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Ethnic differences in cardiovascular morbidity and mortality among breast cancer patients in the Netherlands: a register-based cohort study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-021509
Article Type:	Research
Date Submitted by the Author:	20-Jan-2018
Complete List of Authors:	Deen, Laura; University of Amsterdam, Department of Public Health, Academic Medical Centre; Copenhagen University Hospital, Section of Immigrant Medicine, Department of Infectious Diseases Buddeke, Josefien; University Medical Centre Utrecht, Julius Centre for Health Sciences and Primary Care Vaartjes, Ilonca; University Medical Centre Utrecht, Julius Centre for Health Sciences and Primary Care Bots, Michael; University Medical Centre Utrecht, Julius Centre for Health Sciences and Primary Care Nørredam, Marie; University of Copenhagen, Danish Research Centre for Migration, Ethnicity and Health, Section of Health Services Research, Department of Public Health; Copenhagen University Hospital, Section of Immigrant Medicine, Department of Infectious Diseases Agyemang, Charles; University of Amsterdam, Department of Public Health, Academic Medical Center
Keywords:	Ethnicity, breast cancer, migrant, cardiovascular disease, cardiovascular mortality

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Ethnic differences in cardiovascular morbidity and mortality among breast cancer patients in the Netherlands: a register-based cohort study.

Laura Deen, MSC[1,2]; Josefien Buddeke, MSC[3]; Ilonca Vaartjes, PhD[3]; Michiel L. Bots, MD PhD[3]; Marie Norredam, MD PhD[2,4]; Charles Agyemang, MPH, PhD[1]

[1]Department of Public Health, Academic Medical Centre, University of Amsterdam, Amsterdam Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, The Netherlands

[2]Section of Immigrant Medicine, Department of Infectious Diseases, Copenhagen University Hospital, Kettegård allé 30, 2650 Hvidovre, Denmark

[3]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

[4]Danish Research Centre for Migration, Ethnicity and Health, Section of Health Services Research, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, 1014 København K, Denmark

Corresponding author:

Laura Deen, Department of Public Health, Academic Medical Centre, University of Amsterdam, Amsterdam Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, The Netherlands

e-mail:nhq382@alumni.ku.dk, telephone.: +4527514559

Word count:

Abstract: 239.

Total manuscript (excluding references, tables and figures): 3876

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Abstract

Objectives: Cardiovascular disease (CVD) is of increasing concern among breast cancer survivors. However, evidence on ethnic differences in CVD among women with breast cancer is sparse. We assessed ethnic differences in cardiovascular morbidity and mortality among breast cancer patients in the Netherlands.

Methods: A nationwide register-based cohort study comprising all women with a first admission for breast cancer (n=127,714) between 1996 and 2010 in the Netherlands was conducted. Differences in CVD admission, CVD mortality and overall CVD event, which comprised a CVD admission and/or CVD mortality, between the largest ethnic minority groups (Surinamese, Moroccan, Turkish, Antillean, and Indonesian) and the Dutch general population (henceforth, Dutch) were investigated using Cox proportional hazard models.

Results: The incidence of cardiovascular outcomes varied by ethnic group. The incidence of an overall cardiovascular event was significantly higher for women with breast cancer from Suriname (HR=1.46;95% CI 1.29–1.64) and Turkey (HR=1.25;95% CI 1.03–1.51), compared with Dutch women with breast cancer. In contrast, Indonesian women with breast cancer had a significantly lower risk (HR=0.88; 95% CI 0.81–0.96) of a cardiovascular event compared with Dutch women with breast cancer. There were no significantly differences between Moroccan and Antillean women, and Dutch women with breast cancer.

Conclusions: Our findings suggest that Surinamese and Turkish women with breast cancer are disadvantaged in terms of cardiovascular outcomes compared with Dutch women with breast cancer. More work is needed to unravel the potential factors contributing to these differences.

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Strengths and limitations of this study:

- This study provides important new insights into ethnic differences in cardiovascular morbidity and mortality among breast cancer patients in a European country.
- The study builds on data from nation-wide registries with high validity.
- Although the study is based on a nationwide cohort of breast cancer patients, absolute numbers are somewhat small when divided into different ethnic groups.
- Data on CVD risk factors, such as smoking, alcohol and obesity were not available since the study builds on registry data.

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1. Introduction

Due to earlier diagnosis and more effective treatment, the survival rate among breast cancer patients has now improved resulting in a growing population of breast cancer survivors. In The Netherlands, the 5-year-age-standardized survival rate has increased from 80% in 1995-99 to 85% in 2005-09 [1]. With breast cancer becoming a curable disease, comorbidities and death from other conditions among breast cancer survivors are of increasing concern.

One of the most important comorbidities to consider in women with breast cancer is cardiovascular disease (CVD), and with the growing number of breast cancer survivors, a better understanding of the risk of CVD in this group is crucial. Studies show that women surviving breast cancer have an increased risk of CVD morbidity and CVD-specific mortality compared with women without breast cancer [2,3]. Moreover, among breast cancer survivors, CVD-related mortality is becoming more common than breast cancer-specific mortality [4,5]. This is mainly attributable to cardiotoxic effects of breast cancer therapy [6,7]. Further, survivors are typically older than the general population and may be more likely to develop CVD because of risk factors common to both cancer and CVD [8].

Evidence suggests ethnic inequalities in the prognosis of breast cancer with a higher risk of breast cancer-specific and overall mortality among some ethnic minority groups [9,10]. However, although ethnic variation in cardiovascular outcomes in the general population exists [11,12], the evidence among breast cancer patients is limited. Data from the US show that African American and Pacific Islander women with breast cancer had an increased risk of dying from CVD compared with White American breast cancer patients [4,13]. However, ethnic compositions and the national context vary across countries and, to our knowledge, no European study has

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examined the risk of CVD related outcomes in different ethnic groups among breast cancer patients. Hence, the aim of this study was to explore differences in overall CVD event, CVD admission and CVD mortality following a diagnosis of breast cancer between the largest ethnic minority groups in the Netherlands compared with ethnic Dutch.

