Differences in cardiovascular disease risk between men and women in a multi-ethnic population

Let's talk about sex and gender

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Chapter 1

General introduction

Burden of cardiovascular diseases

Cardiovascular diseases (CVDs) are a major public health problem worldwide.[1] The global burden of CVD has increased significantly in the past three decades. For instance, mortality of CVD has increased from 12.1 million deaths in 1990 to 18.6 million deaths in 2019. Additionally, the number of disability adjusted life years (DALYs) due to CVD has doubled from 17.7 million to 34.4 million in the past 30 years. While CVD mortality in the Netherlands decreased by 70% between 1980 and 2019, CVD still comprise the second highest cause of death, after cancer.[2] On average, 50 men and 53 women died every day in 2019 due to CVD, corresponding to an annual total of more than 37,000 CVD deaths. In the same year, around 152,000 hospitalizations due to CVD were reported among men and around 103,000 among women in the Netherlands.

Differences in cardiovascular disease risk between men and women

Although the burden of CVD is substantial in both men and women, CVD is often still considered primarily a men's disease. This view of CVD as a men's disease is partly due to the generally higher incidence of CVD in men compared to women.[3] In addition, men tend to develop some types of CVD at a younger age than women. For instance, men are more likely than women to present with myocardial infarction as a first CVD event and are on average 10 to 15 years younger at the time of this first CVD event.[3-5] However, while the overall risk of myocardial infarction is about three times higher in men, the difference with women decreases with increasing age, being largest in younger age-groups (below 50 years) and smallest in older age-groups (above 70 years).[3, 5, 6] These age patterns in risk differences vary by type of CVD. For instance, while women also tend to have an overall lower risk of stroke than men, they are at higher risk compared to men at young age (below 35 years) and old age (above 80 years), suggesting a U-shaped pattern of risk differences.[7, 8]

Importance of understanding differences in cardiovascular disease risk between men and women

Due to the generally higher CVD risk among men compared to women, research and policy on CVD has been mainly focussed on men. As a consequence, CVDs in women have been understudied, under-recognised, underdiagnosed, and under-treated.[9] In addition, the causes underlying the differences in CVD risk between men and women are still poorly understood.

Women are likely to benefit most from more insights into differences in factors associated with CVD risk between men and women. Current CVD prevention strategies are suboptimal for women, as risk assessment tools particularly underestimate CVD risk in women.[10, 11] The underestimation of risk is especially

detrimental for women, as survival rates after a CVD event are generally worse in women than in men.[12, 13] These lower survival rates are not only due to more advanced age of women when they first present with CVD, but may also be due to inadequate health care as a result of a lack of prevention, diagnosis, and treatment strategies that are well-tailored for women.[13-15] For instance, women with acute myocardial infarction who are eligible for primary reperfusion therapy are less likely than men to receive this treatment within recommended timeframes.[15] Evidence from the USA suggests that women from ethnic minority groups may have the worst outcomes after a CVD event. For instance, the 5-year risk of death after a first myocardial infarction in 2017 was the highest in black women compared to black men, white women, and white men.[16] It has been argued that this may partly be the result of the particularly high underrepresentation of these groups in research, potentially leading to missed opportunities in (preventive) care specifically targeted at the needs of these groups.[17]

Explanations for differences in cardiovascular disease risk between men and women: the distinction between sex and gender

Differences in CVD risk between men and women may occur because of differences in the occurrence of conventional CVD risk factors, such as hypertension and hypercholesterolemia. In high income countries, these factors are generally more prevalent among men than women, particularly before the age of 60 years.[18, 19] However, these differences only partly explain the disparities in CVD risk.[3, 4, 20] Furthermore, it has been suggested that some conventional CVD risk factors may differentially impact CVD risk in men and women, but this appears to mostly disadvantage women compared to men.[6, 21] For instance, women with diabetes have a 40% higher risk of incident coronary heart disease and a 27% higher risk of incident stroke than men with diabetes.[6, 22, 23]

Other potential explanations for differences between men and women may be sought in factors related to sex and gender.[24-27] Although the distinction between sex and gender is well-established and widely acknowledged in social sciences,[28-30] the concepts are more novel in health research.[31-35] The distinction between sex and gender is important since sex and gender may relate to cardiovascular health differently.

