, despite no association observed between 1-OHP and CIMT (Ruiz-Vera et al., 2015). Another CVD risk marker, asymmetric dimethylarginine (ADMA), was also found to have significant associations with urinary 1-OHP level (Ochoa-Martínez, Ruíz-Vera, Almendarez-Reyna, Orta-García, & Pérez-Maldonado, 2017; Pruneda-Alvarez et al., 2016) and paraoxonase 1 polymorphism (PON1 Q192R), a marker for genetic susceptibility (Ochoa-Martínez, Ruíz-Vera, Almendarez-Reyna, et al., 2017). Regarding further exploration on PAHs in women using different fuels, its metabolite 1-OHP in urine and plasma expression level of miR-126 and miR-155 were higher in wood users than LPG users, and it has also been indicated that plasma expression levels of miR-126 and miR-155 were significantly associated with urinary 1-OHP level (Ruiz-Vera, Ochoa-Martínez, Pruneda-Álvarez, Domínguez-Cortinas, & Pérez-Maldonado, 2019); these MicroRNAs play an important role in the process of modulating vascular malfunctions and arthrosclerosis (Ruiz-Vera, Ochoa-Martínez, Pruneda-Álvarez, Zarazúa, & Pérez-Maldonado, 2019). Therefore, the recommendations were as follows:

Participants recommendation: As indicated in the literatures, solid fuels uses causes indoor air pollution and, it is found to be associated with anemia in pregnant women, low birth weight and respiratory diseases in children. Also, women who are primary cooks at households and most cooking happens inside households, they should be educated for immediate health risks and long term health effects of smokes exposure from cooking fuels use to them. In order to ensure less exposure to emitted pollutants, they should open the doors and/or windows and, in the absence of windows or doors, installing exhaust fans or installing effective vents should be carried out. Moreover, qualified fuels and the standard cook stoves that are designed for less smokes should be used in cooking. Preventive measures such as wearing effective mask should be considered. Women during pregnancy and mothers with very young children cuddled with them should be educated to avoid unhealthy smokes from cooking in which unclean fuels are burnt.

Policy recommendation: Although availability of clean fuels may pose a challenge to most of developing countries due to technical, economic, political and environmental issues, biomass fuels use has been a considerable risk factor for human health. On the other hand, the rise of premature deaths attributed by indoor air pollution is reported both globally and locally. Therefore, standard of cooking fuels, quality assurance of cooking fuels and programs of education to improve awareness of health risks of solid fuels use, to increase knowledge about health problems associated with solid fuels use should be taken into account. Safety guidelines for indoor air pollution should be developed. Importantly, the policy regarding the standard level of indoor/residential air quality of Myanmar should be considered. Laws to maintain standard levels of air pollution should also be one of the priority agenda.

Future study recommendation: To objectively investigate exposure level and to estimate the dose-response relationship, quantitative and specific pollutants measurements mainly on PM, NO_X, SO_X, CO_2, CO, volatile organic compounds, polycyclic aromatic hydrocarbons and black carbons are recommended in future studies. Furthermore, due to a short period of time to study the changes of CIMT from the effect of cooking fuels use, larger cohort with long-term follow-ups is advised to examine the exposure effects not only on the levels of CIMT but also on acute and later health problems of women who has to burn solid fuels in cooking. In addition, due to low prevalence of preeclampsia and to save resources, case-control studies or retrospective cohort studies should be considered for similar objectives.

APPENDIX

Appendix A

Inclusion and exclusion sheet for screening at registration

Effect of cooking fuels use on increased maternal carotid intima-media thickness and preeclampsia among self-cooking pregnant women in Nay Pyi Taw Area, Myanmar: A cohort study

Code No…………..