2. Methods

Study sample

This register-based cohort study builds on data from different Dutch nationwide registers. The registries and linkage procedures used in this cohort study have previously been described in detail [14]. In brief, we linked data between the national Dutch hospital discharge register, the population register and the cause of death register using a record identification number. This number is assigned to each resident in the Netherlands with a unique combination of birth date, sex and postal code (84% of the Dutch population). The Dutch national hospital discharge register and cause of death register were linked to identify all women with a first admission for breast cancer between 1996 and 2010, using the International Classification of Diseases (ICD) 9th revision and ICD 10th revision. Both patients with invasive (ICD-9: 174 and ICD-10: C50) and in situ breast cancer (ICD-9: 233 and ICD-10: D05) were identified and men were excluded. Data from the population register and the cause of death register were available until 2012 and data from the Dutch hospital discharge register were available until 2010. Individuals were followed from the date of their first breast cancer admission until (a) CVD admission, (b) CVD death, (c) death due to other causes, (d) first emigration or (d) study end (31.12.2012), whichever came first. Linkage of data from the different registries was performed in agreement with the privacy legislation in The Netherlands. All linkages and analysis were performed in a secured environment of Statistics Netherlands.

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Ethnic group

Ethnic groups were constructed based on the country of birth of the resident and her parents, according to the definition of Statistics Netherlands [15]. A woman was considered a migrant if she was born abroad or at least one of the parents was born abroad. Women with both parents born in the Netherlands were indicated as being Dutch. The major non-Western migrant groups residing in the Netherlands were included, which are those born in Turkey, Suriname, Morocco, Indonesia, and the Netherlands Antilles.

Outcomes

CVD admission after a diagnosis of breast cancer was defined as all admissions with either the primary or secondary cause of admission coded as ICD-10: 017.2, 093, 228, 289.1–289.3, 390–459, 557,745–747, 780.2, 782.3, 7825, 7826, 785, 786.50–786.59, 789.2, 794.30–794.39. Cardiovascular mortality was defined as dying from a cardiovascular cause after a diagnosis of breast cancer. Overall cardiovascular event combined the two outcomes and comprised a hospital admission for CVD, and/or a dying from a cardiovascular cause.

Data analyses

We first presented baseline characteristics as absolute numbers and percentages according to ethnic group. Continuous variables were summarized as mean and standard deviation or as median and interquartile range where appropriate. Subsequently, we calculated hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) using cox proportional hazard regression analyses to assess ethnic differences in overall cardiovascular events, and separately for hospital admission for CVD and cardiovascular mortality between ethnic minority groups and

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the Dutch (reference group) with adjustment for age, year of admission and type of breast cancer. Cox proportional hazard assumptions were checked and met. All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Table 1 presents the characteristics of the study population by ethnic group. In total, 127,714 women with a first admission for breast cancer between 01.01.1996 and 31.12.2010 were included in the study, of which 5% belonged to an ethnic minority group (table 1). Dutch women were in general followed for a longer period than the ethnic minority groups. Among migrants, the Antilleans presented the smallest group and the Indonesians the largest group. In general, the ethnic minority groups were younger than the Dutch population when diagnosed. During follow-up, 19% of the Dutch population experienced a hospital admission due to CVD, whereas among the ethnic minorities the proportion of CVD admission ranged from 9% for Moroccans to 19% for Surinamese women. 31,203 women with breast cancer died during follow-up, of which 25% were due to a cardiovascular cause.

Table 2 shows the incidence of a CVD event, which comprises a hospital admission for CVD, and/or dying from a cardiovascular cause, among breast cancer patients by ethnic group. Compared with Dutch women with breast cancer, both Surinamese (HR=1.46;95% CI 1.29–1.64) and Turkish (HR=1.25;95% CI 1.03–1.51) women with breast cancer had a higher incidence of CVD event after adjustment for breast cancer diagnosis, period of breast cancer diagnosis and age. In contrast, Indonesian women with breast cancer had a significantly lower risk (HR=0.88; 95% CI 0.81–0.96) of cardiovascular event compared with Dutch women. For Moroccans and Antilleans there were no significantly differences from Dutch women.

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Subsequently, we assessed cardiovascular admission and cardiovascular mortality separately. Table 3 shows the unadjusted and adjusted hazard ratios for a cardiovascular admission. Only women from Suriname had a significantly higher risk (HR=1.45; 95% CI 1.28–1.64) of cardiovascular admission compared with Dutch women with breast cancer, whereas women from Indonesia had a significantly lower risk of a cardiovascular admission (HR=0.85; 95% CI 0.78–0.93). The unadjusted and adjusted hazard ratios for cardiovascular mortality for the different ethnic groups are shown in table 4. The adjusted hazard ratios for cardiovascular mortality were significantly higher for women from Suriname (HR=1.49; 95% CI 1.13-1.97) and Turkey (HR=1.96; 95% CI 1.28-3.01), compared with Dutch women, whereas there were no significantly differences between women from Indonesia and Dutch women. For Moroccan and Antillean women the numbers of deaths due to cardiovascular disease were too small to perform analyses.

4. Discussion

Key findings

In this population-based cohort study of women with breast cancer in the Netherlands, the risk of cardiovascular outcomes varied by ethnic group. Women from Suriname and Turkey had a higher risk of a CVD event compared with Dutch women with breast cancer. When separating cardiovascular admission and cardiovascular mortality, Surinamese women had a higher risk of both cardiovascular admission and cardiovascular mortality, whereas Turkish women only had a higher risk of cardiovascular mortality compared with Dutch women. In contrast, women from Indonesia with breast cancer had a lower risk of cardiovascular event, and cardiovascular admission, but similar risk of cardiovascular mortality compared with ethnic Dutch women with breast cancer. For Moroccan and Antillean women the risk of a cardiovascular event did not differ from Dutch women with breast cancer.

