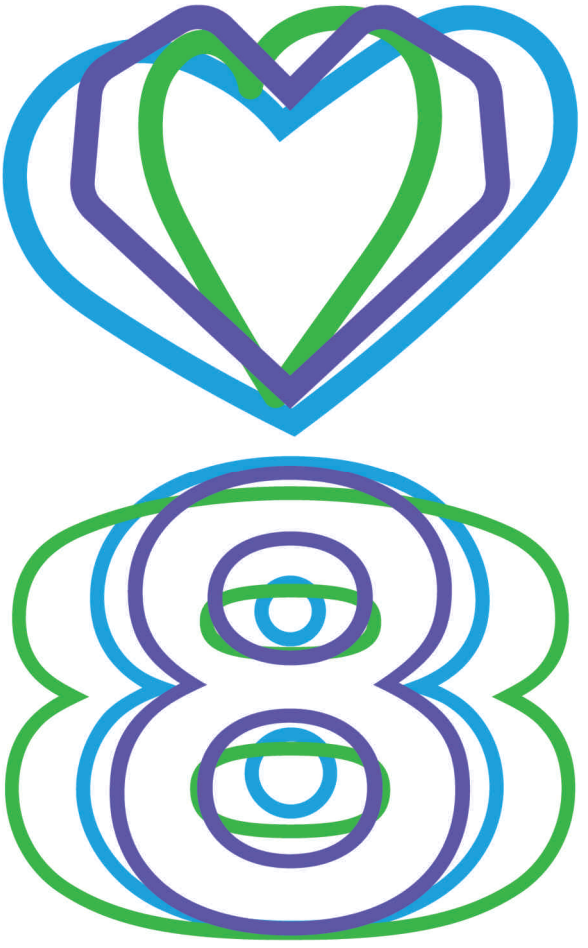
Differences in cardiovascular disease risk between men and women in a multi-ethnic population

Let's talk about sex and gender

Bolijn, R.

Publication date
2022



Chapter 8

General discussion

The objectives of this thesis were 1) to describe sex differences in cardiovascular disease (CVD) risk in a multi-ethnic population, 2) to explore associations between gender characteristics and CVD risk in men and women, and 3) to determine to what extent differences in CVD risk between men and women can be explained by differences in health-related behaviours. Ultimately, this will 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 studies included in this thesis confirm previous evidence that CVD risk and occurrence of CVD events are generally lower in women than in men. Nevertheless, women from ethnic minority groups may not benefit from the female advantage in CVD risk to a similar extent as women from majority populations, depending on the type of CVD. In addition, our findings indicate that gender characteristics are relevant for cardiovascular health, particularly in women. Finally, differences in smoking, a gender-related behaviour, may partly explain differences in CVD risk between men and women in some ethnic groups.

In this final chapter, we present an overview of the most important methodological considerations of the current research, and reflect on the main findings. Additionally, we discuss the implications of the findings for clinical and public health, and provide suggestions for future research.

Methodological considerations

An overview of the main methodological considerations is provided to evaluate our findings in view of potential limitations regarding the research. We also elaborate on the observed associations between health-related behaviours and CVD incidence, and reflect on the operationalisation of sex and gender in cardiovascular research, including our view on the commonly used gender score.

Data quality

The research in this thesis was based on observational data from surveys and registries. Both types of data sources have potential limitations. First, generalizability of findings from survey data may be limited due to selection bias. For the HELIUS study, potential participants were sampled with a random sampling approach, stratified by ethnicity, from the municipality register, in order to create a cohort that is representative for the six major ethnic groups residing in Amsterdam, the Netherlands. Nevertheless, selection bias may have occurred as suggested by the relatively low participation rate (50% of those contacted) and response rate (28% of those invited). Yet, although limited to age, sex, and socioeconomic characteristics, non-response analyses showed few differences between participants and non-

participants across ethnic groups,[1] suggesting that the risk of selection bias was small.

Second, our observational findings may have suffered from bias related to the self-reported nature of survey data. Variables on gender characteristics and related health behaviours, specifically, may be vulnerable to recall bias and social desirability bias. Unwillingness to report answers that are non-conforming to expected gender and cultural behaviours may have led to, for example, men and women under- or overreporting certain gender characteristics. Moreover, all variables were based on single measurements, while behaviours may change over time. This may have led to underestimation of the associations (regression dilution bias).[2]

Third, associations may have been under- or overestimated as registry data possibly suffer from under-registration. For instance, the ARREST registry may have missed out-of-hospital cardiac arrest (OHCA) cases, due to delayed recognition (person was found dead) or the decision not to alarm the emergency medical services (EMS; e.g., because of advanced age), potentially more so among women than among men.[3] Our sensitivity analysis including sudden cardiac death (SCD) in our case definition also indicated that under-registration is more likely to occur among women than among men, which might have led to an overestimation of the sex difference in OHCA incidence. In addition, the hospital admission data on CVD from Statistics Netherlands that were used for **chapters 6** and **7** were not complete. Missing data mainly regarded primary diagnosis and operations, which may have led to missed CVD cases. However, while this potentially underestimates incidence, the percentage of missings that concerned data on primary diagnosis and operations did not differ substantially between men and women or between ethnic groups, making it unlikely that our comparisons were substantially influenced.