Inclusion and exclusion sheet for screening of participants

Inclusion			Exclusion		
Criteria	Yes	No	Criteria	Yes	No
-Women pregnant in early trimester <18 weeks	✓		-Hypertension (≥140/90 mmHg)		✓
-Age between 18-45 years	✓				
-Self-cooking at household at least once a week	✓		-Proteinuria (≥1+)		✓
-Use any of Firewood, Charcoal, Coal, Gas, LPG and Electricity in cook stoves at least 6 months	✓		-Urinary Tract Infection		✓
-Live in household in Nay Pyi Taw and confirmed to continue living in NPT until delivery	✓		-Known renal and liver diseases		✓
-Consent given	✓				

နောက်ဆက်တွဲ (က)

သုတေသနတွင်ပါဝင်မည့်သူများကိုစီစစ်ရန် အသေးစိတ်အချက်အလက်များ

မြန်မာနိုင်ငံ၊ နေပြည်တော်ဧရိယာအတွင်းရှိ ကိုယ်တိုင်ချက်ပြုတ်သည့်ကိုယ်ဝန်ဆောင် အမျိုးသမီးများတွင် အသုံးပြုသော လောင်စာအမျိုး အစားပေါ်မူတည်၍ လည်ပင်းသွေးကြောမကြီးများထူထည်းမှုနှင့် ကိုယ်ဝန်ဆိပ်တက်ခြင်း ဆက်စပ်သက်ရောက်မှုကို လေ့လာသောသုတေသန

ပါဝင်သူကုတ်နံပါတ်.....................

နေပြည်တော်ဧရိယာအတွင်းရှိ ကျေးလက်ကျန်းမာရေးဌာနများသို့ လာရောက်ပြသကြသည့် ကိုယ်ဝန်ဆောင်များ

ဤသုတေသနတွင် ပါဝင်နိုင်ရန် ကျန်းမာရေးဝန်ထမ်းများကစီစစ်ရာတွင် အကျုံးဝင်ရမည့်အချက်များနှင့်

အကျုံးမဝင်သည့်အချက်များ

အကျုံးဝင်ရမည့်အချက်များ	ရှိ	မရှိ	အကျုံးမဝင်သည့်အချက်များ	ရှိ	မရှိ
-ကိုယ်ဝန်ဆောင် ၁၈ ပတ် အတွင်း ဖြစ်သူ	✓		-သွေးတိုးရောဂါရှိသူ (သွေးပေါင်ချိန် ၁၄၀/၉၀ mmHg နှင့်အထက်)		✓
-အသက် ၁၈–၄၅ နှစ်အတွင်းဖြစ်သူ	✓				
-တပတ်လျှင် အနည်းဆုံး (၁) ကြိမ် အိမ်တွင်ကိုယ်တိုင် ချက်ပြုတ်သူ	✓		-ဆီးအနည်အနှစ်ကျသူ (ဆီးတွင်း ပရိုတိန်းဓါတ် 1+နှင့်အထက်)		✓
-ချက်ပြုတ်ရာတွင် ထင်း၊ မီးသွေး ၊ ကျောက်မီးသွေး၊ ဓါတ်ငွေ့ ရေနံဓါတ်ငွေ့ရည်၊ လျှပ်စစ်မီး စသည့် လောင်စာ တစ်ခုခုကို (၆) လ နှင့်အထက်သုံးစွဲသူ	✓		-ဆီးလမ်းကြောင်းပိုးဝင်ရောဂါရှိသူ		✓
-နေပြည်တော်အတွင်းရှိ နေအိမ်တွင် နေထိုင်ပြီး မွေးဖွားသည့်တိုင် နေထိုင်သူ	✓		–အသည်းရောဂါ၊ကျောက်ကပ်ရောဂါဖြစ်ဖူးသူ		✓
-သုတေသနတွင် ပါဝင်လိုပြီး ပါဝင်ရန် သဘောတူခွင့်ပြု ချက်ပေးသူ	✓				

Appendix B

Inspection checklists

Effect of cooking fuels use on increased maternal carotid intima media thickness and preeclampsia among self-cooking pregnant women in Nay Pyi Taw Area, Myanmar: A cohort study

Code No……………

This form is to be used just for ascertainment of cooking fuels use at participant's households.