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Discussion of key findings

Evidence shows that ethnic minority and migrant groups in general have a lower risk of breast cancer compared with the majority population [16,17]. However, the results of this study indicate that among breast cancer patients, some ethnic minority groups are disadvantaged in terms of cardiovascular outcomes compared with Dutch women. The results of this study are in line with the sparse evidence on ethnic differences in CVD mortality among breast cancer patients in the US, which also found some ethnic minority groups to be disadvantaged in terms of cardiovascular mortality [4,13]. For example, African America women with ductal carcinoma in situ of the breast were found to have a higher risk of CVD death compared with White American women diagnosed with ductal carcinoma in situ of the breast [4]. However, even though CVD have been shown to vary by ethnic group [11,18] data among breast cancer patients in Europe have been lacking. Previous European studies on ethnic disparities in breast cancer prognosis have mostly focused on mortality after breast cancer diagnosis, and found that some ethnic minority groups have higher overall and breast cancer-specific mortality [9,10,19]. Our results thereby add a great value to the existing literature by showing that women with breast cancer from Suriname and Turkey are disadvantaged in terms of cardiovascular outcomes compared with Dutch women with breast cancer. The higher incidence of CVD event among Surinamese women with breast cancer reflects the pattern of CVD among Surinamese women in the general Dutch population. Previous studies of the general population in the Netherlands showed that Surinamese women have a higher risk of both AMI and stroke compared with Dutch women [20,21], as well as a higher 5-year CVD mortality after initial admission for CVD [22]. Turkish women with breast cancer were in the present study found to have a higher incidence of CVD event, compared with Dutch women with breast cancer. However, this only partly reflects on the pattern among Turkish women in the general population in the Netherlands. Previous studies of

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the general population in the Netherlands did not find differences in the incidence of stroke or AMI among Turkish women compared with the Dutch majority women [20,21]. However, when stratifying on age, a higher incidence of AMI were observed in 50- to 70-year-old Turkish women compared with the Dutch majority women [20].

The relatively low risk of CVD outcomes among Indonesian women with breast cancer are in contrast to previous studies of the general Dutch population that found no differences in incidence of AMI and a slightly higher risk of stroke among Indonesians compared with Dutch women [20,21]. The reasons for the better CVD prognosis among Indonesian breast cancer patients are unclear. However, Indonesians are well integrated in the Dutch society with respect to language and culture and have similar income levels and are employed at equal rates as the Dutch general population [23]. This possibly results in better access to health care services than other minority groups and may underlie the better cardiovascular health outcomes among Indonesian women with breast cancer.

Possible explanations for the higher risk of cardiovascular events among Surinamese and Turkish breast cancer patients may include disparities in access to health care services and a high risk factor burden among these ethnic minorities in the Netherlands. Regular health visits are important for early diagnosis of risk factors that can lead to CVD progression and it is possible that differences in health service utilisation may contribute to the observed ethnic differences in CVD risk among breast cancer patients. Evidence on health care utilization among breast cancer patients is scarce, but previous evidence of the general population in the Netherlands suggests that some ethnic minority populations use more general practitioner care than Dutch people do, but that they are less likely to use specialised care [24]. Moreover, ethnic differences in use of

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cardiac rehabilitation and lower adherence to medication therapy have been shown [25–28]. A Danish study found that immigrants from Pakistan and Turkey did not receive adequate medical treatment with beta-blockers after a first AMI compared with Danish-born residents [26]. In addition, in the Netherlands, Surinamese people have been found to have poor blood pressure control compared with their Dutch counterparts [28].

The relatively high incidence of CVD admission and mortality among Turkish and Surinamese breast cancer women may be explained by the high prevalence of cardiovascular risk factors in these populations. The current study lacked information on CVD risk factor and we were therefore not able to address the possible contribution of these to the observed ethnic differences. However, previous studies of Surinamese and Turkish populations in the Netherlands showed that hypertension, diabetes mellitus and obesity are more common among these populations compared with the Dutch general population [28–31]. As an example, a previous Dutch study showed that the prevalence of hypertension, the leading risk factor for CVD worldwide, was higher in both Turkish and Surinamese people than in Dutch people [28]. In addition, a study from the US, found that African American breast cancer patients have higher prevalence of certain CVD risk factors, such as hypertension, diabetes and obesity, prior to initiating aromatase inhibitory therapy, compared with White American breast cancer patients of the same age [32]. Evidence suggests that the presence of CVD risk factors among breast cancer patients at diagnosis is a strong predictive factor for the development of cardiovascular damage associated with breast cancer therapy [33]. The higher risk factor burden in some ethnic minority groups may therefore contribute to the higher incidence of CVD in these groups.

Additionally, since the risk of CVD has been shown to vary according to breast cancer therapy [7,34], the observed differences may be explained by variation in the treatment received by

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different ethnic groups. In the current study, data on treatment was not available. However, studies from the US and UK have reported that ethnic minority women were more likely to receive chemotherapy, which was largely explained by more advanced stage and higher grade tumours [35,36].

Our findings have important clinical and public health implications because identifying breast cancer patients who are most vulnerable to cardiovascular outcomes is important in order to guide strategies among breast cancer patients. The findings suggest the need to increase attention for these women in the cardiovascular risk factor management guidelines in the Netherlands and awareness of the observed ethnic differences in the risk of cardiovascular outcomes among breast cancer patients should be raised among clinicians and incorporated into oncology practices. The observed differences suggest the need for further studies to identify factors explaining these differences. More specific, studies addressing the potential contribution of both CVD risk factors and type of treatment to the observed ethnic differences found in this study are needed. This will help to tailor appropriate public health and clinical interventions to improve outcomes among breast cancer patients most at risk of adverse CVD outcomes.

Strength and limitations:

The strength of the current study is the validity of the registries, the linkage methods, and the lack of selection of the cohorts. A high validity of both the Dutch National Hospital Discharge Register and the Dutch Population Register has been demonstrated. In a random sample of the Hospital Discharge Register, 99% of the personal, admission and discharge data and 84% of the principal diagnoses (validated through medical record review by medical specialists) were correctly registered [37]. In addition, over 97% of the uniquely linked hospital admissions

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resulting from linkage of the Hospital Discharge Register with the Population Register were shown to be correctly linked [38].

