CHAPTER 7

General discussion
The main aim for this thesis was to identify both the epidemiological and economic impact of a wide range of interventions to improve women’s health in different settings. Two topics were in particular addressed; i.e. family planning, and gestational hypertension – mainly pre-eclampsia. As explained in Chapters 2 and 3, we focused on the economic evaluation of family planning interventions in low and middle income countries (L-MICs), as the unmet need for family planning interventions is still alarmingly high in these regions, as reflected by a low availability and use of modern contraceptives. In Chapters 4 - 6 we focused on the epidemiological and economic aspects of screening for and management of gestational hypertension and pre-eclampsia. These studies were performed in a high-income setting, as they were part of a larger project developing a novel test for early detection of pre-eclampsia directed at several high-income countries (HICs) 1. In addition, pre-eclampsia is still contributing to a substantial part of maternal morbidity and mortality in high-resource countries, resulting in a considerable amount comprehensive research in this particular field. Although evidence is needed in L-MICs as much as in HICs, and it certainly is a future research priority, currently there is less data particularly on this topic in L-MICs and so our focus at this moment was on HICs.

**Main findings**

*Scaling up family planning interventions in L-MICs*

With the main aim to analyze the current published data on health economic evaluation of family planning interventions in L-MICs, we performed a systematic review of the literature, using several databases, as shown in Chapter 2. Results from nine eligible references showed that there was diversity in strategies and interventions, and more importantly heterogeneity in outcome and effectiveness measures. The findings from this review indicated that interventions to reduce the unmet need for family planning in these regions appeared to be cost-effective; however this evidence is only supported by a very limited number of references, with a variety of measures on the outcomes, hampering comparability. In addition to being cost-effective, interventions to reduce the unmet need for family planning can directly benefit both maternal and child health as a result from reductions in the number of unintended pregnancies, especially in women that are at high risk for maternal, perinatal and child morbidity and mortality 2. Furthermore, it was also indicated from the review that women living with HIV in L-MICs constitute a particularly vulnerable group that has a considerable unmet need for family planning. Although, again, it was only supported by a limited number of studies, integrating family planning and HIV services is potentially efficient and cost-effective, especially in areas with high HIV prevalence.
In Chapter 3, we developed a decision model to estimate the long-term cost-effectiveness of improved family planning interventions to reduce the unmet need in L-MICs, using Indonesia and Uganda as reference cases. The difference in income and unmet need for family planning between these two countries as well as the use of a comparable outcome measure allowed us to comprehensively analyse the clinical and economic benefits of investing in family planning programs in different settings. The results suggested that reducing the unmet need for family planning would be a cost-effective and potentially cost saving strategy coupled with more favorable health outcomes, even in countries with constrained budgets. Notably, even though we were limited to a health care provider perspective in the analysis (and therefore only included direct medical costs), the results suggested that the intervention to reduce the unmet need of family planning would be still cost-effective, even in a low and middle-income setting with a relatively high contraceptive prevalence. Using a broader, societal perspective and more comprehensive outcome measures which capture potential long term benefits to mothers, children and society, might result in even more favorable cost-effectiveness. Indeed, such a broader perspective would better capture the long-term consequences of contraceptives that can be expected from the level of the individual household up to the national income at the aggregate level. In particular, evidence shows that, compared to areas without family planning and reproductive health programmes, improvement in women’s health and consequently productivity would give families more resources for their children, which eventually should escalate prospects for the next generation.

Screening, diagnosis and treatment of pre-eclampsia
In Chapter 4, one predisposing factor that might be associated with gestational hypertension, i.e. exposure to antidepressants during pregnancy, was described. Using a pregnancy sub-dataset of the University of Groningen prescription database IADB.nl, it was indicated that the risk of developing gestational hypertension was doubled for women with prolonged use of antidepressants during the first 20 weeks of gestation, as also shown by previous studies. Notably, this information combined with similar previous studies should serve as essential information when assessing the benefit-risk balance of antidepressants during pregnancy. Chapter 5 focused on overviewing the existing evidence on the health economics of screening, diagnosis and treatment options in pre-eclampsia through a systematic review. The results from this review highlighted the fact that economic evaluation studies on any pre-eclampsia intervention are scarce and heterogeneous in methodologies used. Ergo, valid comparisons between studies were not feasible, and general conclusions were difficult to obtain. The results suggested that novel biomarkers for both screening and
diagnosing pre-eclampsia have the potential to be cost-effective in current clinical practice, however their predictive accuracy as well as prevalence of the disease itself were uncertain factors and were shown to be major drivers of cost-effectiveness. Studies on specific treatment options were equivocal in terms of cost-effectiveness. As delivery remains the most important treatment for pre-eclampsia, it was found that induction of labour in term pre-eclampsia was more cost-effective than expectant monitoring.