Cooking fuels use ascertainment checklists (baseline)			2nd follow-up	Remarks
Is cooking done at home?	Yes ✓	No	Yes	Examine cooking site, record it
Self-cooking per week	Yes ✓	No	Any Cooking	Ask it, record it
What type of fuel do you MAINLY use for cooking? (tick below)				Ask and examine vicinity, record fuel types
Solid fuel	Firewood	✓		
	Charcoal		✓	
	Coal			
Non-solid fuels	Gas			
	LPG		✓	
	Electricity	✓		
Cook stove types in use	Three-stones open fire stove	✓		Examine cooking site, record stoves types for evidences
	Charcoal/multipurpose stove		✓	
	Electric stove			
	Gas stove			
Recent cooking activity	Presence	✓		
	Absence			
Kitchen	Attached home	✓		Examine cooking site, record it
	Separated			
Chimney	Presence	✓		
	Absence			

Definitions:
-Self-cooking refers to the practice of cooking done by the participant by using any one of fuels -Firewood, Coal, Charcoal, LPG, Electricity or Gas.
-Charcoal cook stoves - modeled stoves made of clay or metals
-Three stones cook stoves - cook stoves in three-stones and three-leg iron stoves
-Electric stoves – any stoves usable in connection to electric current
-Gas stoves – any stove used with LPG or gas fuel
✓ Possible responses by participants

Remarks-
Confirmed eligible Solid cooking fuel user
Confirmed eligible Non-solid cooking fuel user

Name of inspector…………………………….
Date…………………………………………………………....

နောက်ဆက်တွဲ (ခ)

သုတေသနတွင် ပါဝင်မည့်သူများအိမ်တွင်လောင်စာအသုံးပြုခြင်းကိုစီစစ်ရန် အသေးစိတ်အချက်အလက်များ
မြန်မာနိုင်ငံ၊ နေပြည်တော်ဇရိယာအတွင်းရှိ ကိုယ်တိုင်ချက်ပြုတ်သည့်ကိုယ်ဝန်ဆောင် အမျိုးသမီးများတွင်
အသုံးပြုသော လောင်စာအမျိုး အစားပေါ်မူတည်၍ လည်ပင်းသွေးကြောမကြီးများထူထည်းမှုနှင့်
ကိုယ်ဝန်ဆိပ်တက်ခြင်း ဆက်စပ်သက်ရောက်မှုကို လေ့လာသောသုတေသန

ပါဝင်သူကုတ်နံပါတ်.....................

လောင်စာအသုံးပြုခြင်းကိုစီစစ်ရန် အသေးစိတ်အချက်အလက်များ (ကနဦးစစ်ဆေးခြင်း)			ဒုတိယအကြိမ် စစ်ဆေးခြင်း	မှတ်ချက်
အိမ်တွင် ချက်ပြုတ်မှု	ရှိ ✓	မရှိ	ရှိ	မေးမြန်း မှတ်သားရန်
တပတ်လျှင် အိမ်တွင်ကိုယ်တိုင်ချက်ပြုတ်မှု	ရှိ ✓	မချက်ပါ	-	
အသုံးပြုသည့် **အဓိက** လောင်စာ (အမှန်ခြစ်ရန်)				မေးမြန်း မှတ်သားရန်
လောင်စာခဲ	ထင်း	✓		ပတ်ဝန်းကျင်ကို ကြည့်ရှု၊ မေးမြန်း မှတ်သားရန်
	မီးသွေး		✓	
	ကျောက်မီးသွေး			
လောင်စာခဲ မဟုတ်သောလောင်စာ	ဓါတ်ငွေ့			
	ရေနံဓါတ်ငွေ့ရည်		✓	
	လျှပ်စစ်			
အသုံးပြုနေသောမီးဖိုအမျိုးအစား	မီးသွေးနှင့်ဘက်စုံသုံးမီးဖို	✓		ပတ်ဝန်းကျင်ကို ကြည့်ရှု၊ မေးမြန်း မှတ်သားရန်
	သုံးချောင်းထောက်မီးဖို			
	ဓါတ်ငွေ့ (သို့မဟုတ်) ဓါတ်ငွေ့ရည်မီးဖို			
	လျှပ်စစ်မီးဖို			
ချက်ပြုတ်မှုအထောက်အထားများ	တွေ့ရှိ	✓		
	မတွေ့ရှိ			
မီးဖိုချောင်တည်ရှိမှု	အိမ်နှင့်တွဲလျက်	✓		ပတ်ဝန်းကျင်ကို ကြည့်ရှု၊ မေးမြန်း မှတ်သားရန်
	အိမ်နှင့်မတွဲ			
မီးခိုးခေါင်းတိုင်	ပါရှိ	✓		
	မရှိ			

