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## Care for women across critical junctures during the reproductive years

*Reproductive choices, pregnancy and menopause*

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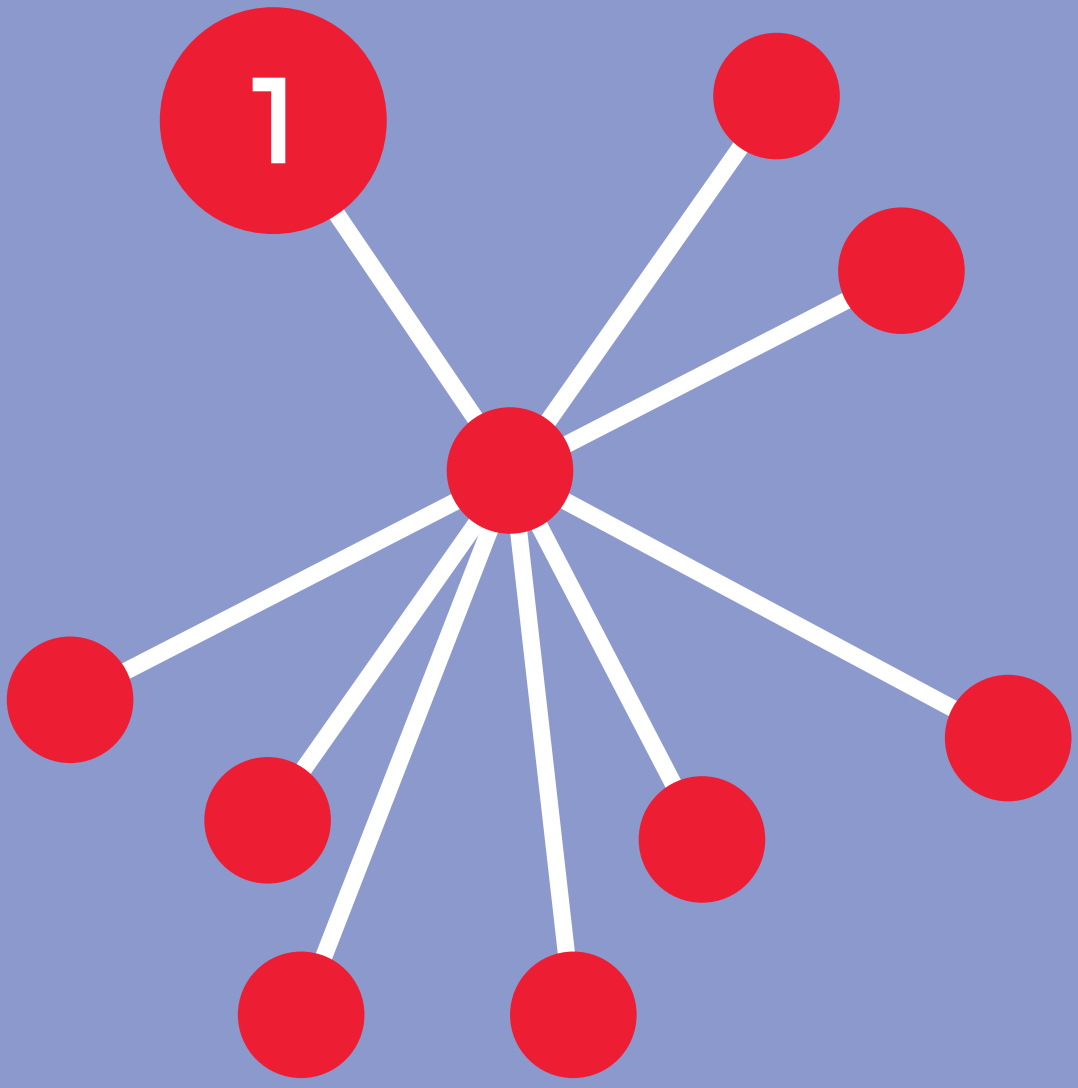
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# GENERAL INTRODUCTION

# Health of women

While women[1] generally live longer than men in all regions of the world, they spend more years in poor health (1, 2). Due to the lower mortality and higher morbidity, women have approximately 500 fewer healthy days over their lifetime compared to men (3, 4). Importantly, the loss of healthy years occurs mainly during working years (ages 20-64), affecting health, well-being, productivity, and economic potential (1, 3). Timely diagnosis and treatment of the most prevalent health challenges that women face (which include experiencing burdensome symptoms during the menopause transition and cardiovascular disease (CVD)) would not only improve the lives and positions of individual women but is also beneficial for society as a whole (4).