Nonetheless, some limitations must be considered. First, although the study is based on a nationwide cohort of breast cancer patients, absolute numbers are somewhat small when divided into different ethnic groups. Consequently, the numbers were too small to investigate different kinds of CVD, which could have afforded a more nuanced picture. Second, inherent to many national-level databases, we lack detailed data on CVD risk factors, such as smoking, alcohol, cholesterol and obesity, and therefore we were unable to do additional analyses to assess the contribution of these to the observed ethnic differences. However, we were able to shed light on the potential contributing risk factors to the observed differences due to previous studies on ethnic differences in risk factors in the Netherlands [28–31]. Additionally, the study lack data on treatment of breast cancer. Since, CVD risk has been shown to vary according to type of treatment [7,34], adjustment for treatment would have been preferable in order to assess the potential impact of differences in treatment to the observed ethnic differences in CVD. Finally, as in numerous studies, the classifications of the various ethnic groups were based on country of birth. Country of birth may reflect ethnicity reasonably well among some ethnic groups but is likely to be an unreliable proxy measure of ethnicity for other groups such as Surinamese [15]. The results may be generalised to other European settings with similar health care services and composition of ethnic groups.

5. Conclusion

The results of the current study suggest that the risk of CVD related outcomes among breast cancer patients vary by ethnicity. Surinamese and Turkey breast cancer patients experienced a

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higher risk, whereas Indonesian patients had a slightly lower risk of CVD event compared with their Dutch counterparts. More extensive cohort studies are needed to identify the forms of CVD that are most common in these groups as well as the potential factors contributing to these differences.

Competing interest: None declared.

Funding

This work was supported by the Dutch Heart Foundation (grant number 2010B296).

Contributor ship statement

LD, JB, IV, MLB, MN, CA were involved in the study design. LD and CA wrote the paper. JB analysed the data. JB, IV, MLB and MN critically revised the manuscript. All Authors approved the final version of the manuscript.

Data sharing statement

No additional data are available.

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Table 1 Demographic and disease characteristics of women admitted for breast cancer between 1996 and 2010 in the Netherlands according to ethnic group

	Ethnic Dutch N %	Antillean N %	Indonesian N %	Moroccan N %	Surinamese N %	Turkish N %
No. of patients	120,809 (100)	454 (100)	3,457 (100)	919 (100)	1,351 (100)	724 (100)
Mean age at diagnosis (y), sd	60.4 (13.3)	52.8 (11.8)	57.0 (13.1)	47.0 (10.7)	52.8 (12.7)	49.5 (11.4)
Attained age (y) end of follow-up						
≤ 44	5,029 (4.2)	53 (11.7)	206 (6.0)	230 (25.0)	172 (12.7)	125 (17.3)
45-59	31,731 (26.3)	197 (43.4)	1,262 (36.5)	476 (51.8)	582 (43.1)	336 (46.4)
60-74	46,671 (38.6)	169 (37.2)	1,199 (34.7)	185 (20.1)	421 (31.2)	225 (31.1)
≥ 75	37.378 (30.9)	35 (7.7)	790 (22.9)	28 (3.0)	176 (13.0)	38 (5.2)
Follow-up time (y), median (IQR)	5.7 (6.8)	4.1 (5.4)	5.6 (6.6)	4.1 (5.0)	4.61 (6.1)	4.7 (5.7)
Breast cancer diagnosis						
In situ	9,774 (8.1)	45 (9.9)	336 (9.7)	91 (9.9)	131 (9.7)	62 (8.6)
Invasive	111,035 (91.9)	409 (90.1)	3,121 (90.3)	828 (90.1).1	1,220 (90.3)	662 (91.4)
Period of breast cancer diagnosis (y)	28,869 (23.9)	66 (14.5)	743 (21.5)	115 (12.5)	230 (17.0)	104 (14.4)
1996-1999	32,196 (26.7)	121 (26.7)	912 (26.4)	201 (21.9)	326 (24.1)	187 (25.8)
2000-2003	33,385 (27.6)	139 (30.6)	990 (28.6)	289 (31.4)	420 (31.1)	222 (30.7)
2004-2007	26,359 (21.8)	128 (28.2)	812 (23.5)	314 (34.2)	375 (27.8)	211 (29.1)
2008-2010						
Marital status						
Single/ widowed/ divorced	53,860 (44.6)	268 (59.0)	1,701 (49.2)	301 (32.8)	820 (60.7)	277 (38.3)
Living with partner/ married	66,949 (55.4)	186 (41.0)	1,756 (50.8)	618 (67.2)	531 (39.3)	447 (61.7)
Hospital admissions						
CVD	23,431 (19.4)	68 (15.0)	515 (14.9)	85 (9.2)	259 (19.2)	101 (14.0)
- Heart failure	3,426 (2.8)	11 (2.4)	66 (1.9)	13 (1.4)	30 (2.2)	16 (2.2)
- Myocardial infarction	1,482 (1.2)	<10[a]	25 (0.7)	<10[a]	<10[a]	<10[a]
- Cerebrovascular disease	3,529 (2.9)	<10[a]	82 (2.4)	<10[a]	34 (2.5)	<10[a]
Death during follow-up						
Total deaths	29,966 (24.8)	101 (22.2)	665 (19.2)	124 (13.5)	251 (18.6)	96 (13.3)
Breast cancer cause	12,279 (10.2)	64 (14.1)	301 (8.7)	82 (8.9)	136 (10.1)	51 (7.0)
Cardiovascular cause	7,438 (6.2)	<10[a]	158 (4.6)	11 (1.2)	50 (3.7)	21 (2.9)
Other causes	10,249 (8.5)	<10	206 (6.0)	31 (3.4)	65 (4.8)	24 (3.3)

Abbreviations: CVD = cardiovascular disease, IQR = Interquartile range, y = years

[a] = Not given in line with the Dutch data protection guideline as the number of cases was less than 10

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Table 2 Unadjusted and adjusted hazard ratios (95% CI) for a cardiovascular event by ethnic group

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Ethnic group		
Dutch	1.00 (Ref.)	1.00 (Ref.)
Surinamese	1.03 (0.92-1.16)	1.46 (1.29-1.64)
Moroccans	0.51 (0.42-0.63)	1.01 (0.83-1.24)
Turkish	0.71 (0.59-0.86)	1.25 (1.03-1.51)
Antilleans	0.83 (0.66-1.04)	1.24 (0.98-1.56)
Indonesians	0.76 (0.70-0.82)	0.88 (0.81-0.96)

