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 4

Sex differences in incidence of out-of-hospital cardiac arrest across ethnic and socioeconomic groups: A population-based cohort study in the Netherlands

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Abstract

Background: Insight into the occurrence of out-of-hospital cardiac arrest (OHCA) within general populations may help to target prevention strategies. Case registries suggest that there may be substantial differences in emergency medical service (EMS)-attended OHCA incidence between men and women, but relative sex differences across ethnic groups and socioeconomic (SES) groups have not been studied. We investigated sex differences in OHCA incidence, overall and across these subgroups.

Methods: We performed a retrospective population-based cohort study, combining individual-level data on ethnicity and income (as SES measure) from Statistics Netherlands of all men and women aged ≥25 years living in one study region in the Netherlands on 01-01-2009 (n=1,688,285) with prospectively collected EMS-attended OHCA cases (n=5,676) from the ARREST registry until 31-12-2015. We calculated age-standardised incidence rates of OHCA. Sex differences were assessed with Cox proportional hazards regression analyses, adjusted for age, ethnicity and income, in the overall population, and across ethnic and SES groups.

Results: The age-standardised incidence rate of OHCA was lower in women than in men (30.9 versus 87.3 per 100,000 person-years), corresponding with a hazard ratio (HR) of 0.33 (95% confidence interval [CI] 0.31-0.35). These sex differences in hazard for OHCA existed in all income quintiles (HR range: 0.30-0.35) and ethnic groups (HR range: 0.19-0.40), except among Moroccans (HR 0.89, 95% CI 0.51-1.57).

Conclusion: Women have a substantial, yet lower OHCA incidence rate than men. The magnitude of these sex differences did not vary across social strata.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major global health problem with low survival rates.[1] OHCA is defined as the out-of-hospital occurrence of cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[2] Current OHCA prevention strategies are suboptimal, partly due to the inability to identify persons at high risk.[3] OHCA incidence rates have been reported extensively across populations.[1] In addition, available data from case registries (e.g.,[4-7]) show that there are substantial absolute differences in the yearly number of registered emergency medical services (EMS)-attended OHCA cases between men and women, with potentially differential underlying aetiology and prognosis.[8, 9] However, OHCA incidence rates based on person-time at risk have not been reported separately for men and women and relative differences between men and women have not been studied, potentially due to a lack of prospective individual-level data. Therefore, more insight into the occurrence of OHCA in men and women within general populations may help to target prevention strategies.

The incidence of OHCA in men and women may differ across subgroups within the population, such as ethnic or socioeconomic (SES) groups. For instance, studies on other relevant cardiovascular disease (CVD) outcomes (e.g., coronary heart disease mortality[10] and major electrocardiographic abnormalities[11]) suggest that sex differences in occurrence of CVD outcomes may be smaller in ethnic minority groups compared to the majority population (in high-income countries), independently of established CVD risk factors. The explanations remain unclear, but may be related to modifying effects of less conventional and potentially overlooked risk factors, such as psychosocial factors (e.g., discrimination).[12] Further research into sex differences across subpopulations is needed to verify and further explain these findings, including research into sex differences in OHCA incidence.

Previous studies from the United States of America (USA),[13, 14] Singapore,[15] and New-Zealand[16] reported substantial ethnic differences in EMS-attended OHCA incidence rates, but these studies did not report on sex differences across ethnic groups. A study from the USA observed that ethnic differences in sudden cardiac death (SCD), which also includes OHCA-related deaths, were more pronounced in women compared to men,[17] suggesting that sex differences in OHCA incidence may vary across ethnic groups.

Sex differences in OHCA incidence may also differ across SES groups. However, whether the magnitude of sex differences varies between people with low and high SES is yet unclear. In general, a lower SES is associated with a higher OHCA

incidence.[18] One study on sex-specific incidence of OHCA and SCD combined reported an association with neighbourhood-level SES in women but not in men, suggesting a possible modifying effect of sex on the association between SES and OHCA+SCD.[19] Such a modifying effect across neighbourhoods implies a possible variation in sex differences across SES strata.

These findings support the need for further examination of sex differences across subgroups within the population. To fulfil this need, we investigated sex differences in EMS-attended OHCA incidence in a population-based cohort study among almost 1.7 million men and women in the region of North Holland, the Netherlands. We assessed whether patterns of sex differences varied across ethnic groups and across SES groups.

Methods

We set up a retrospective cohort study, combining individual-level data from administrative records from Statistics Netherlands on all men and women aged ≥25 years living in one study region in the Netherlands with prospectively collected data on EMS-attended OHCA incidence in this study region from the AmsteRdam REsuscitation Studies (ARREST) registry.

