CHAPTER 1

General introduction
The concern for maternal and reproductive health is a major part of the reproductive, maternal, newborn, and child health (RMNCH) agenda that has been a global health priority worldwide. Maternal and reproductive health—often also referred to as women’s health—encompasses women’s reproductive years, from adolescence until pregnancy and childbirth. An essential framework in order to improve reproductive and maternal health is the continuum of care approach, which recognizes the need for health services across women’s reproductive life span, including integrated and comprehensive preventive and therapeutic health interventions.

**Women’s reproductive health**

Reproductive health is fundamental to the health and wellbeing of individuals, families and communities. Poor reproductive health outcomes for women can affect not only individuals, but also their children, partner and society. Global population trends show that rapid population growth is problematic to wellbeing in the low and middle income countries (L-MICs), while low fertility is alarming for the future of many high-income countries (HICs). Most low-income countries, especially in sub-Saharan Africa, are portrayed by rapid growth of more than 2% per year, while large countries such as India, Indonesia, north Africa and western Latin America are characterized by moderate annual growth of 1-2%. The implementation of family planning programs as one of the main public health policy options should be considered by countries with rapid population growth as an effort to improve the wellbeing of families and communities in general, and of women in particular.

According to The Millennium Development Goals (MDGs) report in 2015, approximately 12% of women of reproductive age worldwide wanted to delay or avoid childbearing but were not using any method of contraception or had an unmet need for family planning. This unmet need is most dominantly present in L-MICs where an estimated of 74 million unintended pregnancies occurred in 2012. As the most substantial reductions in the number of unintended pregnancies especially for those that are in increased risk to maternal and perinatal survival can be obtained by increased contraceptive use, the availability of effective interventions to reduce the unmet need especially in this group of countries is imperative.

Organized family planning was first introduced in the 1950s in L-MICs as a strategy to slow down the rapid population growth. Along the years, it has emerged as an important public health approach to improve both maternal and child health. However, despite an increase in contraceptive use over the past decades, the World Health Organization (WHO) estimated that approximately 225 million women in L-MICs were still experiencing an unmet need for family planning to either delay or limit childbearing.
Provision of effective contraceptive methods in a family planning program is essential to improve reproductive health outcomes. It has also proven to be associated with improved overall health and economic outcomes. In recent years, MDGs and SDGs (Sustainable Development Goals) have considered family planning as one of the prominent drivers of progress towards their targets in ensuring universal access to sexual and reproductive health. Within the reproductive health section, we focused on the interventions to improve reproductive health in L-MICs as the current situation in these countries indicates that implementation of family planning programs to reduce the unmet need for contraception should be a priority as one of their main global health policy options.

Maternal health
Maternal health is vital for sustainable development, as approximately 210 million women become pregnant worldwide, annually. The success of management and intervention with regards to maternal health is usually expressed as the rate of maternal morbidity and mortality. Although maternal mortality has decreased by roughly 43% in last 15 years, the goal of reducing maternal mortality by 75% by 2015 as stated in MDGs point 5, was not met in many countries. Due to increased number of women who survive childbirth, a shifting trend is observed from avoidable deaths towards a progressively diverse range of maternal morbidities. This includes the contribution of non-communicable diseases, such as an increasing incidence of hypertension, heart disease, diabetes mellitus, and other chronic conditions, as well as those related to mental health, reflecting great transitions in demographic, epidemiological, socioeconomic and environmental aspects. Within this thesis’ maternal health section, we highlighted one of the maternal morbidities which is also one of the leading causes of maternal mortality, i.e., gestational hypertension and pre-eclampsia.

Gestational hypertension and pre-eclampsia
Gestational hypertension is one of non-communicable diseases that can be prevented to a certain extent and also managed. The cause of gestational hypertension is still unclear, however some predisposing factors such as genetics, environment and other conditions for instance diabetes mellitus, kidney disease, anxiety and depression may be associated with an increased risk of developing this condition. One of the most prevalent types of gestational hypertension is pre-eclampsia. Pre-eclampsia affects approximately 3-5% of pregnancies and typically involves the presentation of high blood pressure (systolic higher than 140
mm Hg or diastolic higher than 90 mm Hg) after 20 weeks of gestation combined with proteinuria. Recent diagnostic criteria suggested by the International Society for the Study of Hypertension in Pregnancy (ISSHP) further defined that pre-eclampsia could also be characterized by newly diagnosed hypertension in combination with other maternal organ dysfunction e.g. renal insufficiency, uteroplacental dysfunction, impaired liver function, or neurological and hematological complications, without any proteinuria15,16.