In Chapter 6, we conducted an early cost-effectiveness analysis for a new test for early detection of pre-eclampsia, using decision modelling. This new test was the subject of a European study in which Ireland, the United Kingdom, the Netherlands and Sweden collaborate to develop a clinically robust predictive blood test for pre-eclampsia (IMPROvED). In an environment with still much uncertainty, twenty-five plausible exploratory scenario analyses were performed in order to set a benchmark for the minimum test performance that is needed for the test to be considered cost-effective compared to current screening practice and also to estimate the potential driving factors that influence the cost-effectiveness. The results indicated that in the four participating countries, with different settings, substantial drivers of cost-effectiveness of a new screening test for pre-eclampsia were aspirin effectiveness, prevalence of pre-eclampsia, accuracy of the new screening test and cost of regular antenatal care. As such, this study provides crucial insights into the effect of parameters on the cost-effectiveness of the new test. Moreover, the design and methodology presented in this study can serve as a basis for further evaluation when the test has become proven accurate and is readily available, potentially also in LMICs.

Implications
This thesis analyses interventions that warrant special attention in the field of women’s health across different settings. The overarching concept applied, concerns the continuum of care approach, which acknowledges the need for timely health services and interventions across the life course of women. This approach is increasingly endorsed as a means of reducing related morbidity and mortality and improving the health of women, and eventually their children. Obviously, such concepts and approaches directly relate to the goals set by global organisations as the World Health Organization (WHO) and United Nations (UN). For example, in order to achieve the goal of improving women’s and maternal health as specified in the UN Sustainable Development Goals (SDGs), substantial efforts to ensure the quality of reproductive and maternal health care for all women everywhere, are needed. These efforts could entail allocating sufficient resources to subsequently join in and contribute to evidence-based policies and interventions, including
evidence-based implementation strategies. Acknowledging the issues and responding to the specific needs, be they regional or local, is the key to efficient progress and sustainable change.

Given the alarming numbers of unmet need for family planning in L-MICs, we focus on scaling up family planning interventions in these regions as one of the priorities on the global health agenda. In this thesis, we highlight that despite the prominent aspect of family planning in global health, economic evaluation studies of family planning interventions, particularly in L-MICs, are lacking. It has been suggested in previous literature that family planning is considered to be a cost-effective intervention to improve women’s health, family and society. However surprisingly, evidence-based references which support this statement are rather limited (Chapter 2).

In order to generate conclusions regarding the cost-effectiveness of health intervention(s), economic evaluation studies are increasingly used to assist this kind of decision making. These studies are essential to inform decision makers on how to efficiently allocate resources and build a case for implementing certain interventions or strategies. For this particular reason, it is important that more high-quality, comparable and transparent economic evaluations studies be performed, particularly in L-MICs where the need for family planning is most urgent. In recent years, guidelines on how to perform economic evaluations are widely available along with an increasing number of published economic evaluations. In general, these guidelines are intended to improve and standardize the conduct of economic evaluation studies as well as to enable comparisons between studies. In Chapter 2, we employed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist to appraise the quality of reporting of the published studies included in the review. Transparency and structure in reporting is important, as health economic evaluations are largely conducted to inform healthcare resource allocation decisions, and misleading study findings could cause major opportunity costs.

The necessity to maximize outcomes with available scarce resources using economic evaluations has become essential, as demand for health services outweighs available supply. The decision analytic model in two very different settings (Indonesia and Uganda) in terms of contraceptive prevalence, unmet need and cost-effectiveness thresholds as described in Chapter 3 demonstrates how scaling up family planning interventions to reduce the unmet need is not only cost-effective but also a cost saving strategy to improve women’s and eventually children’s health and wellbeing. The results described in Chapter 3 support previous findings suggesting that investment in family planning interventions in L-MICs is a cost-effective approach with improved health outcomes for women at the individual level as well as for society at the aggregate level. Over a short time horizon, implementing a
strategy to reduce the unmet need for modern family planning interventions is probably associated with additional costs, yet it was estimated to be cost-effective. On the longer run however, these additional costs can be compensated by the savings related to the potential health benefits as a result of the interventions. Thus, while short-term net investments might be needed, this analysis provides valuable information to decision makers that these investments will be offset by future savings. The results also suggested that this strategy would be still cost-effective, even in Indonesia where the contraceptive prevalence is considered moderately high. Indonesia used to be recognized as one of the countries with the most successful family planning initiatives in the world. Nevertheless in the last decade, the contraceptive prevalence rate in Indonesia has not improved and remained stagnant. Efforts to strengthening awareness and also intersectoral collaborations among stakeholders to increase further uptake of modern contraceptives are necessary as a way to improve and revitalize family planning programs in Indonesia. Therefore, an evidence based policy to support investment in scaling up family planning programs appears warranted and justified.