Study designs

Chapters 3 and **5** used a cross-sectional design, which may have resulted in reverse causality. For instance, we cannot rule out that the gender characteristics and health-related behaviours are influenced by participants' CVD risk profile. In attempt to correct for this, we excluded participants with prior CVD, although this might not have completely eliminated reverse causality.

For **chapters 4**, **6** and **7**, we were able to set up prospective cohort studies by linking several data sources, using algorithmic deterministic linkage for ARREST (**chapter 4**) or citizen service numbers for HELIUS (**chapters 6** and **7**). Algorithmic deterministic linkage in particular may be prone to selection bias. However, linkage

between ARREST and Statistics Netherlands was successful in 96% of cases. We consider it unlikely that the small proportion of unsuccessful linkages has substantially influenced our findings.

Statistical analyses

Our studies may have suffered from power issues, particularly **chapters 6** and **7**. Due to the young age of the study population (average age at baseline ≈45 years) and a short follow-up duration (5-6 years), the CVD event rate and the total number of events were low. The low occurrence in some of the smaller categories of gender characteristics and health-related behaviours may have resulted in limited statistical power to demonstrate associations.

Nevertheless, the large multi-ethnic sample size of the HELIUS study is unique and enabled us to incorporate an intersectional approach by, for example, stratification of our analyses by sex and ethnicity. Although many different methods have been proposed, there are no consistent or widely adopted methods to incorporate the intersectionality framework into quantitative research.[4, 5] For the studies in this thesis, *a priori* stratification of regression analyses by relevant factors (e.g., sex, ethnicity, gender characteristics) was most often used. In case of two or more intersectional factors of interest, this method has the advantage that it provides similar information as, for example, three-way interaction terms, but is easier to interpret. Moreover, we often chose for such stratification based on previous evidence or theoretical considerations, rather than letting the option of stratification depend on statistical evidence for interaction terms. For instance, we hypothesized that the gender characteristics likely have different implications for men and women. On top of stratification, we also performed regression analyses with two-way interaction terms for the intersections not stratified for, to formally test whether associations statistically differed across subgroups.

To facilitate interpretation, we used interaction terms that were appropriate for the scale of the model (i.e., interaction terms on an additive scale for linear regression analyses and on a multiplicative scale for logistic and Cox regression analyses). However, it has been argued that interaction terms on an additive scale may be most appropriate for intersectional analyses, since they are better aligned with the concept of intersectional multiplicativity, i.e., the effect of combined intersecting identity factors on an health outcome is larger than the *sum* of these individual factors.[4, 6] In contrast, an interaction term on a multiplicative scale measures whether the combined effect of factors is larger than the *product* of the these factors. We are unsure to what extent our findings in **chapters 3**, **4** and **6** would have been altered

if we had derived measures of interaction on an additive scale from the multiplicative interaction terms.

Associations between unhealthy behaviours and CVD incidence

Next to our analyses of the contribution of smoking to differences in CVD risk between men and women (**chapter 7**), we had also planned to report the contribution of other unhealthy behaviours (high alcohol consumption, physical inactivity, low fruit intake, short sleep duration) to differences in CVD risk between men and women. However, these other unhealthy behaviours were not significantly associated with increased CVD risk in our study population (Table 1). Even more unlike our expectations, high alcohol consumption and both short and long sleep duration pointed towards lower hazards for CVD compared to the reference groups. Explanations for the lack of expected associations between sleep duration and CVD incidence in our study are possibly related to large ethnic diversity of our study population. Thus far, evidence from the USA is conflicting on whether associations between sleep duration and cardiometabolic risk exist in all ethnic groups.[7-11] Associations for high alcohol consumption and short sleep duration with CVD incidence were more in line with previous research when we restricted our analyses to participants without self-reported hypertension or diabetes (data not shown), which more resembles previous research. However, since we also consider it likely that the lack of associations is related to the limited power or to limitations of our measurements of health-related behaviours (such as the self-reported nature), we decided not to further report on these findings in **chapter 7**.

Table 1. Associations (hazard ratios) of health-related behaviours with CVD incidence in men and women without prior CVD (n=18,058)

	HR (95% CI)[a]
Smoking status	
Current	**2.26 (1.76-2.90)**
Former	1.04 (0.78-1.39)
Never	1.00 (reference)
Alcohol consumption	
High	0.73 (0.47-1.14)
Moderate	0.83 (0.62-1.12)
Low	1.00 (reference)
Physical activity	
Not physically active	1.19 (0.96-1.47)
Physically active	1.00 (reference)

Table 1. Continued

	HR (95% CI)[a]
Fruit intake[b]	
Low	0.85 (0.67-1.07)
Moderate	0.70 (0.53-0.93)
High	1.00 (reference)
Sleep duration	
Short	0.89 (0.72-1.11)
Moderate	1.00 (reference)
Long	0.91 (0.47-1.79)

CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio.