Sex refers to biologically determined differences between males and females (and intersex persons) and involves physical and physiological features, such as genes, hormones, and anatomy.[31-33, 36] Several effects of sex and sex-related factors on CVD risk have been proposed. For instance, the relative cardiovascular advantage of women compared to men at a younger age is often related to differences in the levels

of sex hormones. Here, a prominent role is ascribed to the protective effects of oestrogen against the development of CVD in premenopausal women.[37-39] However, this hypothesis is under debate as trials on hormone replacement therapy for preventing CVD in postmenopausal women have yielded conflicting results.[40] Moreover, it has been argued that the rise in CVD incidence rates after menopause transition is too small to be mainly explained by the loss of the protective effects of oestrogen.[3] In addition to sex hormones, emerging evidence shows strong associations between female-specific factors related to reproduction and CVD risk.[41-43] For instance, women with a pregnancy complicated by gestational hypertension or preeclampsia have a 1.5 to 2 times higher risk of future CVD compared to women without these pregnancy complications.[41]

Gender is a social construct and refers to effects of social norms and societal expectations that are different for men and women and that create and justify differential opportunities and access to resources for men and women within societies.[31-33, 44, 45] In epidemiological research, gender is about how individuals conform to these norms and expectations, and how this influences the way they perceive and present themselves, their attitudes and experiences, and which behaviours they exhibit in families, workplace, and society. Three interrelated gender domains have been identified that interact on individual and interpersonal levels: gender identity, gender roles, and gender relations (Figure 1).[31] Gender identity refers to the perception of an individual's own masculinity or femininity. Gender roles describe the expected behaviours of men and women. Gender relations reflect interactions between individuals based on their ascribed gender. The gender norms that influence the identity, roles and relations 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, labour market, healthcare, and education. Gender is considered a fluid and contextual concept as gender norms tend to vary by culture, era, and age.[31, 32] Recent studies show that traditional gender roles and gender stereotyping, such as the man being 'the breadwinner' and the woman being 'the main caretaker' within households, are still deeply embedded in contemporary societies,[46-48] also in the Netherlands.[49, 50]

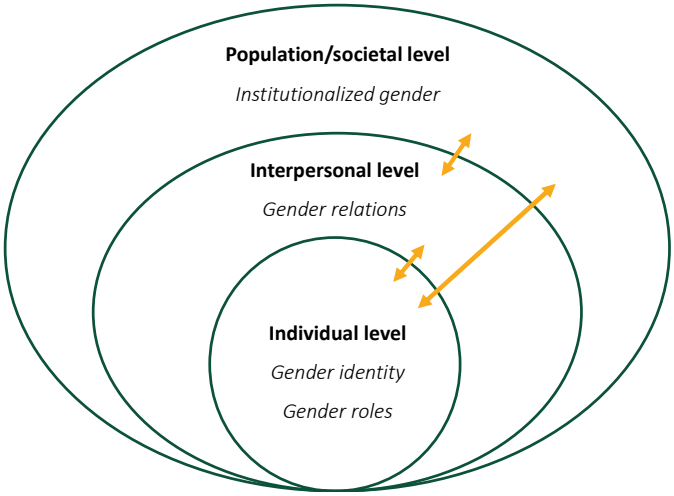

Figure 1. Four gender domains as defined by Johnson et al.[31] Figure adapted from Tadiri et al.[51]

Gender may directly or indirectly, and independently of sex, impact on cardiovascular health, for instance, through differences in health-related behaviour, vulnerability to exposures and stressors, or access to and use of (preventive) treatment (Figure 2).[34-36, 52] For instance, it has been hypothesized that younger men may be at higher risk of CVD than younger women due to higher engagement in behaviours that are considered as 'masculine' in western societies, such as smoking.[53] Moreover, sex and gender may interact in their influence on health.[31-33] For instance, it has been suggested that women who smoke may be at higher risk for CVD than men who smoke, potentially due to the greater absorption of toxic agents from cigarettes.[54]

There has been a strong advocacy for the inclusion of both sex and gender dimensions in health research.[31-36] There is no 'gold standard' for the measurement of gender in health research, but several studies have attempted to operationalise gender. Miani and others have recently provided an extensive overview of gender measures published in epidemiological research up to February 2021.[55] There is also an increasing interest for the inclusion of the gender dimension within cardiovascular research practices.[24-27] One of the first and most well-known attempts is the gender score created by Pelletier and colleagues.[53] In a cohort of hospitalized patients with premature acute coronary syndrome, they created an overall gender score from a selection of seven psychosocial variables that were assumed to differ between men and women (e.g., time spent on household work, primary earner status). Using this gender score, they investigated whether gender was associated with CVD risk factors[53] and recurrent acute coronary syndrome and major adverse cardiac events,[56] independently of sex.