Study population

The source population comprised all individuals living in the study region of North Holland province of the Netherlands on the reference date 01-01-2009. This study region covers 2404 km^2 (urban and rural communities) and has a population of 2.4 million people, and was chosen because it is the catchment area of the ARREST registry, from which the OHCA cases for this study were identified. From the total population, we selected all men and women aged ≥25 years. This lower age bound was chosen under the assumption that individuals are likely financially independent from this age onwards (we used financial position as measure of SES). Individuals were excluded from the analysis if household and personal income data were missing. In total, data of 1,688,285 individuals were available for analysis (Supplemental Figure S1).

ARREST

The ARREST registry is an ongoing prospective registry of all EMS-attended OHCA cases in the study region. The ARREST registry has been described in detail elsewhere.[20, 21] In brief, for each suspected OHCA, the EMS dispatcher sends two

ambulances and a first responder (police, fire brigade, or citizen rescuer) equipped with an automated external defibrillator (AED) to the collapsed individual. Available ECG recordings from either the AED of the first responder or the manual defibrillator of the ambulance are sent to the ARREST study team. Further data (demographics, treatment characteristics, and outcomes) are garnered from the ambulance, first responder, hospital, and dispatch centre. For individuals that survived a cardiac arrest, (written) informed consent was obtained. The AMC Ethical Review Board approved the ARREST study, including the use of deceased patients' data.

Linkage

To obtain data on ethnicity and SES, all records of OHCA cases identified in the ARREST registry from the reference date until 31-12-2015 were linked to Statistics Netherlands records for individuals within the study population with algorithmic deterministic linkage carried out by Statistics Netherlands (Supplemental Figure S1). This was based on 1) date of birth and sex, and 2) postal code, house number, and date at which the individual lived at the address. Linkage was successful for 96% of OHCA cases. After linkage, the cases were pseudonymized by Statistics Netherlands.

OHCA

In the primary analysis, OHCA cases were derived from the ARREST registry. In the ARREST registry, an OHCA event is defined as a resuscitation attempt by EMS personnel or a defibrillation attempt with an AED by a first responder or bystander (such defibrillation attempts are always followed by subsequent treatment by EMS). Arrests are deemed to result from cardiac causes unless an unequivocal non-cardiac cause was documented (e.g., trauma or drowning). We excluded arrests from obvious non-cardiac causes.

There may be subgroup differences in inclusion rates of OHCAs in the registry because of differences in EMS attendance. For instance, we previously showed that women have a lower chance than men to be resuscitated after an OHCA.[8] Thus, for secondary sensitivity analyses, we additionally included SCD events in the death certificate data of Statistics Netherlands, creating a combined outcome for OHCA and SCD. In these secondary analyses, SCD events were defined as deaths occurring out of hospital with International Classification of Diseases 10th revision (ICD-10) codes I21 (acute myocardial infarction), I24 (other acute ischemic heart diseases), I46 (cardiac arrest), or I50 (heart failure), based on cardiologist's consultation.

Independent variables

Data on age, sex, ethnicity, and income were retrieved from Statistics Netherlands. Age on the reference date was calculated from date of birth. Sex was classified as man or woman based on registered sex. Ethnicity was defined according to country of birth of the participant and of the participant's parents.[22] Briefly, a participant was considered to belong to one of the ethnic minority groups 1) if the participant was born in the specified country and has at least one parent that was born in the same country, or 2) if both parents were born abroad. We classified ethnicity into six groups, according to Statistics Netherlands standards: Dutch, Western, Antillean or Aruban, Moroccan, Surinamese, Turkish, and other. As a measure of SES, we used household income data,[23] which are provided to Statistics Netherlands by the Dutch tax authorities.[24] In brief, total disposable household income comprises all sources of income (including income from assets) of individuals living within the household, aggregated over the household, including rebates and social benefits minus taxes and insurance premiums. This is standardised for household composition from the year preceding the reference date. We classified income data into quintiles. Data on OHCA characteristics were retrieved from the ARREST registry. Location of OHCA was classified as at home or public. Witness status of OHCA was classified as yes, no, or by ambulance.

Statistical analyses

Baseline characteristics were expressed as medians (interquartile range [IQR]) or frequencies (percentages) by sex in the total population. We calculated OHCA incidence per 100,000 person-years stratified by sex in the total population and per ethnic group and income group. Then, OHCA incidence per 100,000 person-years was standardised for age using the age structure of the Dutch population in 2009 as the standard. Additionally, 5-year cumulative incidence was estimated by 1 minus the probability of no OHCA, obtained from Kaplan-Meier curves.