Statistically significant associations (p<0.05) are printed in bold.

[a] Adjusted for sex, age, ethnicity, educational status, family history of CVD, and the other health-related behaviours (i.e. mutual adjustment).

[b] Proportional hazards assumption violated. Estimates should thus be treated with caution and are therefore printed in gray.

Operationalisation of sex and gender in cardiovascular research

We measured sex through self-report or via registered sex at birth, which are commonly used methods to measure sex in humans. However, these methods are often limited to the binary distinction of male and female, while it has been argued that this dichotomy is too restricted and does not reflect heterogeneity related to e.g. variation in genetics and hormone levels between as well as among men, women, and intersex persons.[12-14] It may be challenging to take this heterogeneity into account, as e.g. larger sample sizes and additional measurements may be needed, but it will foster more diverse and inclusive research and potentially increase our understanding of differences in disease risk between individuals beyond the binary sex distinction.

We measured gender through multiple self-reported gender characteristics. There is no 'gold standard' yet for the measurement of gender or gender characteristics in health research. In the past years, several studies have attempted to operationalise gender and measure associations with outcomes in health research and in cardiovascular research.[15] The attempts of operationalising gender in cardiovascular research can be divided in two main methods: 1) an overall score or index as proxy for gender, and 2) separate measures for specific gender characteristics. A gender score conceptualizes gender as an average on a continuum or scale with 'feminine' on the one end and 'masculine' on the other. In contrast, assessing gender as separate gender characteristics assumes that individuals may have both feminine and masculine characteristics and that these characteristics may differently associate with health outcomes.

For our studies (**chapters 5** and **6**), we chose the second approach and *a priori* made a deliberate selection of several gender characteristics from previous studies.[16-19] This selection of characteristics was built on the implication that they are traditionally ascribed to either men or women based on social norms and expectations in contemporary Western societies.[20, 21] During the selection process, we made four choices.

First, we could only select characteristics that were available in HELIUS. This means that we were reliant on variables from a secondary dataset with self-reported variables that were not included for the purpose of measuring gender. For instance, we included a variable on participants' time spent on household work, while a ratio for time spent on household work compared to the partner would have been a better measure for the division of household chores within a household and, hence, a better proxy of division of gender roles.

Second, we selected characteristics with an expected difference in prevalence between men and women as a result of differential societal expectations for men and women. We were specifically interested in characteristics that may be used to distinguish between genders. For instance, we did not include civil status, while previous studies considered this variable as a gender characteristic based on the assumption that being married has different implications for men and for women. Indeed, being unmarried is a risk factor for CVD mortality, and it has been suggested that this association is stronger in men than in women.[22] Several underlying mechanisms have been proposed why being unmarried is more detrimental for men compared to women, including gender-related processes, such as the non-adherence to the gender norm of being (financially) responsible for a family, resulting in feelings of perceived inadequacy.[22] However, there are no differential societal expectations in occurrence of being married, divorced or widowed for men and women (e.g., women are not expected to be more often married than men). Thus, civil status by itself cannot be used to distinguish between genders.

Third, we selected characteristics that, in our view, mainly capture gender instead of other social characteristics. For instance, we did not include variables that are considered primary features of other social identities. Other studies have frequently included personal income, education level or related variables as proxies of gender. However, these variables are also often used as dimensions of socioeconomic status. Including these variables as gender characteristics may result in intertwining of distinct social identities, while these identities should be analysed and interpreted as intersecting identities.

Fourth, we did not include health-related behaviours as gender characteristics. Health-related behaviours may be considered suitable gender characteristics as the prevalence differs between men and women as a result of differential societal expectations. However, these behaviours may directly trigger pathogenic processes, and can therefore be perceived as proximal risk factors for CVD.[23, 24] Therefore, we considered health-related behaviours as potential mediators in associations between gender and CVD risk. Moreover, smoking and potentially other behaviours, such as alcohol consumption, also have a biological component.[25] For instance, sex hormones may determine vulnerability to nicotine addiction,[26] suggesting that smoking behaviour is also a mediator in the association between sex and CVD risk. Similarly, we also did not include variables that are also mental disorders, such as depression and anxiety, for similar reasons as for health-related behaviours.

Alternatively, we could have chosen the first approach of operationalising gender, which is the construction and/or application of an overall gender score. However, this approach has several challenges. For instance, the creation of a gender score is often predominantly based on a data-driven approach in which variables to include in the score are selected based on their association with sex, the so called gender diagnosticity approach proposed by Lippa and Connelly.[27] However, this approach blends the distinct constructs of sex and gender.[18, 20] In addition, when candidate characteristics for the score are not conceptually suitable gender characteristics (see the previous reflection on our selection process), the score that is generated may not reflect gender. Finally, while an overall gender score may, on the one hand, provide a more comprehensive indication of the effects of gender on health, specific associations with certain gender characteristics may be missed by a generic measure such as an overall gender score, as associations of specific gender characteristics may be offset by others.