Despite recent increasing advocacy for advancements in research on women's health, women remain underrepresented in research, and funding for research dedicated to improving women's health specifically is insufficient, with less than 1% of research funding in the Netherlands dedicated to women specific health issues (4, 5). As a result, there is still a lack of knowledge to guide targeted prevention, diagnosis, and treatment for women (6-8). To improve women's health and wellbeing, more research is needed on health differences, risk factors, and specific healthcare needs. This is even more relevant for women in vulnerable positions, such as women in lower socioeconomic positions and women from ethnic minority groups, who may face more prevalent risk factors for disease and limited access to care, and more often encounter biases and a disregard for cultural differences (9, 10).

The distinct health care needs of women are shaped by several social and biological factors, including factors related to sex and gender (see Box 1 for details) which can impact disease patterns, such as occurrence and progression, and health care behavior.

1 *The studies in this work mostly involved individuals who selfidentify as women and were assigned female sex at birth. For this reason, the term women is used throughout. However, the experiences concerning reproductive planning, pregnancy, and menopause may be relevant to anyone with a uterus, regardless of gender identity. In some chapters, the terms womxn and mxn are used to acknowledge this diversity and to meet the editorial requirements of the respective journals.*

*Box 1 Understanding Sex and Gender related factors*

**Sex** refers to the biologically determined differences between males, females, and intersex persons. These differences involve physical and physiological features such as genes, hormones, and anatomy. For example, males and females on average have different levels of hormones like testosterone and oestrogen, which influence various biological processes.

**Gender,** encompasses the effects of social norms and societal expectations that differ for men and women. These norms create and justify different opportunities and access to resources for men and women within societies. Gender influences how individuals perceive and present themselves, their attitudes and experiences, and their behaviours in families, workplaces, and in society.

Three interrelated gender domains interact on individual and interpersonal levels: gender identity, gender roles, and gender relations. Gender identity refers to an individual's perception of their own masculinity or femininity. Gender roles describe the expected behaviours of men and women, while gender relations reflect interactions between individuals based on their ascribed gender. These norms are shaped within the domain of institutionalized gender, which refers to the distribution of power between men and women within societal structures such as politics, legislation, the labour market, healthcare, and education.

It is important to understand that while sex and gender are distinct concepts, they also interact. Biological factors (sex) and social/contextual factors (gender) can influence each other in complex ways. For instance, societal expectations (gender) can impact health behaviours, which in turn can affect biological outcomes. Acknowledging the distinction and interplay between sex and gender helps to better understand the diverse experiences and needs of individuals. (Adapted from (11-13))

It is commonly believed that differences in disease patterns between women and men relate to biological factors involving, genetic predispositions, reproductive organs and hormones. For instance, slower disease progression and higher prevalence of chronic kidney disease (CKD) have been related to higher levels of oestrogen and lower levels of testosterone in women (14). Moreover, common risk factors for chronic diseases such as smoking, hypertension and body mass index (BMI), impact the female body differently than the male body, resulting in a higher relative risk increase for several conditions in women compared to men (15). On top of this, women experience on average one or

two female-specific health-related challenges during their lifetime, such as pregnancy complications or menopausal symptoms (4), which may also impact their future health.

It is less commonly considered that sociocultural factors also play an important role shaping the distinct health care needs of women. Health behaviours, care-seeking patterns, as well as ingrained societal biases and societal expectations vary between men and women (11). These variations affect disease presentation, diagnostic efficacy, the availability of effective treatments, and healthcare access and delivery (4). For example, there is ample evidence of sociocultural differences in the diagnostic and care trajectories of men and women from research on CVD, a leading cause of disease and disability among women (5). CVD risk prediction tools tend to underestimate the risk in women (6). The tools were historically calibrated on male populations and clinical norms. Excluding women from such research was common for that period and reinforced systemic biases rooted in gendered assumptions about disease occurrence, presentation and progression. Both women and healthcare providers are also often unaware that women can present with different CVD symptoms than men, potentially contributing to delays in diagnosis (7). For instance, women more often experience symptoms such as fatigue, nausea, or shortness of breath while the more 'classic' chest pain presentation is typically associated with men. Diagnostic delays may subsequently affect prognosis. On top of this, women also have worse prognosis after CVD events because they are less likely to receive timely and adequate treatments due to gendered patterns in healthcare access and provider bias (8).

