GENERAL DISCUSSION AND FUTURE PERSPECTIVES
In this thesis, we explored two aspects of long-term health: maternal cardiovascular health and offspring cognitive development. In the next chapter we will further discuss our findings and formulate future perspectives for both aspects of long-term health. Additionally, we will discuss some challenges and opportunities in studying long-term health outcomes in general.

**PREGNANCY AND MATERNAL CARDIOVASCULAR HEALTH**

**Disorders of uteroplacental dysfunction and CVD risk in relation to ethnicity**

In this thesis, we studied the association between pregnancy disorders characterised by uteroplacental dysfunction and CVD risk in a multi-ethnic population and in relation to ethnicity. We provided evidence that the association between pregnancy disorders and CVD risk factors after pregnancy exists across different ethnic groups, without evidence of a differential association (chapter 5). This adds to the findings of previous studies, that were conducted in predominantly White women.\(^1\)\(^-\)\(^9\) We did however find differences, both in literature (chapter 2) as in our own data (chapter 5), in the absolute risk of both pregnancy disorders and CVD across ethnic groups, with women from non-White ethnic groups often at increased risk compared to White women. This might suggest that there are other factors, such as for example pre-pregnancy cardiovascular health and/or social determinants of health, that influence both the risk of pregnancy disorders and CVD risk later in life. Further research is needed to identify which factors underlie these increased risks, and how they can be effectively modified to reduce both the risk of pregnancy disorders and CVD risk across ethnic groups.

Additionally, the absolute differences in the risk of pregnancy disorders characterised by uteroplacental dysfunction across ethnicities and the increased risk of adverse pregnancy outcomes in non-White women highlights the need for the use of prediction tools that better account for the increased risk of pregnancy disorders among non-White women, for example by incorporating underlying risk factors in their risk calculation. Examples of validated first-trimester prediction tools that might potentially be able to better predict the risk of pregnancy disorders are the FMF algorithm for the prediction of preterm preeclampsia and the EXPECT prediction tool.\(^10\)\(^,\)\(^11\) Besides the fact that overall predictive ability of the FMF and EXPECT tool are superior to that of the NICE guideline criteria, its potential benefit to reduce ethnic inequalities is supported by a recent study from the UK, that showed a spectacular reduction in pregnancy disorders among non-White women to the level of White women after switching from using the NICE guideline criteria to using the FMF tool for the prediction of preterm preeclampsia.\(^11\)\(^-\)\(^15\) It would be very valuable to study if a similar reduction in the rate of pregnancy disorders among non-White women could be realised in a Dutch setting by implementation of the FMF or EXPECT tool for the prediction of preterm preeclampsia.
Cardiovascular origin hypothesis and prediction of pregnancy disorders
As described in the introduction of this thesis, there is increasing evidence that pregnancy disorders characterised by uteroplacental dysfunction are preceded by suboptimal maternal cardiovascular health before conception and during pregnancy. The hypothesis of maternal cardiovascular health as the origin of the most common pregnancy disorders states that this suboptimal maternal cardiovascular health status restrains physiological cardiovascular and hemodynamic adaptations necessary to accommodate pregnancy and for optimal placental development, resulting in pregnancy disorders characterised by uteroplacental dysfunction. From a prevention perspective, it is an attractive theory, as it would provide possibilities for preconception identification and a window of opportunity for reduction of the risk of these pregnancy disorders. In this thesis, we studied the use of pre-pregnancy lipid levels, that are associated with increased CVD risk in previous studies, for identification of a suboptimal maternal cardiovascular health status and thus preconception prediction of the risk of pregnancy disorders characterised by uteroplacental dysfunction (chapter 4). Although some lipid indices were associated with increased risk of pregnancy disorders characterised by uteroplacental dysfunction, we found little evidence that these indices, measured on average two years prior to pregnancy, could improve the prediction of these pregnancy disorders when added to two commonly used screening tools (NICE guideline criteria and EXPECT prediction tool). This could be because other factors in the prediction tools (e.g. BMI) already accounted for the increased risk, or that the interval of two years before conception is too long a period to reliably estimate cardiovascular health at conception and during pregnancy. Further research is needed to find markers that can improve prediction of pregnancy disorder before conception, offering the possibility to modify the risk profile and prevent pregnancy disorders. Two promising alternative candidates for improvement of preconception prediction of pregnancy disorders characterised by uteroplacental dysfunction could be hemodynamic function or autonomic regulation status, which can both be measured non-invasively. Two recent studies showed profound differences in these parameters before diagnoses and even before conception among women who later developed preeclampsia and FGR.16, 17 Further research on the predictive value of hemodynamic and autonomic regulation indices above traditional risk factors for the prediction of preeclampsia and other pregnancy disorders characterised by uteroplacental dysfunction is needed.