We performed Cox proportional hazards regression analyses to examine sex differences in OHCA incidence. Censoring occurred for the following reasons: if an individual appeared in the ARREST registry as having suffered an OHCA, if an individual died, if an individual migrated out of the study region, or for administrative reasons on the end date of follow up (31-12-2015). Prior to the analyses, we checked the proportional hazards assumption by visual inspection of the Kaplan-Meier curves. We adjusted for age (model 1), age and income (model 2), age and ethnicity (model 3), and age, ethnicity, and income (model 4). Then, we stratified our analyses by ethnicity and by income quintiles. To study whether the sex differences varied between ethnic groups or income groups (i.e., effect modification), we added a

statistical interaction term on a multiplicative scale for sex and ethnicity to model 2 and for sex and income to model 3.

Secondarily, we repeated our analyses with a combined outcome of OHCA and SCD events.

All statistical analyses were performed in IBM SPSS Statistics (version 25.0). p-values <0.05 were regarded as statistically significant.

Results

On the reference date, the median age of the study population was 48 years (IQR 23) in men and 49 years (IQR 25) in women (Table 1). The majority of men and women were of Dutch ethnic origin. Median household income was higher in men than in women in the total population. A total of 3,834 men and 1,659 women had an OHCA in 5,378,723 and 5,685,666 person-years, respectively. Female OHCA cases were older (70 years) than male OHCA cases (65 years) on the reference date. OHCA events more often occurred at home among women (87%) compared to men (73%), and were slightly more often unwitnessed in women (29%) than in men (26%).

The age-standardised incidence rate of OHCA was lower in women than in men (30.9 versus 87.3 per 100,000 person-years), overall and across age-groups (Table 2; Figure 1). In most ethnic groups, women had a lower age-standardised OHCA incidence rate (range: 30.0-47.1 per 100,000 person-years) compared to men (range: 59.4-103.1 per 100,000 person-years). In the Moroccan group, women had a higher age-standardised OHCA incidence rate than men (although the crude incidence rate remained higher in men than in women at 20.7 and 13.8 per 100,000 person-years, respectively). In all income groups, the age-standardised OHCA incidence rate was also lower in women (range: 22.6-37.6 per 100,000 person-years) than in men (range: 64.1-104.6 per 100,000 person-years). Accordingly, the age-standardised incidence rate of the combined outcome of OHCA+SCD was lower in women than in men (47.0 versus 118.1 per 100,000 person-years) in the total population, all ethnic groups (except in the Moroccan group), and all income groups (Table 2, Figure 1). A similar direction in sex differences was observed for the estimated 5-year cumulative incidence of OHCA and OHCA+SCD (Supplemental Table S1).

Table 1. Baseline characteristics of the overall study population and OHCA cases, by sex

	Overall study population (n=1,688,285)		**OHCA cases (n=5,493)**	
	Men (n=821,451)	**Women (n=866,834)**	**Men (n=3,834)**	**Women (n=1,659)**
Age in years, median (IQR)	48 (23)	49 (25)	65 (18)	70 (20)
Ethnicity, n (%)				
Dutch	610,862 (74.4)	644,413 (74.3)	3,164 (82.5)	1,353 (81.6)
Western	91,508 (11.1)	102,123 (11.8)	360 (9.4)	162 (9.8)
Antillean or Aruban	6,618 (0.8)	6,794 (0.8)	20 (0.5)	x[a]
Moroccan	23,564 (2.9)	21,227 (2.4)	33 (0.9)	20 (1.2)
Surinamese	27,742 (3.4)	34,382 (4.0)	117 (3.1)	68 (4.1)
Turkish	21,219 (2.6)	19,575 (2.3)	57 (1.5)	19 (1.1)
Other	39,938 (4.9)	38,320 (4.4)	83 (2.2)	x[a]
Income				
Median (IQR)	23,258 (13,801)	21,753 (13,211)	20,844 (11,583)	18,367 (9,380)
N (%)				
First quintile (highest)	178,574 (21.7)	159,075 (18.4)	560 (14.6)	163 (9.8)
Second quintile	173,005 (21.1)	164,660 (19.0)	701 (18.3)	218 (13.1)
Third quintile	167,367 (20.4)	170,208 (19.6)	770 (20.1)	291 (17.5)
Fourth quintile	154,227 (18.8)	183,494 (21.2)	967 (25.2)	499 (30.1)
Fifth quintile (lowest)	148,278 (18.1)	189,397 (21.8)	836 (21.8)	488 (29.4)
Location of OHCA, n (%)				
At home	NA	NA	2,795 (72.9)	1,441 (86.9)
Public	NA	NA	1,026 (26.8)	206 (12.4)
Missing	NA	NA	13 (0.3)	12 (0.7)
Witnessed OHCA, n (%)				
Yes	NA	NA	2,508 (65.4)	994 (59.9)
No	NA	NA	982 (25.6)	474 (28.6)
By ambulance	NA	NA	297 (7.8)	163 (9.8)
Missing	NA	NA	47 (1.2)	28 (1.7)

IQR, interquartile range; NA, not applicable; OHCA, out-of-hospital cardiac arrest.