Interpretation of main findings

Sex differences in cardiovascular disease risk across ethnic groups

Women from ethnic minority populations may not benefit from the female advantage in CVD risk to a similar extent as women from majority populations. In **chapter 3**, we showed that the smaller sex differences in prevalence of major ECG abnormalities among ethnic minority groups compared to the Dutch majority population were mainly driven by the higher prevalence among women of the ethnic minority groups compared to women of the Dutch majority population. Similar observations were done by two previous studies from the USA, which reported a smaller sex disparity in prevalence of CVD[28] and in coronary heart disease mortality[29] in black individuals compared to white individuals. Since conventional cardiovascular risk factors did not

explain the higher prevalence of major ECG abnormalities among women from ethnic minority groups, other factors should be explored, such as psychosocial risk factors. However, the smaller sex differences in ethnic minority groups may also imply that current ECG reference values, that were developed in white men, do not sufficiently differentiate between men and women and between ethnic groups. Variations in measurements may thus also reflect variation in normal values, rather than actual CVD risk. As current ECG reference values may be specifically inappropriate for women form ethnic minority groups due to the intersecting identities of being a woman and belonging to an ethnic minority group, validations of ECG reference values are of great importance for these groups.

The pattern of smaller sex differences in ethnic minority groups was not observed for the other investigated CVD outcomes. Instead, we showed that sex differences in OHCA incidence (**chapter 4**) and CVD incidence (**chapter 7**) were largely consistent across ethnic groups. The heterogeneity between these studies and the study on major ECG abnormalities may be partly related to differences in CVD outcomes. While our measures of CVD and OHCA incidence mainly include 'hard outcomes' such as hospitalizations, deaths and emergency medical service (EMS) attendance, our measure of major ECG abnormalities may also include abnormalities that only require outpatient (preventive) treatment. We speculate that women of ethnic minority populations living in the Netherlands are specifically disadvantaged for these 'softer' CVD outcomes compared to women of Dutch origin.

Our findings seem in contrast with a previous Dutch study that reported larger sex differences in acute myocardial infarction in most ethnic minority populations compared to the Dutch majority population.[30] However, when results were stratified by age-groups, the overall finding of larger sex differences in ethnic minority populations was driven by the youngest age-group (30-55 years), and sex differences were actually smaller in most ethnic minority population than in the Dutch majority population in older age-groups, which approaches more our findings on major ECG abnormalities (**chapter 3**). For instance, the sex difference in prevalence of major ECG abnormalities in ethnic minority groups was smallest in older age-groups than in the youngest age-group. This suggests that women from ethnic minority groups are particularly disadvantaged compared to women from the majority population above the age of 50 years. The underlying causes of the increased risk among this group are unclear, but might be related to language barriers and low health literacy, which have been shown to lead to poorer health status in ageing migrants.[31] Patterns of sex differences in OHCA incidence and CVD incidence across ethnic groups may also vary by age, but this was not assessed.

While men across population groups will generally benefit more from CVD prevention strategies compared to women, women of South-Asian Surinamese origin may be an additional relevant group for targeted prevention strategies due to their higher CVD risk compared to other women and some groups of men. In **chapter 3**, we reported that only South-Asian Surinamese women did not have a lower odds of having a major ECG abnormality compared to men. We also observed that both men and women of South-Asian Surinamese origin have higher CVD incidence rates than most men and women of other ethnic groups (**chapter 7**). We could not confirm this finding in our study on OHCA incidence (**chapter 4**), since we could not differentiate between ethnic groups within the Surinamese group. Nevertheless, our findings are consistent with substantial evidence suggesting that South-Asians living in Europe are generally at higher CVD risk than majority population.[32-34]

Although we did not specifically study the consistency of sex differences in CVD risk across ethnic groups in **chapter 7**, we reported higher CVD incidence rates in Turkish women compared to Turkish men and compared to women of other ethnic groups, even South-Asian Surinamese women. This potentially high CVD risk among Turkish women was not observed in other chapters of this thesis and also not reported by previous studies on acute myocardial infarction[35] or stroke[36] conducted in the Netherlands. However, prior studies using data from the HELIUS cohort have reported a more unfavourable lipid profile[37] and a higher prevalence of obesity[38] among Turkish participants compared to the other groups. Hence, the high CVD incidence rate among Turkish women merits further exploration.

Gender differences in cardiovascular disease risk

Some gender characteristics were associated with estimated 10-year CVD risk (**chapter 5**) and CVD incidence (**chapter 6**), mainly in women. Based on our findings for estimated 10-year CVD risk (**chapter 5**), we hypothesized that more masculine gender characteristics may be associated with higher CVD risk through greater stress among those with a more masculine gender, for instance, through a high allostatic load.[39, 40] Another potential pathway we hypothesized was through a less healthy lifestyle (e.g., smoking, high alcohol consumption). The latter pathway was initially supported by findings from additional analyses on specific components of the SCORE algorithm showing that a particular higher odds of smoking was found among women with more masculine characteristics. In line with this observation, smoking explained some part of the differences in CVD incidence between men and women in some ethnic groups (**chapter 7**). However, most more masculine gender characteristics did not seem to lead to higher CVD incidence (**chapter 6**).