To improve the health of women, it is particularly important to understand the biological and sociocultural factors and how they interplay. This interplay becomes especially visible during key reproductive events, when major biological and sociocultural changes occur. Thus, the reproductive years potentially offer windows of opportunity for improving care for women's health, including prevention. In addition, the reproductive years greatly overlap with the working years. Besides improved health, improvements in care and prevention can contribute to preserving or enhancing women's economic power which is known to reduce substantially around pregnancy and menopause (16-18).

# Critical junctures during women's reproductive years

The reproductive years include major events that can dramatically reshape women's lives, affecting health through their influence on both biological and sociocultural factors. Pregnancy and menopause are obvious examples, involving significant hormonal changes and shifting societal expectations related to motherhood and aging, that may affect health in the short and long term (19). Reproductive choices, although not representing a single reproductive event, are a recurring element during the reproductive years that may affect health and wellbeing. Choices about having children, how many, and their spacing directly impact educational, social, and economic opportunities, which have been associated with future health outcomes (20, 21). Thus, reproductive choices, next to pregnancy and menopause, can be seen as critical junctures for women's health (see Box 2).

*Box 2: Critical junctures in women's health*

A *critical juncture* is a concept borrowed from historical institutionalism, describing a pivotal moment in time with long lasting consequences (22). It marks a period of transition in which choices or conditions can significantly alter future trajectories.

During the reproductive years, women encounter a sequence of critical junctures that are biologically and socially transformative. Reproductive planning, pregnancy, and menopause are examples, though many other critical junctures shape women's health across the life course. These moments potentially represent opportunities in which health can be lost or accumulated, as each stage involves exposures that shape the trajectory of future health and well-being.

At critical junctures, specific care for women, such as contraceptive counselling and care during pregnancy and menopause, may relate to immediate improvements in health and wellbeing. On top of this, these critical junctures may also signal opportunities for prevention of future disease. Some reproductive events have been linked to a higher risk of future diseases and can possibly serve as risk markers or intervention targets. For instance, continued postpartum glucose monitoring in women with a history of gestational diabetes is widely implemented internationally for early detection and prevention of type II diabetes (23).

However, opportunities for care and prevention remain underutilized because knowledge on specific healthcare needs of women and evidence on targeted prevention during the reproductive years, is limited. In particular, a lack of understanding about the barriers and needs for care at critical junctures remains, hindering the development of effective

interventions. Therefore, this work covers three critical junctures during women's reproductive years. Firstly, the focus lies on the critical juncture of reproductive choices, particularly on contraceptive behaviour prior to an unintended pregnancy and the decision making that follows. At the second critical juncture, associations are examined between pregnancy complications and cardiovascular risk factors and, additionally, the related patient and provider experiences with CVD preventive care. Thirdly, age at menopause before the age of 45 years is explored as a potential risk marker for CVD and CKD and whether this factor can help improve sex specific recommendations, such as for screening.

## Reproductive choices

Deciding whether to have children, how many, and when, is a pivotal choice. In 1968, the right to make such reproductive choices freely and responsibly was declared a basic human right, and this has been reinforced in several declarations since (24). Achieving the desired family size requires access to information, methods, and means, collectively known as reproductive planning. Reproductive planning includes both conceiving and avoiding pregnancy and may involve interventions from fertility treatments to contraception (20, 25).

In the last decades, the desired and actual family size have decreased while the age at a first child has increased (26, 27). As a result, women now spend more years preventing pregnancies throughout their lives, sometimes up to 30 years (28). Any behaviour to intentionally prevent a pregnancy falls under the scope of contraception, which can involve modern methods like devices, medication, surgical procedures or practices such as withdrawal and (periodic) abstinence (20). Nevertheless, since all contraceptive methods have a failure rate, unintended pregnancies can never be completely avoided (29).