For the purpose of comparability, we employed a universal metric as an outcome measure, i.e. disability adjusted life years (DALYs). As DALYs are not tied to a specific disease or patient group, but reflect a generic measure of the burden of a disease, they allow comparison across different health problems, countries and settings. The DALY is a coherent and standardized health metric that is widely used, for instance in the Global Burden of Disease Study (GBD), enabling comparative assessments over broad ranges of epidemiological patterns and across different countries and periods of time. Ergo, also the results from Chapter 3 can easily be directly compared to other cost-effectiveness analyses in different settings, diseases or populations that express ICERs per DALY averted.

Reproductive health has a broad meaning and its implementation strategies could differ depending on the situation and need. When scaling up family planning is particularly important in L-MICs, most HICs face issues in quite the opposite direction, such as low fertility growth and also an increasing number of nulliparous women with an advanced maternal age. While countries with rapid population growth may encounter adverse social, economic and environmental pressure, countries with low population growth generally experience problems related to rapid ageing of the population. In addition, the increasing age of first time mothers in HICs is associated with a rise in adverse pregnancy outcomes such as emergency caesarean sections, low birth weight, preterm birth and stillbirth. Another hidden burden with the increase in maternal age is that this could lead to problems with getting pregnant that could result in involuntary childlessness. When talking about reproductive health globally, this appears as two different and contradictory
sides of the same medal. However, both need equal attention and priority in order to improve women’s reproductive health in these different settings.

Within the second part of the thesis on maternal health issues, we focus on gestational hypertension and pre-eclampsia as the major causes of morbidity and mortality in mothers and their offspring. In Chapter 4, we investigate one of the potential factors that may be associated with gestational hypertension i.e. the use of antidepressants during pregnancy. Because it is considered unethical to assess medication use during pregnancy and its association with certain increased risk of pregnancy disorders such as gestational hypertension or pre-eclampsia in clinical trials, for these kind of research questions we must often rely on observational studies. Although randomized controlled trials (RCTs) are often deemed as the gold standard for assessing the effectiveness of an intervention, sometimes an RCT cannot answer all important questions about a given intervention, for instance when it concerns detecting rare or late adverse effects or simply because the intervention is unethical to be assessed in RCTs. In these situations, observational studies are considered more appropriate and feasible. As opposed to RCTs, observational studies are more likely to provide real-world data of what is achieved in daily medical practice. Thus, it often more relevant for implementation. In particular, we used data on a large number of prescriptions based on a pharmacy prescription database (our “in-house” IADB.nl), providing valuable information on the association of antidepressants exposure and gestational hypertension using various medication proxies. Considering the risk-benefit balance of medication during pregnancy, it is the task of maternity care providers to communicate the results of these studies to the patient, to allow them to make an informed decision about their treatment choices.

Currently, there is an ongoing argument whether a screening test additional to the maternal risk factors assessment for pre-eclampsia is cost-effective if introduced into clinical practice. Presently, advanced screening for pre-eclampsia remains to be introduced, despite some developments and novel encouraging findings using predictive biochemical markers in screening tests for pre-eclampsia. Effective screening during early gestation in pregnancy would stratify women based on their risk and consequently, even though there is no prophylactic cure for pre-eclampsia, it would enable improved prevention, management and treatment. Appropriate stratification would also allow for efficient and effective antenatal care in each group, thus reducing the cost of misclassification. Chapter 5 and 6 assess the potential cost-effectiveness of pre-eclampsia interventions, in the context of screening. Results from Chapter 5 indicate that despite extensive clinical studies in pre-eclampsia, the number of economic evaluation studies in screening, diagnosis and treatment options for pre-eclampsia remain limited. This highlights the
fact that very little is known on economic evaluation of pre-eclampsia, likely caused by the absence of a clear treatment path. It also reflects the lack of thorough understanding of its pathophysiology. Current guidelines in several countries recommend maternal risk assessment by means of the medical history of expecting mothers to evaluate their risk factors for developing pre-eclampsia. Although in clinical practice, these assessments predict just approximately 30% of women who develop pre-eclampsia, a screening test to predict pre-eclampsia using biochemical markers, either alone or in combination with maternal risk assessment still needs validation before it can be used in clinical practice. The conclusion retrieved from the systematic review suggests that screening for pre-eclampsia has the potential to be cost-effective, though some uncertainties remain. Nevertheless, given the fact that there are only three current studies on economic evaluation of screening and diagnosis for pre-eclampsia with distinct interventions, it is very difficult to draw solid conclusions.