Our findings hint at U-shaped or J-shaped associations between the characteristics related to paid and unpaid labour within households and CVD incidence in women, with female homemakers specifically showing an increased CVD risk (**chapter 6**). These associations were not mediated through conventional risk factors that are also components of the SCORE algorithm (smoking status, systolic blood pressure, total cholesterol/high-density lipoprotein cholesterol ratio, and diabetes). Altogether, this indicates that associations of gender characteristics with actual CVD risk may work through different pathways, such as physical exposures or access to and use of (preventive) treatment (see also Figure 2 in **chapter 1**). For instance, it has been suggested that there may be gender differences in exposure to air pollution through e.g. work-related or residence-based exposures.[41] Our hypothesis that women in the middle categories of certain gender characteristics are perhaps less exposed to environmental risk factors for CVD, such as air pollution,[42, 43] may be further explored.

Several gender characteristics were not associated with estimated 10-year CVD risk (**chapter 5**) or CVD incidence (**chapter 6**), mostly in men. This suggests that our selected characteristics are less important for CVD risk in men. The selection included mostly characteristics related to the division of paid and unpaid labour as part of the gender roles domain (time spent on household work, doing home repairs, primary earner status, type of employment), as well as one characteristic from the gender relations domain (desire for emotional support) and one that fits within the domain of institutionalized gender (working in a male- or female-dominated occupation). Other aspects of these domains, such as childcare responsibilities, self-employment or type of volunteer work, may thus be explored. In addition, aspects from the gender identity domain, a domain which we did not include, may be assessed. For instance, a study from the USA observed that higher femininity scores on the Bem Sex-Role Inventory,[44] which measures some aspects of gender identity, were associated with lower coronary heart disease mortality in men.[45]

Other studies on associations between gender and CVD outcomes mainly reported worse outcomes among those with a more feminine gender.[16, 45-47] Heterogeneity between studies is likely related to differences in study designs (cross-sectional versus longitudinal), study populations (patients versus general populations), and the variety in the operationalisation of gender. However, it may also reflect that different domains of gender and aspects within domains relate differently to CVD. This explanation is further supported by the weak correlation among our selected gender characteristics, also within domains, and by the fact that associations with CVD incidence did not change substantially after mutual adjustment for other gender characteristics (**chapter 6**).

We found limited evidence that associations between gender characteristics and estimated 10-year CVD risk varied by ethnicity (**chapter 5**). This indicates that the effect of gender characteristics related to the division of paid and unpaid labour may be more universal than initially expected based on the theoretical framework of intersectionality (i.e. the interaction of multiple social factors, such as gender and ethnicity, may differentially influence health outcomes across subpopulations). We did not assess whether these associations differed by level of acculturation of participants from ethnic minority populations, while it is possible that different levels of acculturation may affect attitudes towards gender norms.[48, 49] This may then influence the uptake and interpretation of gender roles, and, hence, its potential association with CVD risk. Unfortunately, we did not have sufficient power to confirm whether associations between gender characteristics and CVD incidence were also consistent across ethnic groups (**chapter 6**).

Implications for clinical and public health

Our findings are in line with the general view that CVD risk is lower in women than in men, indicating that men across population groups are the most important target group for CVD prevention strategies. Not unexpectedly, we also showed that part of the excess risk in men is caused by smoking (**chapter 7**), implying that substantial health gains may still be achieved by improving smoking prevention and cessation strategies. Our survey on the prioritization of risk factors for more research on CVD risk according to the target group may provide additional directions for further investigation of causes of the increased risk in men. For instance, the survey revealed that the majority of men prioritized more research on depression or depressive feelings (**chapter 2**). Depression is indeed a risk factor for CVD in men, and even more so in women, but the underlying mechanisms of the association between depression and increased CVD risk remain not fully resolved.[50, 51]

Our study on sex differences in OHCA incidence provides additional evidence that part of the lower risk in women may be due to under-registration in women (**chapter 4**).[52] Delayed recognition (person was found dead) and delayed action (EMS is not alarmed) after an OHCA may result in an OHCA being registered as a sudden cardiac death. We observed that this occurred more often in women than in men, indicating that there may be relatively more avoidable deaths due to OHCA in women compared to men. This delayed recognition and delayed action in women may be partly resolved by improved awareness of the occurrence of OHCA and of CVD in general among women, and among bystanders. For instance, evidence from the USA suggests that more than half of women are unaware of CVD as the primary cause of death in women, particularly among women from ethnic minority populations.[53, 54]

We identified subgroups of women who may be at high risk for CVD, specifically women of South-Asian Surinamese and Turkish origin. Furthermore, female homemakers pose an additional target group due to their increased risk of CVD. Future research may reveal which mechanisms are responsible for the higher risk among these groups, and thus which prevention strategies will be most effective. Notably, these subgroups had an increased risk irrespective of conventional risk factors, suggesting that opportunities to reduce the burden of CVD might be missed if prevention strategies are solely targeted at those with conventional risk factors.