If left untreated, pregnant women with pre-eclampsia face a risk of severe complications such as eclampsia, pulmonary edema, and kidney failure that can be life-threatening for both the mother and her offspring 17. Pre-eclampsia is also associated with fetal growth restriction and a high rate of preterm birth. Therefore, the clinical importance of pre-eclampsia follows from its relation with maternal and neonatal morbidity and mortality15.

**Prediction, prevention and treatment of pre-eclampsia**

Although effective early prediction for pre-eclampsia remains to be introduced into clinical practice, a certain distinction between those in low and high risk is possible. Specific strong risk factors for developing gestational hypertension or pre-eclampsia are associated with the presentation of comorbidities such as chronic kidney disease, hypertension, diabetes (type 1 or type 2), and autoimmune disorders, including systemic lupus erythematosus or antiphospholipid syndrome18,19. A history of pre-eclampsia or gestational hypertension is also considered to be a strong risk factor18. Besides, there are also several moderate risk factors for developing this condition, i.e. first pregnancy, pregnancy interval more than 10 years, body-mass index more than 35 kg/m², age over 40 years old, family history of pre-eclampsia, and multiple pregnancy18. However, the clinical risk prediction is considered modest as it predicts less than 30% of women who develop pre-eclampsia20.

In the past few years, several maternal biomarkers including serum concentration of maternal placental growth factor, maternal-related plasma proteins, and soluble fms-like tyrosine kinase-1, have been assessed as potential markers to predict pre-eclampsia21–24. However, these tests have not been evaluated thoroughly in intervention studies across populations and were considered as having a too modest predictive value to be introduced in clinical practice. The combination of clinical factors, aforementioned biomarkers and uterine artery Doppler ultrasound at 20 weeks of gestation has a potential to improve the accuracy, although these multivariable prediction models have been suggested to provide modest prediction as well25. Another promising prediction method includes a metabolomics or proteomics approach to predict pre-eclampsia in pregnant women as early as
15 weeks of gestation\textsuperscript{26}. However, before introducing these models to clinical practice, they need to be validated in population studies\textsuperscript{15}.

Several interventions have been suggested to prevent the onset of pre-eclampsia i.e. diet-related approaches such as garlic consumption and advice to reduce salt, physical activity, vitamins, antioxidants, marine/fish oils, nitrates, and various anticoagulant and antiplatelet medications such as heparin and low-dose aspirin. Few of these interventions showed benefit in preliminary studies; yet the only intervention that has been shown to reduce the risk of pre-eclampsia in rigorous randomized trials is low-dose aspirin only\textsuperscript{27}. Several meta-analyses showed the moderate benefit of low-dose aspirin in the prevention of pre-eclampsia, with reported relative risks (RR) around 0.76, 95% CI 0.49-0.97 \textsuperscript{27,28} for high-risk women and approximately 0.88, 95% CI 0.49-0.97 \textsuperscript{27} and 0.90, 95% CI 0.84-0.97 \textsuperscript{29} for women with moderate risk factors. Calcium supplementation is also recommended for pregnant women with low dietary calcium intake as it reduces the risk for developing pre-eclampsia (RR 0.36, 95% CI 0.20-0.65)\textsuperscript{30}. Although WHO states the recommendation on high dose calcium supplementation (1.5-2 g daily) for women with low dietary calcium intake starting from their second trimester, further robust assessment needs to be done in order to strengthen the evidence of the effectiveness of this intervention\textsuperscript{31}.

Clinical management of women diagnosed with pre-eclampsia includes increased monitoring, antihypertensive drugs for severe hypertension, magnesium sulphate for convulsions and eclampsia prevention, and most importantly, induced delivery. Despite substantial efforts concerning research and development on potential novel therapies for pre-eclampsia, delivery of the fetus remains the most important and most effective treatment for pre-eclampsia\textsuperscript{15,32}. Thus, optimal timing of delivery is really crucial and should be based on benefit and risk assessment in both mother and offspring on either continuing or ending the pregnancy\textsuperscript{15}.