[a] Frequencies not reported due to small number of cases (<10) in at least one of the groups.

Table 2. Crude and age-standardised OHCA and OHCA+SCD incidence rates, overall and per ethnic group and income group, by sex

	OHCA incidence rates (per 100,000 person-years)				OHCA+SCD incidence rates (per 100,000 person-years)			
	Crude		Age-standardised		Crude		Age-standardised	
	Men	Women	Men	Women	Men	Women	Men	Women
Overall	71.3	29.2	87.3	30.9	88.5	43.5	118.1	47.0
Ethnicity								
Dutch	79.4	32.2	88.6	30.5	98.9	49.1	119.3	46.5
Western	59.9	24.0	82.0	30.0	74.4	33.7	108.6	45.8
Antillean or Aruban	46.8	x[a]	59.4	x[a]	56.1	x[a]	112.9	x[a]
Moroccan	20.7	13.8	38.7	69.8	28.3	16.6	61.0	77.2
Surinamese	64.9	29.7	103.1	47.1	76.0	37.5	129.0	63.0
Turkish	39.8	14.2	70.8	31.8	47.4	21.7	86.8	71.1
Other	31.3	12.4	82.7	40.3	37.3	14.8	106.0	58.3
Income								
First quintile (highest)	47.3	15.4	64.1	22.6	56.2	19.2	94.5	31.8
Second quintile	61.0	19.8	82.7	26.1	71.2	26.4	106.7	38.9
Third quintile	69.7	25.8	87.1	28.8	85.7	35.3	114.7	42.3
Fourth quintile	97.0	41.8	98.5	36.1	124.5	64.5	131.9	53.9
Fifth quintile (lowest)	88.5	40.6	104.6	37.6	115.6	67.7	142.9	58.4

OHCA, out-of-hospital cardiac arrest; SCD, sudden cardiac death.

[a] Incidence rates not reported due to small number of cases (<10).

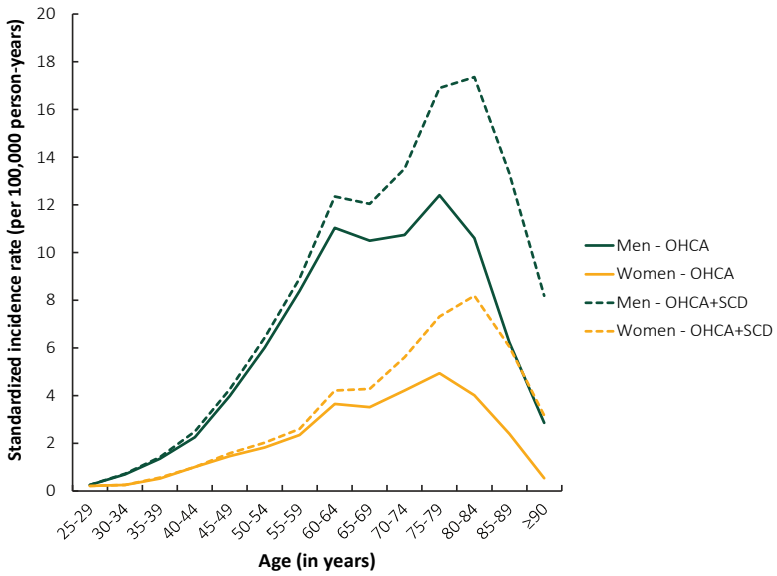

Figure 1. Standardized incidence rates of OHCA (solid lines) and OHCA+SCD (dashed line) per 100,000 person-years by age, stratified by sex

The hazard for OHCA was lower in women compared to men (Table 3; fully adjusted hazard ratio (HR) 0.33, 95% confidence interval [CI] 0.31-0.35). This sex difference in hazard for OHCA was largely consistent across ethnic groups, with HRs ranging from 0.19 in the Antilleans and Arubans to 0.40 in the Surinamese and other groups. In contrast to these groups, the hazard for OHCA was more similar in Moroccan men and women (HR 0.89, 95% CI 0.51-1.57). Across income groups, women had a consistently lower hazard for OHCA compared to men (HR range: 0.30-0.35). These patterns of sex differences were similar to sex differences in hazard for OHCA+SCD (Supplemental Table S2).