Prediction and prevention of cardiovascular disease risk
Over the past two decades, research convincingly and repetitively showed that a history of pregnancy disorders is associated with increased CVD risk.19 In this thesis (chapter 5) we build on these results and extended the knowledge on the association between pregnancy disorders characterised by uteroplacental dysfunction and long-term cardiovascular health, that was previously studied predominantly in White women, to a more diverse population. It is important that we now learn how to use the window of opportunity that pregnancy disorders offer us to prevent long-term cardiovascular
morbidity and mortality. Most professional bodies of obstetricians, general practitioners and cardiologists nowadays emphasise the need for cardiovascular follow-up after pregnancy disorders, mostly hypertensive disorders. However, there is considerable variation in recommendations, and recommendations are often vague, due to lack of evidence on optimal postpartum screening and management.\textsuperscript{15, 18-20}

A key element to improve evidence-based cardiovascular follow-up and to allow optimal use of available resources, is adequate prediction of CVD risk and identification of those at highest risk. Two previous studies investigated whether adding HDP to an established cardiovascular risk score improved discrimination or reclassification of cardiovascular risk.\textsuperscript{21, 22} Both studies found that it did not, potentially because the incremental information provided by adverse pregnancy outcomes had been partly captured by the traditional cardiovascular risk factors that were already part of the risk score. Therefore, some argue that it might be better to use history of pregnancy disorders as a screening tool for these traditional risk factors, including hypertension, diabetes and dyslipidaemia.\textsuperscript{23} Our results (chapter 5) unfortunately are not supportive of such an approach, as we found no improvement of the prediction of CVD risk factors when history of pregnancy disorders was added to a set of eligibility criteria for formal CVD risk screening, as provided in the Dutch CVRM guideline. However, the eligibility criteria in this guideline are a non-weighted set of criteria and not a formally tested weighted prediction model. This might have influenced our results. It would be interesting to test the additive value of history of pregnancy disorders in a prediction model for CVD risk factors. Additionally, effective CVRM depends on good uptake of screening, and having a history of pregnancy disorders might function as a red flag for women - when adequately educated about the associated risks - to ensure timely screening. It would be valuable to explore whether educating women about the CVD risk after a complicated pregnancy would indeed improve uptake of screening and eventually reduce CVD risk through effective CVRM.

Alternatively, one could focus on better identification of those at highest risk of CVD specifically among women with a history of pregnancy disorders based on additional characteristics, such as postpartum blood pressure, lipid levels or transthoracic echocardiography measurements. Two such prediction models were recently developed for the prediction of chronic hypertension among women with a history of preeclampsia or HDP.\textsuperscript{24, 25} Both author groups report good-to-excellent discriminative ability.\textsuperscript{25} These models should be externally validate. Once externally validated, these prediction models would be promising tools to target resources to those at greatest risk, as we know that a substantial part of the long-term CVD risk is mediated through hypertension.\textsuperscript{23}

Another approach, which is low-cost and low-effort and therefore might not necessarily rely on prediction of those at highest CVD risk, is blood pressure self-management.
Educating women about the increased CVD risk after a complicated pregnancy, and enabling them to periodically measure their own blood pressure, would put women in control of their own health. It would allow timely identification of those that develop hypertension, while at the same time keeping the majority of women that will never develop hypertension out of the system. Besides optimisation of the use of resources, a recent RCT also indicated that blood pressure self-management with physician-guided titration of antihypertensive medication might be superior in blood pressure control compared to standard outpatient care. While promising, it is crucial to ensure that such programmes are culturally sensitive, accessible and easily understandable, so they can benefit all women, and not just those in more favourable positions. Further research with long-term follow-up in a diverse population is needed to assess whether blood pressure self-management is effective in reducing the burden of CVD in women with a history of pregnancy disorders that are associated with increased CVD risk.

Finally, to be able to effectively reduce the burden of CVD, we need evidence-based interventions to modify the increased CVD risk among women with a history of pregnancy disorders. Currently, high-quality evidence is lacking, both for blood pressure management as for lifestyle interventions. Further research is needed to assess the effectiveness of programmes that ideally combine good blood pressure regulation with lifestyle modifications (i.e. diet, exercise, smoking cessation) for the reduction of the CVD burden in women with a history of pregnancy disorders.