It is often assumed that those who do not have an active desire to get pregnant will use contraception and will do so consistently. However, pregnancy intentions do not always align with contraceptive behaviour. Many people who do not want to get pregnant, do not use contraception despite access to contraceptive care (30, 31). Studies on contraceptive behaviour have, so far, mainly focused on adolescents and high-risk populations, leaving contraceptive behaviour of other (adult) groups understudied (32). Qualitatively investigating the lived experiences that resulted in failed, non-use or inconsistent use of contraceptives, can help improve contraception counselling and support the design of patient-centered reproductive health programs.

When faced with an unintended and unwanted pregnancy, women can either decide to carry the pregnancy to term (and become a parent, choose adoption, or foster care)

or choose an abortion. In 2022, the government of the Netherlands called for research on the reasons for abortion to inform policy and to improve prevention and care (33). Literature reviews show that women consider multiple factors when deciding for abortion, including their own needs, their partners' perspectives, responsibilities towards family, and their material context (34-36). These motivations are rarely singular and are often interdependent. Decision making is multifaceted and involves the initial emotional reactions upon discovery of the pregnancy (37-40). Life circumstances also play a role, and while certain sociodemographic characteristics are linked to abortion, their influence on decision-making is unclear. Combining qualitative and quantitative data on rational, emotional and contextual motivations for abortion may help understand the lived reality of women. This deeper understanding can guide and how to best support women and ensure they receive the care they need, regardless of their decision.

## Cardiovascular risk after complicated pregnancy

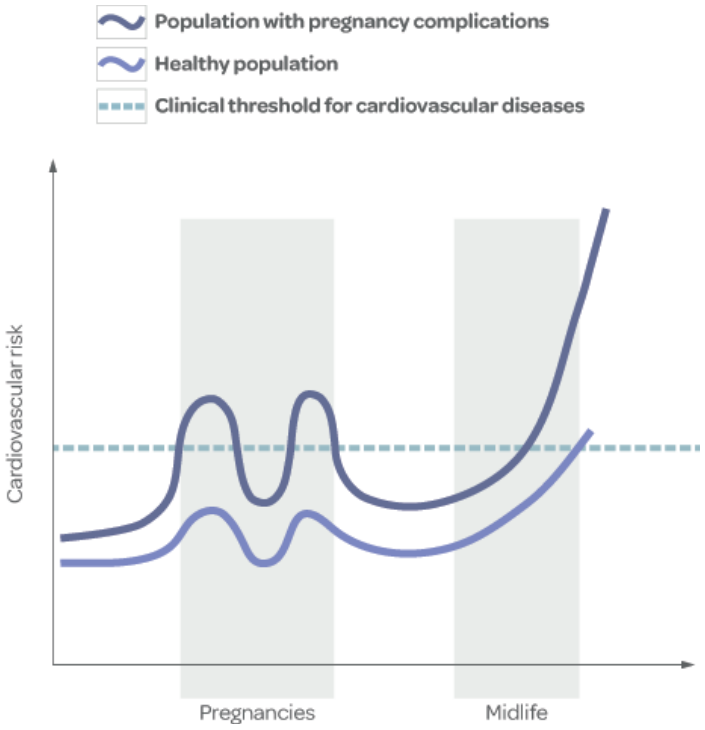
Pregnancy, whether intended or unintended, is not without risks. Pregnancy complications such as those related to uteroplacental disorders are common. For instance, hypertensive disorders of pregnancy (HDP) affect about 10 to 22% of pregnancies globally while gestational diabetes affects 4 -14% of pregnancies (41-44). The prevalence of both HDP and gestational diabetes varies based on region and living conditions, with ethnic minority groups at higher risk compared to white majority populations in Europe (42, 45, 46). These complications can not only harm the child, but also the mother (46, 47).

Pregnancy complications have been associated with a 2-to-4-fold increased risk of maternal CVD later in life (47-51). In women who experienced a pregnancy complication, CVD may also occur at a younger age than in women who experienced a healthy pregnancy. For example, women with HDP experience their first cardiovascular event on average five years earlier than women with a healthy pregnancy (64.8 versus 71.8 years, respectively (52)). Yet, prevention strategies are traditionally targeted at those over 50 years of age (53, 54). Having an obstetric history with pregnancy complications may serve as an early risk marker and highlights a window of opportunity to identify women at higher risk and to prevent CVD (55).