Adjusted for age, year of admission and type of breast cancer

Table 3 Unadjusted and adjusted hazard ratios [95% confidence interval] for a cardiovascular admission by ethnic group

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Ethnic group		
Dutch	1.00 (Ref.)	1.00 (Ref.)
Surinamese	1.09 (0.96-1.23)	1.45 (1.28-1.64)
Moroccans	0.53 (0.43-0.66)	0.92 (0.75 -1.14)
Turkish	0.76 (0.63-0.93)	1.21(0.99-1.47)
Antilleans	0.89 (0.70-1.13)	1.24 (0.98-1.57)
Indonesians	0.75 (0.69-0.82)	0.85 (0.78-0.93)

Adjusted for age, year of admission and type of breast cancer

Table 4 Unadjusted and adjusted hazard ratios for cardiovascular mortality by ethnic group

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Ethnic group		
Dutch	1.00 (Ref.)	1.00 (Ref.)
Surinamese	0.70 (0.53-0.93)	1.49 (1.13-1.97)
Turkish	0.55 (0.36-0.84)	1.96 (1.27-3.01)
Indonesians	0.76 (0.65-0.89)	0.99 (0.84-1.16)

Adjusted for age, year of admission and type of breast cancer

The number of cardiovascular mortality for the Antilleans and Moroccan women were too low.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 and 6
Bias	9	Describe any efforts to address potential sources of bias	6 and 7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6 and 7
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	-

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 and 21 (table 1)
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	21 (table 1)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7 and 21 (table 1)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8, and 22 (table 2, 3,4)
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12 - 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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BMJ Open

Ethnic differences in cardiovascular morbidity and mortality among breast cancer patients in the Netherlands: a register-based cohort study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-021509.R1
Article Type:	Research
Date Submitted by the Author:	13-Apr-2018
Complete List of Authors:	Deen, Laura; University of Amsterdam, Department of Public Health, Academic Medical Centre; Copenhagen University Hospital, Section of Immigrant Medicine, Department of Infectious Diseases Buddeke, Josefien; University Medical Centre Utrecht, Julius Centre for Health Sciences and Primary Care Vaartjes, Ilonca; University Medical Centre Utrecht, Julius Centre for Health Sciences and Primary Care Bots, Michiel; University Medical Center Utrecht, Julius Centre for Health Sciences and Primary Care Nørredam, Marie; University of Copenhagen, Danish Research Centre for Migration, Ethnicity and Health, Section of Health Services Research, Department of Public Health; Copenhagen University Hospital, Section of Immigrant Medicine, Department of Infectious Diseases Agyemang, Charles; University of Amsterdam, Department of Public Health, Academic Medical Center
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Oncology, Cardiovascular medicine
Keywords:	Ethnicity, breast cancer, migrant, cardiovascular disease, cardiovascular mortality

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Ethnic differences in cardiovascular morbidity and mortality among breast cancer patients in the Netherlands: a register-based cohort study.

Laura Deen, MSC[1,2]; Josefien Buddeke, MSC[3]; Ilonca Vaartjes, PhD[3]; Michiel L. Bots, MD PhD[3]; Marie Norredam, MD PhD[2,4]; Charles Agyemang, MPH, PhD[1]

[1]Department of Public Health, Academic Medical Centre, University of Amsterdam, Amsterdam Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, The Netherlands

[2]Section of Immigrant Medicine, Department of Infectious Diseases, Copenhagen University Hospital, Kettegård allé 30, 2650 Hvidovre, Denmark

[3]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

[4]Danish Research Centre for Migration, Ethnicity and Health, Section of Health Services Research, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, 1014 København K, Denmark

Corresponding author:

Laura Deen, Department of Public Health, Academic Medical Centre, University of Amsterdam, Amsterdam Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, The Netherlands

e-mail:nhq382@alumni.ku.dk, telephone.: +4527514559

Word count:

Abstract: 250.

Total manuscript (excluding references, tables and figures): 3214.

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Abstract

Objectives: Cardiovascular disease (CVD) is of increasing concern among breast cancer survivors. However, evidence on ethnic differences in CVD among women with breast cancer is sparse. We assessed ethnic differences in cardiovascular morbidity and mortality among breast cancer patients in the Netherlands.

Methods: A nationwide register-based cohort study comprising all women with a first admission for breast cancer (n=127,714) between 1996 and 2010 in the Netherlands was conducted. Differences in CVD admission, CVD mortality and overall CVD event, which comprised a CVD admission and/or CVD mortality, between the largest ethnic minority groups (Surinamese, Moroccan, Turkish, Antillean, and Indonesian) and the Dutch general population (henceforth, Dutch) were investigated using Cox proportional hazard models.

Results: The incidence of cardiovascular outcomes varied by ethnic group. The incidence of an overall cardiovascular event was significantly higher for women with breast cancer from Suriname (HR=1.46;95% CI 1.29–1.64) and Turkey (HR=1.25;95% CI 1.03–1.51), compared with Dutch women with breast cancer. In contrast, Indonesian women with breast cancer had a significantly lower risk (HR=0.88; 95% CI 0.81–0.96) of a cardiovascular event compared with Dutch women with breast cancer. The risk of a cardiovascular event did not differ between Moroccan and Dutch women with breast cancer, whereas for Antillean women the risk was not significantly higher.

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Conclusions: Our findings suggest that Surinamese and Turkish women with breast cancer are disadvantaged in terms of cardiovascular outcomes compared with Dutch women with breast cancer. More work is needed to unravel the potential factors contributing to these differences.

Strengths and limitations of this study:

- The study builds on data from nationwide registries which resulted in a large sample size.
- The validity of the linkage of the included registries has proved to be high.
- Although the study is based on a nationwide cohort of breast cancer patients, absolute numbers are somewhat small when divided into different ethnic groups.
- Data on CVD risk factors, such as smoking, alcohol and obesity were not available since the study builds on registry data.

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1. Introduction

Due to earlier diagnosis and more effective treatment, the survival rate among breast cancer patients has now improved resulting in a growing population of breast cancer survivors. In The Netherlands, the 5-year-age-standardized survival rate has increased from 80% in 1995-99 to 85% in 2005-09 [1]. With breast cancer becoming a curable disease, comorbidities and death from other conditions among breast cancer survivors are of increasing concern.