Table 3. Hazard ratios for OHCA in women compared to men, overall, and stratified by ethnicity and by income

Overall	**HR (95% CI)**	**p-value**	
Model 1: Adjusted age	0.34 (0.32-0.36)	**<0.001**	
Model 2: Adjusted age and income	0.33 (0.31-0.35)	**<0.001**	
Model 3: Adjusted age and ethnicity	0.34 (0.32-0.36)	**<0.001**	
Model 4: Adjusted age, ethnicity, and income	0.33 (0.31-0.35)	**<0.001**	
Ethnicity[a]	**HR (95% CI)**	**p-value**	**p-value for sex*ethnicity interaction**
Dutch	0.32 (0.30-0.34)	**<0.001**	Reference
Western	0.33 (0.28-0.40)	**<0.001**	0.45
Antillean or Aruban	0.19 (0.07-0.52)	**<0.01**	0.38
Moroccan	0.89 (0.51-1.57)	0.70	**<0.01**
Surinamese	0.40 (0.30-0.55)	**<0.001**	0.10
Turkish	0.35 (0.21-0.58)	**<0.001**	0.69
Other	0.40 (0.27-0.61)	**<0.001**	0.24
Income[b]	**HR (95% CI)**	**p-value**	**p-value for sex*income interaction**
First quintile (highest)	0.31 (0.26-0.37)	**<0.001**	Reference
Second quintile	0.30 (0.26-0.35)	**<0.001**	0.76
Third quintile	0.33 (0.29-0.37)	**<0.001**	0.67
Fourth quintile	0.35 (0.32-0.39)	**<0.001**	0.32
Fifth quintile (lowest)	0.33 (0.30-0.37)	**<0.001**	0.82

CI, confidence interval; HR, hazard ratio; OHCA, out-of-hospital cardiac arrest.

Statistically significant p-values (p<0.05) are marked in bold.

[a] Model 2 adjustments.

[b] Model 3 adjustments.

Discussion

In our population-based cohort study of almost 1.7 million men and women, we observed substantial rates of age-standardised EMS-attended OHCA incidences in both men and women. In most ethnic groups and in all SES groups, women have a lower OHCA incidence rate than men.

Our study has limitations. First, we may have missed OHCA cases due to delayed recognition (person was found dead) or the decision not to alarm the EMS (e.g., because of advanced age). This may have led to under-registration. In order to take the potential under-registrations into account, we conducted a sensitivity analysis including SCD in our case definition, which did not alter the interpretation of our finding that sex differences occur. Second, we may have included people at baseline with recurrent OHCA (after having experienced an OHCA in the past), since we had no data on OHCAs before the reference date. Recurrent OHCA may occur more often among men than women, as men are more likely to survive a OHCA compared to women.[8] Since recurrent OHCAs are common among OHCA survivors,[25] this may have somewhat overestimated our observed sex differences in OHCA incidence. However, overall survival rates of OHCA are low,[1] making it unlikely that our results were substantially influenced by the inclusion of recurrent OHCAs. Third, our measurement of SES may be suboptimal, as there may be differences in access to household income between men and women, with women generally being disadvantaged.[26] Hence, household income may be less suitable to capture the risks associated with SES in women compared to men.[23] Other common measures of SES (educational level and occupational level) were not available. Fourth, although country of birth is a commonly used indicator for ethnicity,[22] this definition does not distinguish subgroups (e.g., Surinamese of African origin or of South-Asian origin). This limits comparisons with other studies using more fine-grained indicators.

The absolute OHCA incidence rates in men and women reported in our study are likely representative of the Dutch population and were similar to another study from the Netherlands,[7] although this study also included non-resuscitated OHCA cases and cases with non-cardiac causes. Our incidence rates differed from those reported in previous studies from other countries. For instance, our incidence rates were higher compared to a South-Korean study[5] and lower compared to two studies from France[4] and Australia.[6] Differences in incidence rates between studies are well-known and may be explained by various reasons, including differences in study population characteristics (e.g., age), in OHCA case definition (e.g., inclusion of non-cardiac causes), and in true risk.[1] The last reason may be supported by the broad range in absolute OHCA incidence rates across subgroups observed in our study.