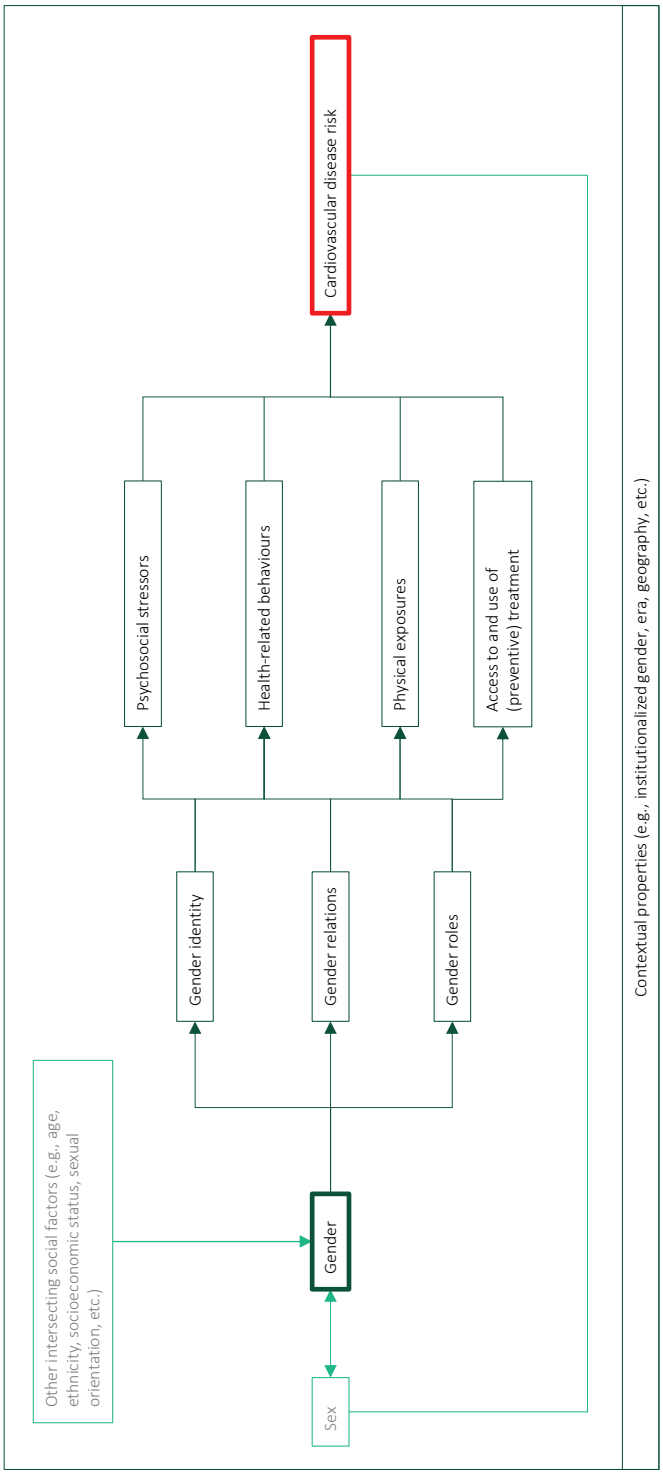

Figure 2. Conceptual framework of the association between gender and CVD risk (R. Bolijn and I.G.M. van Valkengoed)

Differences in cardiovascular disease risk between men and women across ethnic groups

Ethnic disparities in CVD risk within populations have been widely reported. For instance, some ethnic minority groups, such as South-Asians living in Europe, are at higher risk for CVD compared to majority populations.[57-59] However, few studies have investigated whether differences in CVD risk between men and women vary by ethnicity. Nevertheless, the limited evidence thus far suggests that differences between men and women cannot be generalized to all ethnic groups within a similar context. For instance, two studies from the USA observed that the sex disparity in prevalence of CVD[60] and in coronary heart disease mortality[61] is smaller in black individuals compared to white individuals. Both studies observed that the smaller sex gap was driven by higher rates of CVD in black women compared to white women, while these rates were more similar among black men compared to white men. In contrast, a Dutch study on sex disparities in myocardial infarction incidence found a smaller sex difference in the Dutch majority population compared to most minority populations, with the most pronounced sex disparity among groups originating from Morocco, South-Asia and Turkey.[62]

The evidence that patterns of differences in CVD risk between men and women may differ across subpopulations, such as ethnic groups, fits well within the theoretical framework of intersectionality. This framework may help to better understand if and why differences in CVD risk between men and women are not equal across subgroups within populations. The intersectionality perspective states that a person's identity factors (e.g., gender, ethnicity, socioeconomic status, sexual orientation) interact, which may affect individual experiences differently than when only single identity factors are considered.[63-65] Within the public health context, this interaction of multiple social factors may create health inequalities that are ultimately the result of power and oppression systems, such as racism and sexism, leading to privilege for some individuals and marginalisation of others.[63, 66] Although very common in qualitative research, this framework is more novel within the field of quantitative research.[67-69]

Aims and objectives of this thesis

The ultimate general aim of our research is to enhance our understanding of differences in CVD risk between men and women across ethnic groups, and of the sex- and gender-related factors associated with these differences.