A key knowledge gap is whether pregnancy complications directly contribute to the elevated future CVD risk or whether they reveal an a priori elevated risk (see Figure 1). Current evidence from available longitudinal cohort studies, mostly in non-European contexts and in white populations, is inconclusive (56-60). Moreover, young women with high CVD risk, particularly those from minority groups, are underrepresented in most of these studies limiting our understanding of the impact of pregnancy complications on cardiovascular health across different groups of women living within a similar context

(61). In Europe, women from several ethnic minority groups have a higher burden of cardiovascular risk markers and a higher prevalence of pregnancy complications compared to majority populations (46, 62). Investigating the relationship between pregnancy complications and changes in CVD risk profile around pregnancy can enhance the understanding of their role in the development of CVD. In addition, consideration of pregnancy complications as a risk marker may help identify those at high risk, and guide more timely interventions in multi-ethnic populations.

*Figure 1: Depicts the development of cardiovascular risk in a healthy population versus a population with pregnancy complications. Made by Consortius for the HELIUS-Perined project.*




Recently, guidelines have been introduced for cardiovascular risk management (CVRM) after a reproductive disorder, including pregnancy complications. These guidelines recommend periodic monitoring of blood pressure and glucose levels for women after HDP and gestational diabetes (63). It is unclear how well these recommendations are adhered to in practice. Moreover, the guidelines fall short on providing concrete strategies for implementation of CVRM, largely due to limited evidence on how best to prevent CVD in younger women following pregnancy complications. Information is lacking on the preferences, needs, and barriers of women with diverse ethnic backgrounds and their care providers in the Dutch healthcare system. Qualitative research can help address these gaps and inform more targeted and inclusive prevention efforts.

## Early menopause and chronic disease

Menopause marks the end of the reproductive years and is defined as the last day of a woman's final menstrual cycle, determined retrospectively after 12 consecutive months without menstruation (64). Although menopause itself is a single moment, the transition spans three to seven years on average and involves a significant reduction in oestrogen production. During the transition, women may experience symptoms related to this oestrogen decline, such as issues with body temperature regulation, sexual functioning, sleep quality, and mood (65). Oestrogen also plays a role in many other physiological functions, such as bone formation and vascular function.

While most women experience menopause between 45 and 55 years of age, about 8% of women living in high-income countries experience menopause before the age of 45 years, defined as early menopause (EM, (66)). Women who enter menopause earlier, lose the physiological benefits of oestrogen sooner, which has been linked to a higher risk of chronic conditions like osteoporosis, heart disease, and renal disease (67). For instance, a large study, across 15 regions in the US, UK, Scandinavia and Japan has shown that EM is associated with a 30% increased risk of incident CVD up to the age of 60 years (68). Just like with pregnancy complications, the mechanisms through which EM and CVD are associated are complex and whether the relation is causal or partly correlational is not fully understood. Still, the fact that EM marks a group of women with an increased risk of CVD later in life, potentially advances the window of opportunity in which these women can be identified through periodic monitoring and additionally, in which modifiable risk factors can be addressed as part of CVRM (69).

In the Netherlands, systematic CVD risk screening in general practice is currently indicated for women who fulfill one or more eligibility criteria for CVD risk screening such as being over 50 years of age, with a family history of CVD or with hypertension or elevated lipid levels (53, 54). EM could serve as an additional criterion for screening, as it can be identified from patient history. This may be particularly relevant in younger women from minority groups, who often have a higher CVD risk at a younger age and are frequently missed by the current eligibility criteria for CVD risk screening (70, 71). Investigating the contribution of EM to existing eligibility criteria can identify a relevant opportunity improve the detection of women with high CVD risk in multi-ethnic populations in the Netherlands.