The relative sex difference in OHCA incidence rates was in line with absolute differences in OHCA incidence rates in women compared to men reported in previous studies.[4-7] Even after adjustments for age, ethnicity and SES, we observed that the hazard for OHCA was one third in women compared to men. These findings are not unexpected and correspond with the general assumption that men are at higher risk of CVD than women. Nevertheless, our sensitivity analyses assessing under-registration showed that there may be relatively more avoidable deaths (SCDs) in women compared to men, as the proportional difference between OHCA and OHCA+SCD incidence rates is larger in women (30.9 versus 47.0 [52%]) than in men (87.3 versus 118.1 [35%]), consistently across most ethnic and SES groups. Delayed recognition of and delayed action after an OHCA may occur more often in women compared to men and may be caused by a differential interpretation of an OHCA in women, due to the lack of awareness of the occurrence of OHCA in women by women themselves,[27] and potentially by bystanders. Furthermore, an OHCA in women may occur unwitnessed more often compared to men. Due to a higher life expectancy among women compared to men, women at older age are more likely to have outlived their partner (presuming heterosexual relationships) and live alone. Indeed, particularly in older age groups in which OHCA incidence rates are the highest, most OHCA events occur at a private location and may occur unwitnessed more often.[8, 28] Moreover, women in younger age groups may more often than men have an unwitnessed OHCA at home, because of a lower labour force participation and less working hours among women compared to men.[29] Even when witnessed, women are less likely to receive a cardiopulmonary resuscitation attempt by bystanders than men[20] (and are therefore less likely to be included in the ARREST registry), potentially due to fear of inappropriate touching or causing injury when performing cardiopulmonary resuscitation on women.[30]

In contrast to previous limited evidence on other CVD outcomes,[10, 11] we observed that sex differences in OHCA incidence are consistent across most ethnic groups, independently of SES. Only in the Moroccan group, the OHCA incidence is more similar between men and women, which is mainly due to the lower OHCA incidence among Moroccan men compared to other men. This lower OHCA incidence rate is in line with lower incidence rates of other CVD outcomes among Moroccans compared to other ethnic groups in the Netherlands.[31, 32] A potential explanation for this general pattern is the low prevalence of smoking among Moroccan men compared to other ethnic minority groups living in the Netherlands,[33] while smoking is an important risk factor for OHCA.[34] The underreporting of OHCA cases or low resuscitation rates may also play a role, as the proportional difference between OHCA incidence rates and OHCA+SCD incidence rates is larger among Moroccan

men (58%) compared to most other ethnic groups (range 2-35%), although smaller than among Antillean or Aruban men (90%).

Sex differences in OHCA incidence, regardless of ethnicity, are also consistent across individual-level SES groups. In contrast, a study from the UK reported that neighbourhood-level SES was predominantly associated with OHCA+SCD incidence in women, suggesting a modifying effect of sex on the association between SES and OHCA+SCD.[19] Future studies need to confirm whether other SES classifications impact OHCA incidence in men and women differently.

The differential underlying aetiology of OHCA may play a role in differences in OHCA incidence between men and women. For instance, a recent autopsy study found that women were more likely to have non-ischemic causes of autopsy-defined sudden arrhythmic death than men.[9] This indicates that women may also benefit from targeted prevention strategies, but that other strategies next to the existing strategies focused on coronary heart disease may be needed. Further research into sex- and gender-specific differences into which combinations of risk factors are at play in women versus men is warranted. In general, differences in cardiovascular health between men and women are not merely caused by biological sex differences related to, for instance, sex hormones.[35] Sociocultural gender differences may directly or indirectly impact on health, e.g., through differences in health-related behaviour or participation in preventive treatment. Our observation of the consistency of differences in OHCA incidence between men and women across social strata shows that sociocultural factors should be sought within those not substantially modified by household income and ethnicity.

In conclusion, we observed that women had a substantial, yet lower EMS-attended OHCA incidence than men, consistently across SES groups and most ethnic groups. Therefore, our findings confirm that men across social strata are an important target group for OHCA prevention strategies. Nevertheless, in light of potentially differential aetiology and lower survival rates, women may also benefit from targeted prevention strategies.