Only few economic evaluation studies also exist for the treatment and clinical management of women diagnosed with pre-eclampsia. In addition, despite strong recommendations from international guidelines for the use of antihypertensive drugs in case of severe hypertension during pregnancy, we could not find any economic evaluation studies on this topic. Ergo, evidence on effectiveness and cost-effectiveness of antihypertensive drugs during pregnancy that includes potential effects on both the mother and their infant is currently sparse.

In the light of the current interest on the potential application of a screening test for pre-eclampsia using novel predictive biochemical markers, either alone or in combination with current maternal risk assessment, we conducted an early cost-effectiveness analysis of screening for pre-eclampsia as described in Chapter 6. An early cost-effectiveness analysis can assist the development of cost-effective novel medical interventions efficiently, while the development is still in progress. The progressive integration of evidence-based insights through feedback during the development of new technologies will likely result in a more informed decision by the test developers about its application in both the target population as well as in the healthcare system.

With current developments on potentially reliable risk prediction for pre-eclampsia, interventions to effectively prevent pre-eclampsia become more feasible. Treatment with aspirin is the only intervention that has been proven to prevent pre-eclampsia and is recommended by several guidelines, although its effect is considered modest. The WHO also recommends calcium supplementation around 1.5 – 2 g daily, for women with low dietary calcium intake, in line with evidence that low dietary calcium and low serum calcium concentrations are associated with pre-eclampsia and that high-
dose calcium supplementation is suggested to reduce pre-eclampsia. However, this recommendation is only applied in settings in which the main dietary sources of calcium are limited, because calcium supplementation is not recommended for those with normal dietary calcium intake. Therefore, in response to this recommendation as well as considering the country settings that we used in the analysis (i.e. several countries in Europe) we excluded calcium supplementation in the parameters and only included low-dose aspirin.

Before implementation in clinical practice, more research is needed to further prove accuracy and clinical utility of the test, which will enhance the view on its cost-effectiveness. Another important aspect that needs to be addressed before the implementation of this kind of new technologies concerns its affordability. Budget impact analysis can be conducted alongside economic evaluation studies to estimate the expected changes in spending of a health care system, due to the adoption of a new technology.

Last, but not least, and as a more general issue, there is a need for the advocacy of increased attention for reproductive and maternal healthcare by the stakeholders at a global and regional level. This will enhance improvement of women’s health in general and ensure women’s rights, including empowerment of women concerning their own health and healthcare. These efforts should also include fundamental shifts towards more women-centred and also family-centred care, including more comprehensive functional ties between reproductive and maternal health-care services, for instance by combining quality family planning services before planning a pregnancy, antental care during pregnancy and newborn care provision during post-partum care. These kinds of linkages are often difficult to implement and sustain, and different contexts and settings are likely to require different implementation strategies. Yet, such efforts are warranted and justified to attain maximum possible gains for the continuum of reproductive and maternal healthcare approach, globally.

**Recommendation for future research**

*Scaling up family planning interventions in L-MICs*

Following the importance of scaling up family planning interventions in L-MICs, further studies need to focus on cost-effectiveness of interventions to stimulate demand and so increase the uptake of modern contraceptive methods and assess its consequences on family planning outcomes. Interventions to generate demand comprise strategies to drive awareness on and interest in the use of modern family planning methods. Several strategies that have been implemented to escalate the demand for modern contraceptive methods over the years include community- and facility-based interventions (such as community and social mobilization, counseling with
health providers or community health workers and also home visits), financial-related instruments (voucher schemes, loan funds, or cash incentives) and mass media campaigns through radio, television, as well as commercials and advertisements 38. Overall, these interventions have shown to be associated with improvement in uptake of modern contraceptive methods, and evidence exists on the effectiveness of these strategies in improving sexual and reproductive health outcomes 39. However, recent systematic reviews reported that currently there is no evidence on implementation success and costs or cost-effectiveness related to interventions generating demand and its influence on family planning outcomes 39,40. Evaluating family planning progress is essential for driving improved programming and policy. Evidence on the cost-effectiveness of demand generation in family planning is imperative to support intervention efficiencies and to avoid repeating unsuccessful interventions 39.