Another chronic disease linked to EM is CKD, which affects 800 million individuals worldwide (72). In the Netherlands, the overall prevalence of CKD has been estimated to be approximately 9% (73). CKD is a progressive disease, with high morbidity and mortality rates, and is also a risk factor for CVD (74). Compared to men, women have a higher prevalence of CKD, but its progression is often slower (75). Oestrogen exposure

reduces CKD risk. This potentially explains why EM, and thus earlier decline of oestrogen, is associated with higher CKD risk and adverse changes in kidney function (76-78). Both the prevalence of EM and CKD have been shown to differ by ethnicity, and both have been independently associated with increased health risks (19, 73, 77, 79). However, there is a lack of longitudinal studies exploring the relationship between EM and CKD incidence and progression across different ethnic groups and exploring to what extent associations may, in part, be mediated by traditional CKD risk factors (80). Since traditional CKD risk factors are important targets for prevention that partly overlap with factors targeted for CVRM, a better understanding of their role may help inform the development and improvement of preventive strategies.

## Aim of this thesis

The aim of the studies presented in this thesis is to identify opportunities to improve care, including preventive interventions, for women around three critical junctures during the reproductive years. Specifically, the work is divided in three parts that focus on contraceptive behaviour and reproductive decisions, on opportunities for care and prevention of cardiometabolic disease after complicated pregnancy and on opportunities after early menopause: The specific research questions for each part are:

1. What shapes failed use, inconsistent use and discontinuation of contraception preceding unintended pregnancies? After the discovery of an unintended and unwanted pregnancy, how do emotional, rational and contextual motivations for abortion interplay?
2. What are the changes in the maternal CVD risk factor profile around pregnancy in women with a complicated pregnancy compared to women with a healthy pregnancy, in a multi-ethnic population? Additionally, what are the experiences, barriers, and potential improvements in postpartum CVRM from the perspective of women and healthcare providers.
3. Can early menopause (EM) status contribute to the identification of women at high risk of CVD on top of current eligibility criteria for CVD risk screening? Additionally, how does EM associate with kidney function decline in women from a multi-ethnic population and to what extent this is mediated by traditional CKD risk factors?

## Outline of this Thesis

Following the introduction and aims, this thesis is organized into three parts:

In **Part I**, the immediate consequences of reproductive planning for women are explored, focusing on contraceptive behaviour preceding unintended pregnancies and the interplay of various motivating factors for abortion.

In **Chapter 2**, what shapes the use, non-use, inconsistent use, or discontinuation of contraception before an unintended pregnancy is investigated. This analysis is based on qualitative data from 56 in-depth interviews within the Aanvullende Vragen Onbedoelde Zwangerschap (AVOZ) study (81).

In **Chapter 3**, women's rational, emotional and contextual motivations for abortion are explored and combined into motivational patterns related to personal and contextual circumstances. This chapter uses secondary qualitative analyses of data from the Dutch Abortion and Mental Health Study (DAHMS ,(82, 83)) and the BluePrInt study (84, 85).

In **Part II** of this thesis, the temporal association of pregnancy complications with CVD risk is examined and the healthcare needs and preferences of women and providers for management of CVD risk factors after a complicated pregnancy are explored.

In **Chapter 4**, changes in maternal cardiovascular risk profiles surrounding complicated versus uncomplicated pregnancies in a multi-ethnic population are investigated. This analysis uses quantitative data from the Healthy Life In an Urban Setting (HELIUS) study, linked to Dutch perinatal registry data from Perined (86-88).

In **Chapter 5**, experiences, barriers, and potential improvements in postpartum CVRM from the perspectives of women and healthcare providers are investigated, aiming to enhance cardiovascular disease prevention in multi-ethnic contexts. Qualitative data were collected from 25 women of different ethnic backgrounds who experienced pregnancy complications and 16 healthcare providers, including midwives, general practitioners, practice nurses, gynaecologists, and internal medicine specialists.

**Part III** of this thesis focuses on the timing of menopause, specifically EM, in relation to long-term chronic cardiometabolic disease risk and its contribution to existing CVD risk screening criteria. Both chapters use data from the HELIUS study (86, 88).

**Chapter 6** investigates the contribution of early menopause (EM) to current criteria from patient history (family history of CVD, current smoking, obesity, and age over 50) for identifying women eligible for CVD risk screening in a multi-ethnic population.

**Chapter 7** examines whether EM is associated with faster age-related kidney function decline in women from a multi-ethnic population and to what extent this is mediated by traditional CKD risk factors.

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