–ကိုယ်တိုင် ချက်ပြုတ်သူဆို သည်မှာ ထင်း၊ မီးသွေး ၊ ကျောက်မီးသွေး၊ ဓါတ်ငွေ့ ရေနံဓါတ်ငွေ့ရည်၊ လျှပ်စစ်မီး စသည့်လောင်စာတစ်ခုခု ကို အသုံးပြုပြီး တပတ်လျှင် အနည်းဆုံး (၁) ကြိမ် အိမ်တွင် ကိုယ်တိုင် ချက်ပြုတ်သူ ချက်ပြုတ်ခြင်းကိုဆိုလိုခြင်း ဖြစ်သည်။
–မီးသွေးနှင့်ဘက်စုံသုံးမီးဖို – သံထည် (သို့မဟုတ်) ရွှံ့မြေဖြင့်ပြုလုပ်နိုင်သည်။
–သုံးချောင်းထောက်မီးဖို – သံထည် (သို့မဟုတ်) တခုခုဖြင့် သုံးချောင်းထောက်ပုံစံဖြစ်နိုင်သည်။
–ဓါတ်ငွေ့ (သို့မဟုတ်) ဓါတ်ငွေ့ရည်မီးဖို– ဓါတ်ငွေ့ (သို့မဟုတ်) ဓါတ်ငွေ့ရည်ဖြင့် သုံးသောမီးဖို။
–လျှပ်စစ်မီးဖို– လျှပ်စစ်မီးဖြင့် ချက်သောမီးဖို
– ✓ ပါဝင်သူများက ဖြေကြားနိုင်သော အဖြေ

လောင်စာခဲအသုံးပြုသူ....................................
လောင်စာခဲမဟုတ်သောလောင်စာ အသုံးပြုသူ..................

ကြည့်ရှုစစ်ဆေးသူလက်မှတ်................................
ရက်စွဲ...

Appendix C

Questionnaire Form

Effect of cooking fuels use on increased maternal carotid intima-media thickness and preeclampsia among self-cooking pregnant women in Nay Pyi Taw Area, Myanmar: A cohort study

Code No...…………....
Date…………………

Part 1

A. Sociodemographic factors

(1) Completed age …………………………………………………………… Years

(2) Gestation at entry ……………………………………………………….. ………… Weeks

(3) Education level……………………………………………………………. .Grade

(4) Occupation
- (i) Government employee
- (ii) Agriculturist
- (iii) Marchant and trader
- (iv) Company employee
- (v) Laborer
- (vi) House-wife

(5) Monthly family income ……………………………………………………. ...Kyats

(6) Are you a current smoker?
No Yes, if yes, number of …………………,………….. Per week

(7) Do you drink alcohol?
No Yes, if yes, types ……………….and …………….cups per week

Part 2

B. Residential factors

(8) Dose your household burns incense sticks inside?
No Yes,

(9) Does your household use mosquito coils inside?