One of the most important comorbidities to consider in women with breast cancer is cardiovascular disease (CVD), and with the growing number of breast cancer survivors, a better understanding of the risk of CVD in this group is crucial. Studies show that women surviving breast cancer have an increased risk of CVD morbidity and CVD-specific mortality compared with women without breast cancer [2,3]. Moreover, among breast cancer survivors, CVD-related mortality is becoming more common than breast cancer-specific mortality [4,5]. This is attributable to improvements in breast cancer survival due to early detection by screening programs and improved treatments [6,7]. Additionally, cardiotoxic effects of breast cancer therapy play a role [8,9]. Further, survivors are typically older than the general population and may be more likely to develop CVD because of risk factors common to both cancer and CVD [10].

Evidence suggests ethnic inequalities in the prognosis of breast cancer with a higher risk of breast cancer-specific and overall mortality among some ethnic minority groups [11,12]. However, although ethnic variation in cardiovascular outcomes in the general population exists [13,14], the evidence among breast cancer patients is limited. Data from the US show that African American and Pacific Islander women with breast cancer had an increased risk of dying from CVD

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compared with White American breast cancer patients [4,15]. However, ethnic compositions and the national context vary across countries and, to our knowledge, no European study has examined the risk of CVD related outcomes in different ethnic groups among breast cancer patients. Hence, the aim of this study was to explore differences in overall CVD event, CVD admission and CVD mortality following a diagnosis of breast cancer between the largest ethnic minority groups in the Netherlands compared with ethnic Dutch.

2. Methods

Study sample

This register-based cohort study builds on data from different Dutch nationwide registers. The registries and linkage procedures used in this cohort study have previously been described in detail [16]. In brief, we linked data between the national Dutch hospital discharge register, the population register and the cause of death register using a record identification number. This number is assigned to each resident in the Netherlands with a unique combination of birth date, sex and postal code (84% of the Dutch population). The Dutch national hospital discharge register and cause of death register were linked to identify all women with a first admission for breast cancer between 1996 and 2010, using the International Classification of Diseases (ICD) 9th revision and ICD 10th revision. Both patients with invasive (ICD-9: 174 and ICD-10: C50) and in situ breast cancer (ICD-9: 233 and ICD-10: D05) were identified and men were excluded. Data from the population register and the cause of death register were available until 2012 and data from the Dutch hospital discharge register were available until 2010. Individuals were followed from the date of their first breast cancer admission until (a) CVD admission, (b) CVD death, (c) death due to other causes, (d) first emigration or (d) study end (31.12.2012), whichever came first. Linkage of data from the different registries was performed in agreement with the privacy

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legislation in The Netherlands. All linkages and analysis were performed in a secured environment of Statistics Netherlands. The data set was made available and analysed in an anonymous form in a secured environment of Statistics Netherlands. Prior to publication, Statistics Netherlands made sure that none of the analysis results showed potential reducibility to the individual level.

Ethnic group

Ethnic groups were constructed based on the country of birth of the resident and her parents, according to the definition of Statistics Netherlands [17]. A woman was considered a migrant if she was born abroad or at least one of the parents was born abroad. Women with both parents born in the Netherlands were indicated as being Dutch. The major migrant groups residing in the Netherlands were included, which are those born in Turkey, Suriname, Morocco, Indonesia, and the Netherlands Antilles.

Outcomes

CVD admission after a diagnosis of breast cancer was defined as all admissions with either the primary or secondary cause of admission coded as ICD-9: 017.2, 093, 228, 289.1–289.3, 390–459, 557,745–747, 780.2, 782.3, 7825, 7826, 785, 786.50–786.59, 789.2, 794.30–794.39. Cardiovascular mortality was defined as dying from a cardiovascular cause after a diagnosis of breast cancer.

Overall cardiovascular event combined the two outcomes and comprised a hospital admission for CVD, and/or a dying from a cardiovascular cause.

Data analyses

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We first presented baseline characteristics as absolute numbers and percentages according to ethnic group. Continuous variables were summarized as mean and standard deviation or as median and interquartile range where appropriate. Subsequently, we calculated hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) using cox proportional hazard regression analyses to assess ethnic differences in overall cardiovascular events, and separately for hospital admission for CVD and cardiovascular mortality between ethnic minority groups and the Dutch (reference group) with adjustment for age as a continuous variable, year of admission and type of breast cancer. Cox proportional hazard assumptions were tested by plotting the log minus log functions for the continuous variable age. The assumptions were met in all analyses. All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Patient and Public Involvement

No patient or public were involved in this study.

3. Results

Table 1 presents the characteristics of the study population by ethnic group. In total, 127,714 women with a first admission for breast cancer between 01.01.1996 and 31.12.2010 were included in the study, of which 5% belonged to an ethnic minority group (table 1). Women with more adverse outcomes were in general followed for a shorter period. Among migrants, the Antilleans presented the smallest group and the Indonesians the largest group. In general, the ethnic minority groups were younger than the Dutch population when diagnosed. During follow-up, 19% of the Dutch population experienced a hospital admission due to CVD, whereas among the ethnic minorities the proportion of CVD admission ranged from 9% for Moroccans to 19%

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for Surinamese women. 31,203 women with breast cancer died during follow-up, of which 25% were due to a cardiovascular cause.

Table 2 shows the incidence of a CVD event, which comprises a hospital admission for CVD, and/or dying from a cardiovascular cause, among breast cancer patients by ethnic group. Compared with Dutch women with breast cancer, both Surinamese (HR=1.46;95% CI 1.29–1.64) and Turkish (HR=1.25;95% CI 1.03–1.51) women with breast cancer had a higher incidence of CVD event after adjustment for breast cancer diagnosis, period of breast cancer diagnosis and age. In contrast, Indonesian women with breast cancer had a significantly lower risk (HR=0.88; 95% CI 0.81–0.96) of cardiovascular event compared with Dutch women. Although not significant, the Antillean women had a higher incidence of CVD event compared with Dutch women. For Moroccans, there were no significantly differences from Dutch women.