Suggestions for future research

The findings from our studies add to a small but increasing body of evidence that differences in CVD risk between men and women may differ across ethnic groups. As European populations are becoming more ethnically diverse in the near future,[55] insights into the variations in CVD risk across ethnic groups within populations will become even more relevant. Thus, we advocate for more research into sex and gender differences in CVD risk across subpopulations in order to increase the evidence base to ultimately improve CVD risk profiles among those with the highest risk. For instance, we encourage confirmation of our work in observational studies with longer follow-up duration. This will also enable exploration of sex and gender differences in CVD risk across other potentially relevant intersecting factors, such as socioeconomic position or sexual orientation, and across generations of migrant populations to examine variations in associations by different levels of acculturation. Furthermore, the inclusion of primary care data on CVD may increase our understanding of differences in 'soft' CVD outcomes, such as transient ischemic attack or non-invasively managed angina, across subpopulations, which may be specifically relevant for women from ethnic minority populations.

It has been suggested that underrepresented sex and gender groups, such as intersex persons, transgender persons, or persons not identifying as cisgender women or men, have a higher burden of CVD.[28, 56] In addition, our findings from the Harteraad panel suggest that gender minority groups have different perspectives on priorities for research on cardiovascular risk factors than the majority groups, potentially due to differential experiences (**chapter 2**). Therefore, it is important that future surveys and registries implement strategies to identify these groups beyond the binary distinction of men and women, in order to improve current insights into cardiovascular health among these groups. For instance, surveys may apply a two steps approach to gain more insights into participants' sex and gender identities.[57, 58] First, a question may be asked on the participants' sex assigned at birth, with response options on female, male, and intersex. Then, an additional question may be entered on participants' gender identity, with response options on woman, man,

non-binary, and gender queer. Instead of a categorical question on gender identity, researchers may also consider self-rated scales for masculinity and femininity,[58, 59] although these may be more challenging to incorporate into intersectional analyses.

Our work provides additional evidence that gender is relevant for cardiovascular health, particularly in women (**chapters 5** and **6**). In line with some studies,[16, 60] we mostly observed associations between variables related to the division of paid and unpaid labour and CVD outcomes. However, comparisons between studies on gender in relation to cardiovascular health are currently limited due to the wide variety of operationalisations of gender. Although finding consensus on the operationalisation of gender may be challenging due to the contextual nature of the construct, it will foster comparisons across studies and enhance interpretation of the effect of gender on cardiovascular health. To facilitate consensus, we make two recommendations for the operationalisation of gender in cardiovascular research.

First, the goal of the inclusion of gender in the research needs to be specified, as it may determine which of the two methods, as previously described in our reflection, will be most suitable given the aim and outcome under study. We identify two goals: 1) subgroup identification (who are at risk?), and 2) improving the understanding of mechanisms (why are they at risk?). We consider the construction of an overall gender score to be a suitable approach for subgroup identification, as a score may be a pragmatic tool to identify those that are at the highest risk in a certain population. If the goal is to unravel mechanisms explaining differences between men and women, studying separate gender characteristics may be a more suitable approach because it allows for more in-depth analysis.

Second, following our reflection on the operationalisation of gender, we recommend researchers to include or select variables with an expected difference in prevalence between men and women as a result of differential societal expectations for men and women. In addition, we recommend to avoid the inclusion of variables that 1) are commonly used to measure other social characteristics, and 2) directly trigger pathogenic processes and may thus serve as mediators in the association between gender and CVD. Importantly, we highly recommend to select potential gender characteristics in this deliberate manner also in case an overall gender score is constructed so that the score reflects gender.

To conclude, the operationalisation of gender requires further development, for which we have provided recommendations. If our findings are confirmed in future research, gender characteristics may pose valuable additional factors for the identification of CVD risk groups, especially for women.