No Yes, If yes, Daily ……. Non-daily…………….

(10) Is there any family member who smokes at household?

No Yes, If yes, Daily ……………. Non-Daily…………….
If yes, how many people smoking………….. ; total …………………… Per day

(11) How long was the current household built?
………………………………………………………………………..................................Years

(12) Air condition use at household?
No Yes

If yes, Bedroom living room

Part 3

C. Cooking fuel use factors

(13) Self-cooking per week at household is………………………………………….. Times

(Please write frequencies responded by participants)

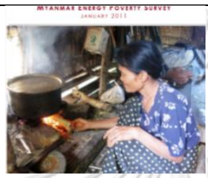
(14) How long does cooking last per time when you cook? ……………………… ….Minutes

(Please write duration responded by participants)

(15) How many years have you been doing self-cooking?

……………………………..……………………………………………..................Years

(16) What cooking fuels type do you MAINLY use in your household now? How long (years) have you been using the above mentioned cooking fuels?

Types of cooking fuels		Main fuels use type	Fuels use years
Firewood	 Picture source: Myanmar energy poverty survey, 2011		
Charcoal	 Picture source: Asia's Improved Cook Stoves		
Coal	 Picture source: http://www.investmyanmar.biz/infoNews.php?id=1398		
Gas	 Picture source: google		
LPG			
Electricity			

(17) What cook stove (s) do you **mainly** use at your household **now**? How long **(years)** have you been using the above mentioned cook stove?

Name of cook stoves		Main stove type use	Stove use years
Charcoal/ multipurpose stove			
Three-stones open fire stove	 Picture source: Google		
Gas stove			
Electric stove			

Interviewing ends. Thanks for your cooperation.

……………………………………………...END……………………………………

နောက်ဆက်တွဲ (ဂ)

သုတေသနမေးခွန်းလွှာ (အချက်အလက်များမေးမြန်းခြင်း)

မြန်မာနိုင်ငံ၊ နေပြည်တော်ဧရိယာအတွင်းရှိ ကိုယ်တိုင်ချက်ပြုတ်သည့်ကိုယ်ဝန်ဆောင် အမျိုးသမီးများတွင် အသုံးပြုသော လောင်စာအမျိုး အစားပေါ်မူ တည်၍ လည်ပင်းသွေးကြောမကြီးများထူထည်းမှုနှင့် ကိုယ်ဝန်ဆိပ်တက်ခြင်း ဆက်စပ်သက်ရောက်မှုကို လေ့လာသော သုတေသန

ကုတ်နံပါတ်..........................

နေ့စွဲ....................................

အပိုင်း **(၁)**

(က) လူမှုစီးပွားဆိုင်ရာ အချက်အလက်များ

(၁) ယခုပြည့်ပြီးအသက်...နှစ်

(၂) ယခုရောက်ရှိနေသောကိုယ်ဝန်ပတ်ပေါင်း..ပတ်

(၃) သင်ကြားခဲ့သောအမြင့်ဆုံးပညာအရည်အချင်း...တန်း

(၄) အလုပ်အကိုင်အမျိုးအစား ....