Subsequently, we assessed cardiovascular admission and cardiovascular mortality separately. Table 3 shows the unadjusted and adjusted hazard ratios for a cardiovascular admission. Only women from Suriname had a significantly higher risk (HR=1.45; 95% CI 1.28–1.64) of cardiovascular admission compared with Dutch women with breast cancer, whereas women from Indonesia had a significantly lower risk of a cardiovascular admission (HR=0.85; 95% CI 0.78–0.93). The unadjusted and adjusted hazard ratios for cardiovascular mortality for the different ethnic groups are shown in table 4. The adjusted hazard ratios for cardiovascular mortality were significantly higher for women from Suriname (HR=1.49; 95% CI 1.13-1.97) and Turkey (HR=1.96; 95% CI 1.28-3.01), compared with Dutch women, whereas there were no significantly differences between women from Indonesia and Dutch women. For Moroccan and Antillean women the numbers of deaths due to CVD were too small to perform analyses. In order to determine the impact of breast cancer treatment on the observed differences in CVD outcomes a sensitivity analysis was performed excluding all women with in situ breast cancer. This did not

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change the results significantly, suggesting that cancer status and treatment of cancer is not strongly related to CVD outcomes in our study.

4. Discussion

Key findings

In this population-based cohort study of women with breast cancer in the Netherlands, the risk of cardiovascular outcomes varied by ethnic group. Women from Suriname and Turkey had a higher risk of a CVD event compared with Dutch women with breast cancer. When separating cardiovascular admission and cardiovascular mortality, Surinamese and Turkish women had a higher risk of both cardiovascular admission and cardiovascular mortality compared with Dutch women, though in Turkish women the results for CVD admission was not significant. In contrast, women from Indonesia with breast cancer had a lower risk of cardiovascular event, and cardiovascular admission, but similar risk of cardiovascular mortality compared with ethnic Dutch women with breast cancer. For Moroccan women, the risk of a cardiovascular event did not differ from Dutch women with breast cancer, whereas for Antillean women the risk was not significantly higher.

Discussion of key findings

Evidence shows that ethnic minority and migrant groups in general have a lower risk of breast cancer compared with the majority population [18,19]. However, the results of this study indicate that among breast cancer patients, some ethnic minority groups are disadvantaged in terms of cardiovascular outcomes compared with Dutch women. The results of this study are in line with the sparse evidence on ethnic differences in CVD mortality among breast cancer patients in the US, which also found some ethnic minority groups to be disadvantaged in terms of

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cardiovascular mortality [4,15]. For example, African America women with ductal carcinoma in situ of the breast were found to have a higher risk of CVD death compared with White American women diagnosed with ductal carcinoma in situ of the breast [4]. However, even though CVD have been shown to vary by ethnic group [13,20] data among breast cancer patients in Europe have been lacking. Previous European studies on ethnic disparities in breast cancer prognosis have mostly focused on mortality after breast cancer diagnosis, and found that some ethnic minority groups have higher overall and breast cancer-specific mortality [11,12,21]. Our results thereby add a great value to the existing literature by showing that women with breast cancer from Suriname and Turkey are disadvantaged in terms of cardiovascular outcomes compared with Dutch women with breast cancer. The higher incidence of CVD event among Surinamese women with breast cancer reflects the pattern of CVD among Surinamese women in the general Dutch population. Previous studies of the general population in the Netherlands showed that Surinamese women have a higher risk of both AMI and stroke compared with Dutch women [22,23], as well as a higher 5-year CVD mortality after initial admission for CVD [24]. Turkish women with breast cancer were in the present study found to have a higher incidence of CVD event, compared with Dutch women with breast cancer. However, this only partly reflects on the pattern among Turkish women in the general population in the Netherlands. Previous studies of the general population in the Netherlands did not find differences in the incidence of stroke or AMI among Turkish women compared with the Dutch majority women [22,23]. However, when stratifying on age, a higher incidence of AMI were observed in 50- to 70-year-old Turkish women compared with the Dutch majority women [22].

The relatively low risk of CVD outcomes among Indonesian women with breast cancer are in contrast to previous studies of the general Dutch population that found no differences in

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incidence of AMI and a slightly higher risk of stroke among Indonesians compared with Dutch women [22,23]. The reasons for the better CVD prognosis among Indonesian breast cancer patients are unclear. However, Indonesians are well integrated in the Dutch society with respect to language and culture and have similar income levels and are employed at equal rates as the Dutch general population [25]. This possibly results in better access to health care services than other minority groups and may underlie the better cardiovascular health outcomes among Indonesian women with breast cancer.

Possible explanations for the higher risk of cardiovascular events among Surinamese and Turkish breast cancer patients may include disparities in access to health care services and a high risk factor burden among these ethnic minorities in the Netherlands. Regular health visits are important for early diagnosis of risk factors that can lead to CVD progression and it is possible that differences in health service utilisation may contribute to the observed ethnic differences in CVD risk among breast cancer patients. Evidence on health care utilization among breast cancer patients is scarce, but previous evidence of the general population in the Netherlands suggests that some ethnic minority populations use more general practitioner care than Dutch people do, but that they are less likely to use specialised care [26]. Moreover, ethnic differences in use of cardiac rehabilitation and lower adherence to medication therapy have been shown [27–30]. A Danish study found that immigrants from Pakistan and Turkey did not receive adequate medical treatment with beta-blockers after a first AMI compared with Danish-born residents [28]. In addition, in the Netherlands, Surinamese people have been found to have poor blood pressure control compared with their Dutch counterparts [30].