COGNITIVE DEVELOPMENT OF THE OFFSPRING

Balancing short- and long-term risks
We showed in this thesis (chapter 6 and 7) that rates of labour induction are increasing in Australia, both in complicated and uncomplicated pregnancies. Similar trends have been reported in other high-income countries. Reasons for induction of labour are diverse, but essentially, they all boil down to two primary objectives: prevention of morbidity or mortality in the mother, and prevention of morbidity or mortality in the child. It is always a balance of risks that underlies the decision to induce labour. Sometimes it is the health risk for the mother that is balanced against the health risk for the child. Sometimes it is short-term versus long-term risks for the child. What complicates the balancing of these risks, is that not only the chance of a certain adverse outcome is relevant, but also the severity of the outcome, which is often hard to quantify and can be interpreted differently from person to person. In the case of labour induction to prevent the rare but very severe outcome of intra-uterine fetal death, we accept that we induce labour in many women to prevent a single case, and consequently, put all these children at a considerably higher risk of less severe long-term health problems related to prematurity. While this is in many cases a defensible strategy, it is crucial that it is based on accurate data on both short- and long-term risks.
and that these risks are appropriately weighed and communicated to patients. Especially long-term risks might sometimes be less visible to the obstetric care provider, and are more difficult to study reliably. In chapter 8 and 10 of the thesis, we examined such long-term outcomes, and showed that prematurity and FGR are associated with lower school performance at age 12. School performance is considered a relevant outcome, but it is still a relatively narrow measurement of long-term development. Further broad and systematic research is needed on long-term offspring development after different pregnancy disorders and interventions, to get a good understanding of the long-term effects. Additionally, attempts should be made to retrieve long-term outcomes of trials on timing of delivery and labour management published in the last two decades using registry data and advanced data linkage. This would allow targeted support for children that suffer from these long-term effects, and would aid obstetric care providers in adequately balancing the short- and long-term risks. Additionally, it is important to be aware of societal risk perception and the trend of increasing short-term risk aversity among patients and healthcare professionals, that might influence the weighing of risks.

Restrictive use of labour induction in absence of medical indication
As set out in the previous paragraph, inductions of labour often aim to reduce the risk of intra-uterine fetal death. However, we showed in this thesis (chapter 6 and 7), that the increase in induction of labour between 2007 and 2017 among uncomplicated pregnancies in Victoria, Australia, was not accompanied by a reduction in the perinatal mortality rate. At the same time, we found that labour induction even at term was associated with a subtle reduction in school performance in the offspring (chapter 9). While these results should be interpreted with caution because of the observational nature and possible confounding, it does underline the importance of continuous balancing and re-evaluation of short- and long-term risks, as set out in the previous paragraph. At the same time, it raises the question whether among low-risk populations, the current balance has perhaps shifted too much towards labour induction, potentially driven by an increased short-term risk aversion among both patients and healthcare professionals, at the cost of subtle but widespread long-term consequences. Based on our findings, we argue that it might be sensible to be restrictive in the use of labour induction in the absence of a medical indication or evidence of clinical benefit for the mother or child.

CHALLENGES IN STUDYING LONG-TERM HEALTH OUTCOMES

Use of registry and observational data
The research in this thesis was based on data from registries and observational studies. The observational nature of such research is an important limitation, as causality cannot be established. Despite our effort to adjust for confounding factors, potential residual
confounding may remain, and results should therefore always be interpreted with caution. However, use of data from registries and observational studies also has advantages, especially in combination with advanced data linkage. Primary advantages are the large available study population, time and costs efficiency and generalisability of findings. Especially for long-term outcomes, with sometimes more than 20 years between the event and the outcome, observational cohort studies and registry data offer possibilities to improve health through research and monitoring in situations where intervention studies are simply unfeasible.

It is crucial for the monitoring and improvement of long-term outcomes, that data from registries and observational cohorts are well available to researchers on the individual level, and that different datasets can be linked, while safeguarding privacy of individuals. Although the infrastructure in the Netherlands for secure data linkage is in place (i.e. the secured research environment of Statistics Netherlands), regulations, time consuming administrative processes and costs restrict the actual availability. Similar issues with complicated regulations and lengthy administrative processes are faced by researchers who want to use data collected as part of standard care to study (long-term) outcomes. To facilitate research of long-term outcomes, access to registry and other observational data should be improved, for example by removing financial barriers and by adjusting regulations that prohibit the use of important data to improve health outcomes. An important example of such regulation changes would be switching from an opt-in to an opt-out consent procedure for all observational research, preferably at the moment the patient first enters the healthcare system.

**Incorporation of long-term outcomes in intervention studies**

Besides improving possibilities for observational research, it is important to incorporate long-term outcomes in intervention studies where feasible, as long-term outcomes in many situations bear great significance to patients. Currently the incentive for brisk results and publications might stand in the way of such actions, as well as limited availability of funding. Funders and policy makers setting the research agenda should stimulate and facilitate incorporation of long-term outcomes in intervention studies in situations where these outcome matter.

**CONCLUSION**

In this thesis, we explored different long-term effects of pregnancy disorders for both mother and child. We showed that women, irrespective of ethnicity, are at increased risk of CVD after a complicated pregnancy. At the same time, pregnancy disorders offer a window of opportunity to identify this increased risk early in life and to modify it in order to reduce the burden of CVD later in life. We need better tools to predict both pregnancy disorders and CVD after pregnancy, and better screening and intervention
strategies aimed at risk reduction. For the offspring, we concluded that pregnancy characteristics and obstetric management are associated with long-term cognitive development and that short- and long-term risks should be appropriately weighed. Overall, we argued that it is important that long-term outcomes are incorporated in future research, providing a scientific basis to positively impact long-term maternal and offspring health.
REFERENCES


Chapter 12