အစိုးရဝန်ထမ်း	စိုက်ပျိုးရေး	ကုန်သည်	ကုမ္ပဏီဝန်ထမ်း	အလုပ်ကြမ်းသမား	အိမ်ရှင်မ

(၅) မိသားစု တစ်လဝင်ငွေစုစုပေါင်း..ကျပ်

(၆) သင်သည် လက်ရှိ ဆေးလိပ်သောက်သူ ဟုတ်ပါသလား။

မဟုတ်ပါ။ ဟုတ်ပါသည်။

ဟုတ်ပါက တစ်ပတ်လျှင်သောက်သည့်ဆေးလိပ် စုစုပေါင်း.................., ...နှစ်။

(၇) သင်သည် အရက်သောက်သူ ဟုတ်ပါသလား။

မဟုတ်ပါ။ ဟုတ်ပါသည်။

ဟုတ်ပါက သောက်သည့်အရက် အမျိုးအစား......................။

တစ်ပတ်လျှင်သောက်သည့်ပမာဏစုစုပေါင်း.................ခွက်

အပိုင်း **(၂)**

(ခ) နေအိမ်ဆိုင်ရာအကြောင်းအရာများ

(၈) သင်၏အိမ်အတွင်းတွင် အမွှေးတိုင်များထွန်းလေ့ရှိပါသလား။

မထွန်းပါ။ ထွန်းပါသည်။ ထွန်းပါက နေ့စဉ် နေ့စဉ်မထွန်းပါ။

(၉) သင်၏အိမ်အတွင်းတွင် ခြင်ဆေးခွေများ ထွန်းပါသလား။

မထွန်းပါ။ ထွန်းပါသည်။ ထွန်းပါက နေ့စဉ် နေ့စဉ်မထွန်းပါ။

(၁၀) သင့်မိသားစုဝင်များတွင် ဆေးလိပ်သောက်သူရှိပါသလား။

မရှိပါ။ ရှိပါသည်။ ရှိပါက ဘယ်နှစ်ဦးသောက်ပါသလဲ......................။

တစ်ရက်လျှင်သောက်သည့် ဆေးလိပ်အရေအတွက်.......................................လိပ်။

(၁၁) လက်ရှိအိမ်ကို ဆောက်လုပ်ထားသည်မှာ ဘယ်လောက်ကြာပြီလဲ။

....နှစ်

(၁၂) သင်၏အိမ်တွင် လေအေးပေးစက်(အဲယားကွန်း) သုံးပါသလား။

မသုံးပါ။ သုံးပါသည်။

သုံးပါက အိမ်ခန်း ဧည့်ခန်း

အပိုင်း **(၃)**

(ဂ) ချက်ပြုတ်ရာတွင်သုံးစွဲသည့်လောင်စာအကြောင်းအရာများ

(၁၃) တစ်ပတ်လျှင် ဘယ်နှစ်ကြိမ်လောက် ကိုယ်တိုင်ချက်ပြုတ်လေ့ရှိပါသလဲ။

....ကြိမ်

(၁၄) ကိုယ်တိုင်ချက်ပြုတ်မှုတစ်ကြိမ်တွင် အချိန်မည်မျှကြာလေ့ရှိပါသလဲ။

....မိနစ်

(၁၅) ကိုယ်တိုင်ချက်ပြုတ်သည်မှာနှစ်ပေါင်း ဘယ်လောက်ကြာပြီလဲ။

....နှစ်

(၁၆) သင့်အိမ်တွင်ချက်ပြုတ်ရာ၌ လက်ရှိတွင် မည်သည့်လောင်စာအမျိုးအစားကို အဓိက အားဖြင့် သုံးပါသလဲ။ ဖော်ပြခဲ့သော ချက်ပြုတ်လောင်စာကို သုံးစွဲသည်မှာ နှစ်ပေါင်း ဘယ်လောက်ကြာပြီလဲ။

ချက်ပြုတ်လောင်စာအမျိုးအစားများ		**လက်ရှိအဓိက**သုံးလောင်စာ	လောင်စာသုံးသည့်နှစ်ပေါင်း
ထင်း	 Picture source: Myanmar energy poverty survey, 2011		
မီးသွေး	 Picture source: Asia's Improved Cook Stoves		
ကျောက်မီးသွေး	 Picture source: http://www.investmyanmar.biz/infoNews.php?id=1398		
ဓါတ်ငွေ့	 Picture source: google		
ရေနံဓါတ်ငွေ့ရည်			
လျှပ်စစ်			