The specific objectives are:

1. To describe sex differences in CVD risk in a multi-ethnic population.
2. To explore associations between gender characteristics and CVD risk in men and women.
3. To determine to what extent differences in CVD risk between men and women can be explained by differences in health-related behaviours.

Outline of this thesis

The increased attention in academia for research into sex- and gender-related CVD risk factors in men and women raises the question whether this vision is shared by the target population (people with CVD or at increased risk), and, if so, which risk factors according to them should be prioritised for investigation of factors underlying risk differences between men and women. Insights into the prioritization among the target group may guide both funders and researchers. In **part 1** of this thesis, we therefore studied which conventional risk factors and sex- and gender-related risk factors were prioritized for more research in our study and beyond by a panel of men and women with CVD or at increased risk in the Netherlands (**chapter 2**). This provided inspiration for the work described in **part 3** in this thesis and for other studies not included in this thesis.

In **part 2**, we assessed questions related to objective 1. Specifically, we examined sex differences in prevalence of major ECG abnormalities (**chapter 3**) and in incidence of out-of-hospital cardiac arrest (OHCA; **chapter 4**). We also investigated whether these sex differences were consistent across ethnic groups (**chapters 3** and **4**) and across socio-economic groups (**chapter 4**).

In **part 3**, we examined questions related to objectives 2 and 3. Specifically, we investigated whether gender-related characteristics were associated with estimated 10-year risk of CVD (**chapter 5**) and CVD incidence (**chapter 6**). In **chapter 5**, we also analysed whether the associations were similar across ethnic groups. In addition, we studied whether differences in CVD incidence between men and women were explained by differences in health-related behaviours, also across ethnic groups. In **chapter 7**, we describe our findings regarding smoking. The findings on the other health-related behaviours are discussed in the general discussion.

Data sources

For the research in this thesis, three data sources were used.

Harteraad panel

For **chapter 2**, we invited all members of a panel of a Dutch national CVD patient advocacy group (*Harteraad*) to take part in an online survey (https://harteraad.nl/harteraadpanel/). At the time of invitation, the panel consisted of 2,369 CVD patients, persons linked to CVD patients (partners, parents/legal guardians, and caregivers), and people at self-reported, increased risk of CVD (e.g., those with diabetes, hypertension, overweight). The panel regularly receives surveys from healthcare professionals, researchers, and policymakers to report on their experiences with cardiovascular health.

HELIUS

For **chapters 3** and **5**, we used baseline data from the Healthy Life in an Urban Setting (HELIUS) study.[70, 71] HELIUS is a multi-ethnic population-based cohort study and includes participants of Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Turkish, and Moroccan origin aged 18-70 years living in Amsterdam, the Netherlands. Potential participants were sampled with a simple random sampling method from the municipality registry, after stratification by ethnicity. Around 90,000 inhabitants of Amsterdam were invited, of whom 24,789 agreed to participate (response rate was 28%). Baseline data were collected between 2011 and 2015 and were obtained by questionnaire and physical examinations (including biological samples). For **chapters 6** and **7**, we created a prospective study by linking baseline data from the HELIUS study to hospital admission and death records from Statistics Netherlands, the Dutch national statistical office. Linkage was performed using citizen service numbers.

ARREST

For **chapter 4**, we used data from the AmsteRdam REsuscitation Studies (ARREST) registry.[72, 73] The ARREST registry is an ongoing prospective registry of all emergency medical services (EMS)-attended OHCA cases in the province North Holland in the Netherlands (excluding the area of Gooi en Vechtstreek). We created a retrospective cohort by linking records of almost 5,500 OHCA cases identified in the ARREST registry between 2009 and 2015 to individual-level data on ethnicity and socioeconomic status from administrative records from Statistics Netherlands on almost 1,7 million men and women aged 25 years and older living in the study region of ARREST on 1 January 2009. Linkage was performed using an algorithmic deterministic linkage procedure based on 1) date of birth and sex, and 2) postal code, house number, and date at which the individual lived at the address.

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