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Marieke Blom	Validation, writing - review & editing
Hanno L. Tan	Methodology, writing - review & editing, funding acquisition
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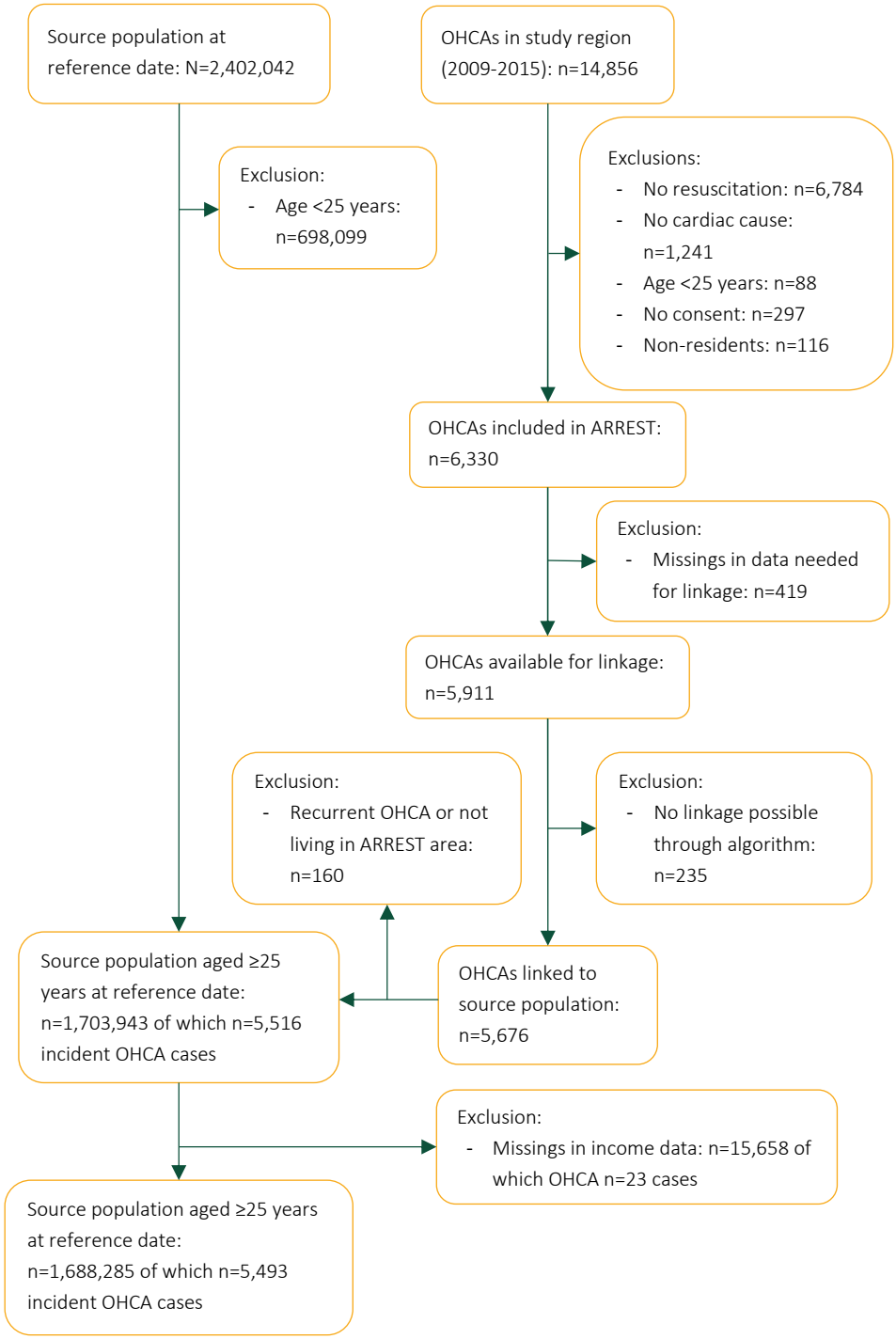

Supplemental Figure S1. Flow diagram of study population

Supplemental Table S1. Estimated cumulative incidence of OHCA and OHCA+SCD for the first 5 years by sex, by sex and ethnicity, and by sex and income