(၁၇) သင့်အိမ်၌ **လက်ရှိတွင်** မည်သည့်မီးဖိုကို **အဓိက** သုံးစွဲပါသလဲ။ ဖော်ပြခဲ့သောမီးဖိုကို သုံးစွဲသည်မှာ **(နှစ်ပေါင်း)** မည်မျှကြာပြီလဲ။

မီးဖိုအမျိုးအမည်		မီးဖိုအမျိုးအစား	မီးဖိုသုံးသည့်နှစ်ပေါင်း
မီးသွေးနှင့် ဘက်စုံသုံးမီးဖို			
သုံးချောင်းထောက်မီးဖို	 Picture source: google		
ဓါတ်ငွေ့ (သို့မဟုတ်) ဓါတ်ငွေ့ရည်မီးဖို			
လျှပ်စစ်မီးဖို			

မေးခွန်းမေးမြန်းခြင်း ပြီးပါပြီ။ ကျေးဇူးအထူးတင်ပါသည်။

Appendix D

Table 1 Characteristics of participants lost to follow-up (n=16)

Variable	Total (n=16)	Cooking fuels use status			P value
		Firewood (n=2)	Charcoal (n=2)	Electricity (n=12)	
Reason					
Delivery	4	-	-	4	
Lost contact	6	-	-	6	
Return to native village	3	1	1	1	
Abortion	3	1	1	1	

Table 2 Comparison of characteristics of participants (lost to follow-up) by fuels use status (n=16)

Socio-demographic characteristics	Total (n=16)	Solid fuel user (n=92)		Non-solid fuel user (n=12)	P value
		Firewood (n=2)	Charcoal (n=2)	Electricity (n=12)	
Age years (mean ±SD)	26.38±7.09	23.50±3.53	30.50±14.84	26.17±6.54	0.635[a]
Gestational weeks by USG (mean ±SD)	13.67±4.11	14.80±2.54	15.00±2.82	13.26±4.58	0.811[a]
Parity, n (%)					0.450[b]
Parity=0	14 (87.5)	2(100.0)	1 (50.0)	11 (91.7)	
Parity ≥ 1	2 (12.5)	-	1 (50.0)	1 (8.3)	
Education level, n (%)					0.100[b]
> Primary	11 (68.8)	1 (50.0)	2 (100.0)	8 (66.7)	
≤ Primary	5 (31.3)	1 (50.0)	-	4 (33.3)	
Occupation, n (%)					0.118[b]
House-wife	10 (55.1)	-	1 (50.0)	9 (75.0)	
Others	6 (44.9)	2 (100.0)	1 (50.0)	3 (25.0)	
Monthly family income (Kyats), n (%)					0.118[b]
> 200,001	6 (48.3)	2 (100.0)	1 (50.0)	3 (25.0)	
≤ 200,000	10 (51.7)	-	1 (50.0)	9 (75.0)	
Residential characteristics					
Kitchen Type (n, %)					0.547[b]
Home attached	11(68.8)	1 (50.0)	1 (50.0)	9 (75.0)	
Separated	5 (31.3)	1 (50.0)	1 (50.0))	3 (25.0)	
Daily incense sticks burning inside home, n (%)					0.713[b]
Yes	8 (50.0)	2 (100.0)	1 (50.0)	5 (41.7)	
No	8 (50.0)	-	1 (50.0)	7 (58.3)	
Daily mosquito coils burning, inside home, n (%)					0.728[b]
Yes	4 (25.0)	1 (82.4)	-	3 (25.0)	
No	12 (75.0)	1 (17.6)	2 (100.0)	9 (75.0)	
Smokers at home, n (%)					0.753[b]
Yes	6 (37.5)	-	1 (50.0)	5 (41.7)	
No	10(62.5)	2 (100.0)	1 (50.0)	7 (58.3)	
Fuels use					
Cooking frequency at household per week	9.62±5.50	1.50±0.70	10.50±4.94	10.83±5.02	0.072[a]
Cooking duration per time (min) (mean ±SD)	66.56±39.10	60.00± 0.00	60.00±0.00	68.75±45.43	0.937[a]
Fuels use duration years (mean ±SD)	11.62±5.22	11.50±4.94	12.50±10.60	11.50±4.96	0.973[a]