**Health economic evaluation**

Health economic evaluations are increasingly common nowadays in public health and medical care research, as they can provide comprehensive insights for both effective and efficient healthcare for decision makers\textsuperscript{33}. Due to an increasing amount of potential interventions to improve reproductive, maternal and women’s health in contrast to the scarce resources (in terms of people, time, facilities, equipment, and knowledge), it is necessary to have a full assessment on how to efficiently allocate these resources. Such assessments can be implemented within the setting of a randomized controlled trial or other health-related research, or can be undertaken through decision analytic modelling approaches.
Three main types of economic evaluations are cost minimization analysis (CMA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). In CMA, the interventions are compared based on their costs and benefits valued in monetary terms. This type of economic evaluation is deemed as the simplest form of economic evaluation study. Due to its simplicity, CMA only applies to interventions that have been proven equal or are expected to be equivalent in their effectiveness. In contrast, CEA and CUA are the types of economic evaluations that value the effectiveness or consequences of interventions in terms of clinical event and/or health outcome measure. In CEA, natural effects or physical unit such as life-years gained are used to measure the effectiveness of health interventions. In reproductive, maternal and women’s health, the outcome measure can be in the form of costs per pregnancy-related case averted (e.g. unintended pregnancy averted, maternal death averted, or pre-eclampsia case averted). Furthermore, CUA is another type of economic evaluations that uses utility weights as outcome measure, commonly expressed in terms of quality adjusted life year (QALY) or disability adjusted life year (DALY). This means that it is possible to assess the quality of life-years gained, not only the number of years gained. Therefore, CUA is often considered as a more comprehensive analysis than CEA. In CEA and CUA, an incremental cost-effectiveness ratio (ICER) is used as a summary measure expressing the economic value of an intervention compared to its comparator. The ICER is defined by dividing the difference in cost between interventions by the difference in their effect.

The range of costs (and effects) included in the economic evaluation study depends upon the perspective taken, which could be that of the healthcare payer perspective (e.g. national health insurance, government) or society. The healthcare payer perspective takes into account direct medical costs such as medication cost, cost of healthcare personnel, and hospitalization cost which are type of costs that are directly paid by -for instance- health insurance or government. The societal perspective considers not only direct medical costs, but also indirect costs (e.g. productivity losses).
Chapter 1

Thesis objectives
As the continuum of care in women’s health is very broad, this thesis covers a small part of this topic. This thesis is arranged into two sections; family planning in the reproductive health section (I) and gestational hypertension and pre-eclampsia in the maternal health section (II), with the following main aims:

1. To perform the economic evaluation of scaling up family planning interventions in L-MICs.
2. To evaluate both the epidemiological and economic impact of screening, diagnosis and treatment of gestational hypertension and pre-eclampsia.

Thesis outline
Section I: Reproductive health
In many L-MICs, the provision of any modern family planning method is relatively low despite the increasing demand for contraceptive use, indicating the unmet need of family planning. Chapter 2 systematically summarizes the existing economic evaluations of strategies to improve family planning interventions in L-MIC, followed by a decision analytic study in Chapter 3 that assesses the long-term cost-effectiveness of scaling up family planning interventions in L-MICs with varying levels of unmet need, with Indonesia and Uganda as reference cases.

Section II: Maternal health
In Chapter 4, one of the predisposing factors that may be associated with the risk of developing gestational hypertension, i.e. depression and exposure to antidepressants, is described. Chapter 5 provides a comprehensive insight into the current evidence on both the clinical and economic impact of screening, diagnosis and treatment options for preeclampsia. In Chapter 6, an early cost-effectiveness analysis using decision analytic modeling was developed to evaluate costs and health effects of a new screening test for pre-eclampsia in four European countries i.e. United Kingdom, the Netherlands, Ireland and Sweden. This analysis is used to guide the implementation of a novel screening technology for pre-eclampsia that is currently being developed. Chapter 7 summarizes and discusses the overall results of this thesis, including main findings, implementations and recommendations for future research.
REFERENCES


Chapter 1

General Introduction
SECTION I

REPRODUCTIVE HEALTH