Long term consequences of pre-eclampsia
There is growing evidence that pre-eclampsia is related to later health consequences for both mother and their offspring. For the mothers, it is suggested that those with pre-eclampsia are at increased risk of developing cardiovascular disease later in life 41,42. Recently, the American Heart Association reported to consider a previous history of gestational diabetes or any hypertensive disorders such as pre-eclampsia to be a major risk factor for cardiovascular disease in their guidelines 43. Thus, yearly follow up assessment on blood pressure, lipid profile, and blood glucose concentration for women who experienced hypertension in pregnancy is recommended as part of the risk evaluation. In addition, women with gestational hypertension often experience an unfavourable cardiovascular risk factor profile in the short to intermediate term following pregnancy. Cardiovascular risk factor studies estimate that approximately 30% of women who had pre-eclampsia at term during pregnancy, have hypertension and metabolic syndrome around 2 years after the delivery 44,45. Nevertheless, whether early screening and prophylactic treatment could reduce these increased short-term and/or long-term risks remains uncertain 41. Interventions aiming to create awareness to promote a healthy lifestyle in the postpartum period might help to reduce the risk, as evidence shows that lifestyle interventions including healthy dietary habits, exercise and smoking cessation could decrease cardiovascular risk by 4-13% 46.

Moreover, pre-eclampsia is known to be associated with higher rates of fetal growth restriction, preterm birth and low birthweight 47,48. Children from pre-eclamptic pregnancies are at increased risk of cerebral palsy and also bronchopulmonary dysplasia, as a result of being born preterm or small for
gestational age. Extreme preterm birth is also associated with cognitive and neurologic impairment, especially at school age.

Considering these potential long term consequences of pre-eclampsia, research on cost-effectiveness in this area is even more imperative as it could help build a strong case for the relevance of prevention, detection and treatment. Further economic evaluation research needs to explicitly take into account these long-term costs and consequences.

Pre-eclampsia in L-MICs

Pre-eclampsia along with its potential immense consequences are much more common in L-MICs than in HICs. Since pathogenesis of pre-eclampsia remains unknown, efforts to identify those at high-risk for developing pre-eclampsia are vital especially in L-MICs, to allow more intensive observation and care, for development and improvement of risk management strategies and to target only those who really need it to control costs of prevention. However, available studies have mostly been performed in high-income settings, while in L-MICs the issue of pre-eclampsia has been explored less, resulting in limited data and currently limited applicability to this setting. Given the fact that the prevalence and severity of pre-eclampsia’s adverse maternal and perinatal outcomes is higher in this particular setting as opposed to HICs, there seems to be ample room for improvement and reliable prediction of pre-eclampsia risks, holding future promises in terms of reducing the burden of this disease and improving maternal and perinatal health. Although the cost of such a screening test might be an important driver for budgets and cost-effectiveness in L-MICs in particular, the long-term benefits of testing might offset the required investment.

In line with aspects discussed in earlier sections, prevention of unintended pregnancies through accessible family planning services is also one of the important strategies to reduce pre-eclampsia especially for those at the extremes of the reproductive range. Besides the recommended low dose aspirin for the prevention of pre-eclampsia, treatment with calcium supplementation should be considered in clinical practice, as dietary calcium intake in low-income countries is generally poor. Notably, more quality research and a joint effort in the areas of maternal health, provision of quality health services and implementation of effective interventions targeting risk factors for pre-eclampsia are needed in L-MICs. Transferring results from our analyses into such settings might present a first step in this respect.
General conclusion

The continuum of care in women’s health comprises a wide range of aspects, and the interventions assessed in this thesis only cover a small fraction of it. However the findings in this thesis could contribute to inform and assist decision makers to make appropriate plans and priority actions for healthcare in the different settings. It also highlights the need for continuous research in the field of reproductive and maternal health, in order to improve women’s health and reduce preventable morbidity and mortality for women and their children in general.

Most importantly, assessment and implementation of functional linkages between reproductive and maternal healthcare services should be strongly encouraged. As this thesis emphasizes, different settings are likely to require different interventions and implementation strategies. Acknowledgment of proper and timely interventions is necessary in order to comprehensively improve women’s health. In an era with major interest for cost-effectiveness and affordability, this thesis has contributed to that overall aim with reporting on the economic aspects of family planning and controlling pre-eclampsia, with a special interest for the contexts of L-MICs.
REFERENCES