[a] = One-way analysis of variance, [b] = Fisher's Exact test

Table 3 Comparison of clinical characteristics of participants (lost to follow-up) by fuels use status (n=16)

Characteristics of clinical assessments	Total (n=16)	Solid fuel user (n=4)		Non-solid fuel user (n=12)	P value
		Firewood (n=2)	Charcoal (n=2)	Electricity (n=12)	
Clinical assessments					
Body Mass Index (kg/m^2) (mean ±SD)	20.67±4.22	17.83±0.60	17.38±2.49	21.69±17.31	0.259[a]
Heart rate per minute (mean ±SD)	89.50±15.56	90.00±5.67	98.50±10.60	87.92±9.97	0.702[a]
BP (mmHg) (mean ±SD)					
Systolic Blood Pressure	104.94±8.89	98.50±4.95	116.00±8.48	104.17±8.28	0.116[a]
Diastolic Blood Pressure	66.44±6.64	59.50±0.70	70.00±0.00	67.00±6.98	0.255[a]
Random blood sugar (60-180mg/dl) (mean ±SD)	91.43±17.28	91.88±4.26	87.90±18.52	91.94±19.28	0.959[a]
Random blood cholesterol (mg/dl) (mean ±SD)					
Total cholesterol (up to 220)	186.88±37.86	169.49±43.99	172.90±27.15	192.10±39.89	0.662[a]
HDL cholesterol (35-45)	52.70±15.58	50.86±25.50	50.45±7.70	53.39±16.26	0.960[a]
LDL cholesterol <150)	108.88±24.48	100.20±18.10	90.50±16.26	113.40±25.80	0.438[a]
Triglycerides cholesterol (<200)	126.71±50.62	92.80±2.96	158.55±19.30	127.06±55.37	0.460[a]
Cholesterol and HDL ratio	3.70±0.80	3.55±0.91	3.40±0.00	3.77±0.88	0.820[a]

[a] = One-way analysis of variance

Table 4 Comparison of CIMT by age groups at follow-up (n=176)

CIMT	Age group		P value
	≤ 26 (n=88)	> 26 (n=88)	
Overall mean CIMT	0.395±0.044 mm	0.420±0.041 mm	<0.001
Combined mean CIMT of the LCCA	0.390±0.039 mm	0.417±0.042 mm	<0.001
Combined mean CIMT of the RCCA	0.399±0.054 mm	0.422±0.050 mm	0.004

Independent t-test

Table 5 Comparison of CIMT by parity groups at follow-up (n=176)

CIMT	Parity group		P value
	Parity=0 (n=103)	≥ 1 (n=73)	
Overall mean CIMT	0.398±0.045 mm	0.423±0.050 mm	0.001
Combined mean CIMT of the LCCA	0.393±0.041 mm	0.418±0.041 mm	<0.001
Combined mean CIMT of the RCCA	0.402±0.054 mm	0.423±0.050 mm	0.011

Independent t-test

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VITA

NAME	Myo Min
DATE OF BIRTH	18 March 1983
PLACE OF BIRTH	Indaw, Myanmar
INSTITUTIONS ATTENDED	Defence Services Medical Academy The University of Sydney
HOME ADDRESS	No. 132, Sathorn Nua Road, Silom, Bangrak, Bangkok,10500
PUBLICATION	Cooking fuels use and carotid intima-media thickness during early pregnancy of women in Myanmar
AWARD RECEIVED	The 100TH Anniversary Chulalongkorn University for Doctoral Scholarship The 90TH Anniversary of Chulalongkorn University Fund