	Estimated cumulative incidence of OHCA, per year (%)									
	Men					**Women**				
	1 yr	**2 yr**	**3 yr**	**4 yr**	**5 yr**	**1 yr**	**2 yr**	**3 yr**	**4 yr**	**5 yr**
Overall	0.0	0.1	0.2	0.3	0.4	0.0	0.1	0.1	0.1	0.1
Ethnicity										
Dutch	0.1	0.2	0.2	0.3	0.4	0.0	0.1	0.1	0.1	0.2
Western	0.1	0.1	0.2	0.2	0.3	0.0	0.0	0.1	0.1	0.1
Antillean or Aruban	0.0	0.1	0.1	0.1	0.2	0.0	0.0	0.0	0.0	0.1
Moroccan	0.0	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.1
Surinamese	0.1	0.1	0.2	0.2	0.3	0.0	0.1	0.1	0.1	0.1
Turkish	0.0	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.1
Other	0.0	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.1
Income										
First quintile (highest)	0.0	0.1	0.1	0.2	0.2	0.0	0.0	0.0	0.1	0.1
Second quintile	0.1	0.1	0.2	0.2	0.3	0.0	0.0	0.1	0.1	0.1
Third quintile	0.1	0.1	0.2	0.3	0.4	0.0	0.0	0.1	0.1	0.1
Fourth quintile	0.1	0.2	0.3	0.4	0.5	0.0	0.1	0.1	0.2	0.2
Fifth quintile (lowest)	0.1	0.2	0.3	0.4	0.4	0.0	0.1	0.1	0.2	0.2
	Estimated cumulative incidence of OHCA+SCD, per year (%)									
	Men					**Women**				
	1 yr	**2 yr**	**3 yr**	**4 yr**	**5 yr**	**1 yr**	**2 yr**	**3 yr**	**4 yr**	**5 yr**
Overall	0.1	0.2	0.3	0.4	0.5	0.1	0.1	0.2	0.2	0.2
Ethnicity										
Dutch	0.1	0.2	0.3	0.4	0.5	0.1	0.1	0.2	0.2	0.3
Western	0.1	0.2	0.3	0.3	0.4	0.0	0.1	0.1	0.1	0.2
Antillean or Aruban	0.0	0.1	0.2	0.2	0.3	0.0	0.1	0.1	0.1	0.1
Moroccan	0.0	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1	0.1
Surinamese	0.1	0.2	0.2	0.3	0.4	0.0	0.1	0.1	0.2	0.2
Turkish	0.0	0.1	0.2	0.2	0.2	0.0	0.0	0.1	0.1	0.1
Other	0.0	0.1	0.1	0.2	0.2	0.0	0.0	0.0	0.1	0.1
Income										
First quintile (highest)	0.1	0.1	0.2	0.2	0.3	0.0	0.0	0.1	0.1	0.1
Second quintile	0.1	0.1	0.2	0.3	0.4	0.0	0.1	0.1	0.1	0.1
Third quintile	0.1	0.2	0.3	0.4	0.5	0.0	0.1	0.1	0.2	0.2
Fourth quintile	0.1	0.3	0.4	0.6	0.7	0.1	0.2	0.2	0.3	0.4
Fifth quintile (lowest)	0.1	0.3	0.4	0.5	0.6	0.1	0.2	0.3	0.4	0.4

OHCA, out-of-hospital cardiac arrest; SCD, sudden cardiac death; yr, years.

Supplemental Table S2. Hazard ratio for OHCA+SCD in women compared to men, overall, and stratified by ethnicity and by income

Overall	**HR (95% CI)**	**p-value**	
Model 1: Adjusted age	0.39 (0.37-0.41)	**<0.001**	
Model 2: Adjusted age and income	0.37 (0.36-0.39)	**<0.001**	
Model 3: Adjusted age and ethnicity	0.38 (0.37-0.40)	**<0.001**	
Model 4: Adjusted age, income and ethnicity	0.37 (0.35-0.39)	**<0.001**	
Ethnicity[a]	**HR (95% CI)**	**p-value**	**p-value for sex*ethnicity interaction**
Dutch	0.37 (0.35-0.39)	**<0.001**	Reference
Western	0.36 (0.31-0.42)	**<0.001**	0.95
Antillean or Aruban	0.28 (0.13-0.62)	**<0.01**	0.57
Moroccan	0.84 (0.51-1.38)	0.48	**<0.01**
Surinamese	0.44 (0.33-0.57)	**<0.001**	0.26
Turkish	0.44 (0.28-0.68)	**<0.001**	0.36
Other	0.39 (0.27-0.57)	**<0.001**	0.65
Income[b]	**HR (95% CI)**	**p-value**	**p-value for sex*income interaction**
First quintile (highest)	0.32 (0.27-0.37)	**<0.001**	Reference
Second quintile	0.34 (0.29-0.42)	**<0.001**	0.70
Third quintile	0.36 (0.32-0.40)	**<0.001**	0.35
Fourth quintile	0.41 (0.37-0.44)	**<0.001**	**0.02**
Fifth quintile (lowest)	0.39 (0.36-0.43)	**<0.001**	0.09

CI, confidence interval; HR, hazard ratio; OHCA, out-of-hospital cardiac arrest; SCD, sudden cardiac death.
Statistically significant p-values are marked in bold.

[a] Model 2 adjustments.

[b] Model 3 adjustments.