References

1. Snijder MB, Galenkamp H, Prins M, et al. Cohort profile: The Healthy Life in an Urban Setting (HELIUS) study in Amsterdam, the Netherlands. *BMJ Open* 2017; 7: e017873.
2. MacMahon S, Peto R, Collins R, et al. Blood pressure, stroke, and coronary heart disease: Part 1, prolonged differences in blood pressure: Prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; 335: 765-774.
3. Blom MT, Oving I, Berdowski J, et al. Women have lower chances than men to be resuscitated and survive out-of-hospital cardiac arrest. *Eur Heart J* 2019; 40: 3824-3834.
4. Guan A, Thomas M, Vittinghoff E, et al. An investigation of quantitative methods for assessing intersectionality in health research: A systematic review. *SSM Popul Health* 2021; 16: 100977.
5. Bauer GR, Churchill SM, Mahendran M, et al. Intersectionality in quantitative research: A systematic review of its emergence and applications of theory and methods. *SSM Popul Health* 2021; 14: 100798.
6. Bauer GR. Incorporating intersectionality theory into population health research methodology: Challenges and the potential to advance health equity. *Soc Sci Med* 2014; 110: 10-17.
7. Kim Y, Wilkens LR, Schembre SM, et al. Insufficient and excessive amounts of sleep increase the risk of premature death from cardiovascular and other diseases: The Multiethnic Cohort Study. *Prev Med* 2013; 57: 377-385.
8. Petrov ME, Howard G, Grandner MA, et al. Sleep duration and risk of incident stroke by age, sex, and race: The REGARDS study. *Neurology* 2018; 91: e1702-e1709.
9. Zizi F, Pandey A, Murrray-Bachmann R, et al. Race/ethnicity, sleep duration, and diabetes mellitus: Analysis of the National Health Interview Survey. *Am J Med* 2012; 125: 162-167.
10. Vishnu A, Shankar A and Kalidindi S. Examination of the association between insufficient sleep and cardiovascular disease and diabetes by race/ethnicity. *Int J Endocrinol* 2011; 2011.
11. Curtis DS, Fuller-Rowell TE, El-Sheikh M, et al. Habitual sleep as a contributor to racial differences in cardiometabolic risk. *Proceedings of the National Academy of Sciences* 2017; 114: 8889-8894.
12. Ainsworth C. Sex redefined. *Nature* 2015; 518: 288-291.
13. Fausto-Sterling A. *Sexing the body: Gender politics and the construction of sexuality*. Basic books, 2000.
14. Blackless M, Charuvastra A, Derryck A, et al. How sexually dimorphic are we? Review and synthesis. *Am J Hum Biol* 2000; 12: 151-166.
15. Miani C, Wandschneider L, Niemann J, et al. Measurement of gender as a social determinant of health in epidemiology—A scoping review. *PLoS One* 2021; 16: e0259223.
16. Pelletier R, Ditto B and Pilote L. A composite measure of gender and its association with risk factors in patients with premature acute coronary syndrome. *Psychosom Med* 2015; 77: 517-526.
17. Smith PM and Koehoorn M. Measuring gender when you don't have a gender measure: Constructing a gender index using survey data. *Int J Equity Health* 2016; 15: 82.
18. Lacasse A, Pagé MG, Choinière M, et al. Conducting gender-based analysis of existing databases when self-reported gender data are unavailable: The GENDER Index in a working population. *Can J Public Health* 2020; 111: 155-168.
19. Ballering AV, Bonvanie IJ, Olde Hartman TC, et al. Gender and sex independently associate with common somatic symptoms and lifetime prevalence of chronic disease. *Soc Sci Med* 2020; 253: 112968.
20. Johnson JL, Greaves L and Repta R. Better science with sex and gender: Facilitating the use of a sex and gender-based analysis in health research. *Int J Equity Health* 2009; 8: 1-11.
21. Phillips SP. Defining and measuring gender: A social determinant of health whose time has come. *Int J Equity Health* 2005; 4: 1-4.
22. Wang Y, Jiao Y, Nie J, et al. Sex differences in the association between marital status and the risk of cardiovascular, cancer, and all-cause mortality: A systematic review and meta-analysis of 7,881,040 individuals. *Glob Health Res Policy* 2020; 5: 1-16.
23. Assari S. Distal, intermediate, and proximal mediators of racial disparities in renal disease mortality in the United States. *J Nephropathol* 2016; 5: 51-59.

24. Krieger N. *Epidemiology and the people's health: Theory and context*. Oxford University Press, 2011.
25. Pogun S, Yararbas G, Nesil T, et al. Sex differences in nicotine preference. *J Neurosci Res* 2017; 95: 148-162.
26. Lynch WJ and Sofuoglu M. Role of progesterone in nicotine addiction: Evidence from initiation to relapse. *Exp Clin Psychopharmacol* 2010; 18: 451-461.
27. Lippa R and Connelly S. Gender diagnosticity: A new Bayesian approach to gender-related individual differences. *J Pers Soc Psychol* 1990; 59: 1051-1065.
28. Acosta JN, Leasure AC, Both CP, et al. Cardiovascular health disparities in racial and other underrepresented groups: initial results from the All of Us research program. *J Am Heart Assoc* 2021; 10: e021724.
29. Ho JE, Paultre F and Mosca L. The gender gap in coronary heart disease mortality: Is there a difference between blacks and whites? *J Womens Health* 2005; 14: 117-127.
30. Van Oeffelen AA, Vaartjes I, Stronks K, et al. Sex disparities in acute myocardial infarction incidence: Do ethnic minority groups differ from the majority population? *Eur J Prev Cardiol* 2015; 22: 180-188.
31. Kristiansen M, Razum O, Tezcan-Güntekin H, et al. Aging and health among migrants in a European perspective. *Public Health Rev* 2016; 37: 1-14.
32. Cainzos-Achirica M, Fedeli U, Sattar N, et al. Epidemiology, risk factors, and opportunities for prevention of cardiovascular disease in individuals of South Asian ethnicity living in Europe. *Atherosclerosis* 2019; 286: 105-113.
33. Agyemang C and Van den Born B-J. Non-communicable diseases in migrants: An expert review. *J Travel Med* 2019; 26: tay107.
34. Sohail QZ, Chu A, Rezai MR, et al. The risk of ischemic heart disease and stroke among immigrant populations: A systematic review. *Can J Cardiol* 2015; 31: 1160-1168.
35. Van Oeffelen A, Vaartjes I, Stronks K, et al. Incidence of acute myocardial infarction in first and second generation minority groups: Does the second generation converge towards the majority population? *Int J Cardiol* 2013; 168: 5422-5429.
36. Agyemang C, Van Oeffelen AA, Norredam M, et al. Ethnic disparities in ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage incidence in the Netherlands. *Stroke* 2014; 45: 3236-3242.
37. Gazzola K, Snijder MB, Hovingh GK, et al. Ethnic differences in plasma lipid levels in a large multiethnic cohort: The HELIUS study. *J Clin Lipidol* 2018; 12: 1217-1224.e1211.
38. Perini W, Van Valkengoed IG, Snijder MB, et al. The contribution of obesity to the population burden of high metabolic cardiovascular risk among different ethnic groups. The HELIUS study. *Eur J Public Health* 2020; 30: 322-327.
39. Juster R-P and Lupien S. A sex-and gender-based analysis of allostatic load and physical complaints. *Gend Med* 2012; 9: 511-523.
40. Juster R-P, McEwen BS and Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci Biobehav Rev* 2010; 35: 2-16.
41. Clougherty JE. A growing role for gender analysis in air pollution epidemiology. *Environ Health Perspect* 2010; 118: 167-176.
42. Cosselman KE, Navas-Acien A and Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol* 2015; 12: 627-642.
43. Al-Kindi SG, Brook RD, Biswal S, et al. Environmental determinants of cardiovascular disease: Lessons learned from air pollution. *Nat Rev Cardiol* 2020; 17: 656-672.
44. Bem SL. The measurement of psychological androgyny. *J Consult Clin Psychol* 1974; 42: 155-162.
45. Hunt K, Lewars H, Emslie C, et al. Decreased risk of death from coronary heart disease amongst men with higher 'femininity' scores: A general population cohort study. *Int J Epidemiol* 2007; 36: 612-620.
46. Azizi Z, Gisinger T, Bender U, et al. Sex, gender factors and cardiovascular health in Canadian and Austrian populations. *Can J Cardiol* 2021; 37: 1240-1247.
47. Pelletier R, Khan NA, Cox J, et al. Sex versus gender-related characteristics: Which predicts outcome after acute coronary syndrome in the young? *J Am Coll Cardiol* 2016; 67: 127-135.
48. Van Klingeren M and Spierings N. Acculturation, decoupling, or both? Migration's impact on the linkage between religiosity and gender equality attitudes. *J Ethn Migr Stud* 2020; 46: 3079-3100.

49. Röder A and Mühlau P. Are they acculturating? Europe's immigrants and gender egalitarianism. *Soc Forces* 2014; 92: 899-928.
50. Vaccarino V, Badimon L, Bremner JD, et al. Depression and coronary heart disease: 2018 position paper of the ESC working group on coronary pathophysiology and microcirculation. *Eur Heart J* 2020; 41: 1687-1696.
51. Carney RM and Freedland KE. Depression and coronary heart disease. *Nat Rev Cardiol* 2017; 14: 145-155.
52. Vogel B, Acevedo M, Appelman Y, et al. The Lancet women and cardiovascular disease Commission: Reducing the global burden by 2030. *Lancet* 2021; 397: 2385-2438.
53. Bairey Merz CN, Andersen H, Sprague E, et al. Knowledge, attitudes, and beliefs regarding cardiovascular disease in women: The Women's Heart Alliance. *J Am Coll Cardiol* 2017; 70: 123-132.
54. Cushman M, Shay CM, Howard VJ, et al. Ten-year differences in women's awareness related to coronary heart disease: Results of the 2019 American Heart Association National Survey: A special report from the American Heart Association. *Circulation* 2021; 143: e239-e248.
55. Stoeldraijer L, Van Duin C and Huisman C. *Bevolkingsprognose 2017–2060: 18,4 miljoen inwoners in 2060*. 2017. Centraal Bureau voor de Statistiek.
56. Streed Jr CG, Beach LB, Caceres BA, et al. Assessing and addressing cardiovascular health in people who are transgender and gender diverse: A scientific statement from the American heart association. *Circulation* 2021; 144: e136-e148.
57. GenIUSS Group. *Best practices for asking questions to identify transgender and other gender minority respondents on population-based surveys*. 2014. eScholarship, University of California.
58. Magliozzi D, Saperstein A and Westbrook L. Scaling up: Representing gender diversity in survey research. *Socius* 2016; 2: 1-11.
59. Hart CG, Saperstein A, Magliozzi D, et al. Gender and health: Beyond binary categorical measurement. *J Health Soc Behav* 2019; 60: 101-118.
60. Nielsen MW, Stefanick ML, Peragine D, et al. Gender-related variables for health research. *Biol Sex Differ* 2021; 12: 1-16.