The relatively high incidence of CVD admission and mortality among Turkish and Surinamese breast cancer women may be explained by the high prevalence of cardiovascular risk factors in

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these populations. The current study lacked information on CVD risk factor and we were therefore not able to address the possible contribution of these to the observed ethnic differences. However, previous studies of Surinamese and Turkish populations in the Netherlands showed that hypertension, diabetes mellitus and obesity are more common among these populations compared with the Dutch general population [30–33]. As an example, a previous Dutch study showed that the prevalence of hypertension, the leading risk factor for CVD worldwide, was higher in both Turkish and Surinamese people than in Dutch people [30]. A previous study found that Antillean women have higher risk of certain CVD risk factors then Dutch women [34]. Further, since Antilleans resemble other ethnic groups who have been found to have higher risk of some CVD risk factors, such as Surinamese women with African background, this might be the case for Antillean women as well and suggests the need for further study among this population in the Netherlands. In addition, a study from the US, found that African American breast cancer patients have higher prevalence of certain CVD risk factors, such as hypertension, diabetes and obesity, prior to initiating aromatase inhibitory therapy, compared with White American breast cancer patients of the same age [35]. Although the ethnic groups are not directly comparable, this may also be the case for some of the ethnic groups in the current study, such as the African Surinamese and Antillean women. Evidence suggests that the presence of CVD risk factors among breast cancer patients at diagnosis is a strong predictive factor for the development of cardiovascular damage associated with breast cancer therapy [36]. The higher risk factor burden in some ethnic minority groups may therefore contribute to the higher incidence of CVD in these groups.

Additionally, since the risk of CVD has been shown to vary according to breast cancer therapy [9,37], the observed differences may be explained by variation in the treatment received by different ethnic groups. In the current study, data on treatment was not available. However,

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studies from the US and UK have reported that ethnic minority women were more likely to receive chemotherapy, which was largely explained by more advanced stage and higher grade tumours [38,39].

Our findings have important clinical and public health implications because identifying breast cancer patients who are most vulnerable to cardiovascular outcomes is important in order to guide strategies among breast cancer patients. The findings suggest the need to increase attention for these women in the cardiovascular risk factor management guidelines in the Netherlands and awareness of the observed ethnic differences in the risk of cardiovascular outcomes among breast cancer patients should be raised among clinicians and incorporated into oncology practices. The observed differences suggest the need for further studies to identify factors explaining these differences. More specific, studies addressing the potential contribution of both CVD risk factors and type of treatment to the observed ethnic differences found in this study are needed. This will help to tailor appropriate public health and clinical interventions to improve outcomes among breast cancer patients most at risk of adverse CVD outcomes.

Strength and limitations:

The strength of the current study is the validity of the registries, the linkage methods, and the lack of selection of the cohorts. A high validity of both the Dutch National Hospital Discharge Register and the Dutch Population Register has been demonstrated. In a random sample of the Hospital Discharge Register, 99% of the personal, admission and discharge data and 84% of the principal diagnoses (validated through medical record review by medical specialists) were correctly registered [40]. In addition, over 97% of the uniquely linked hospital admissions

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resulting from linkage of the Hospital Discharge Register with the Population Register were shown to be correctly linked [41].

Nonetheless, some limitations must be considered. First, although the study is based on a nationwide cohort of breast cancer patients, absolute numbers are somewhat small when divided into different ethnic groups. Consequently, the numbers were too small to investigate different kinds of CVD, which could have afforded a more nuanced picture. Second, inherent to many national-level databases, we lack detailed data on CVD risk factors, such as smoking, alcohol, cholesterol and obesity, and therefore we were unable to do additional analyses to assess the contribution of these to the observed ethnic differences. However, we were able to shed light on the potential contributing risk factors to the observed differences due to previous studies on ethnic differences in risk factors in the Netherlands [30–33]. Additionally, the study lack data on treatment of breast cancer. Since, CVD risk has been shown to vary according to type of treatment [9,37], adjustment for treatment would have been preferable in order to assess the potential impact of differences in treatment to the observed ethnic differences in CVD. Finally, as in numerous studies, the classifications of the various ethnic groups were based on country of birth. Country of birth may reflect ethnicity reasonably well among some ethnic groups but is likely to be an unreliable proxy measure of ethnicity for other groups such as Surinamese [17]. The results may be generalised to other European settings with similar health care services and composition of ethnic groups.

5. Conclusion

The results of the current study suggest that the risk of CVD related outcomes among breast cancer patients vary by ethnicity. Surinamese and Turkey breast cancer patients experienced a higher risk, whereas Indonesian patients had a slightly lower risk of CVD event compared with

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their Dutch counterparts. More extensive cohort studies are needed to identify the forms of CVD that are most common in these groups as well as the potential factors contributing to these differences.

Competing interest: None declared.

Funding

This work was supported by the Dutch Heart Foundation (grant number 2010B296).

Contributor ship statement

LD, JB, IV, MLB, MN, CA were involved in the study design. LD and CA wrote the paper. JB analysed the data. JB, IV, MLB and MN critically revised the manuscript. All Authors approved the final version of the manuscript.

Data sharing statement

No additional data are available.

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Table 1 Demographic and disease characteristics of women admitted for breast cancer between 1996 and 2010 in the Netherlands according to ethnic group

	Ethnic Dutch N %	Antillean N %	Indonesian N %	Moroccan N %	Surinamese N %	Turkish N %
No. of patients	120,809 (100)	454 (100)	3,457 (100)	919 (100)	1,351 (100)	724 (100)
Mean age at diagnosis (y), sd	60.4 (13.3)	52.8 (11.8)	57.0 (13.1)	47.0 (10.7)	52.8 (12.7)	49.5 (11.4)
Attained age (y) end of follow-up						
≤ 44	5,029 (4.2)	53 (11.7)	206 (6.0)	230 (25.0)	172 (12.7)	125 (17.3)
45-59	31,731 (26.3)	197 (43.4)	1,262 (36.5)	476 (51.8)	582 (43.1)	336 (46.4)
60-74	46,671 (38.6)	169 (37.2)	1,199 (34.7)	185 (20.1)	421 (31.2)	225 (31.1)
≥ 75	37.378 (30.9)	35 (7.7)	790 (22.9)	28 (3.0)	176 (13.0)	38 (5.2)
Follow-up time (y), median (IQR)	4.5 (6.5)	3.6 (5.8)	4.6 (5.5)	3.6 (6.0)	3.8 (??)	4.0 (6.0)
Breast cancer diagnosis						
In situ	9,774 (8.1)	45 (9.9)	336 (9.7)	91 (9.9)	131 (9.7)	62 (8.6)
Invasive	111,035 (91.9)	409 (90.1)	3,121 (90.3)	828 (90.1).1	1,220 (90.3)	662 (91.4)
Period of breast cancer diagnosis (y)	28,869 (23.9)	66 (14.5)	743 (21.5)	115 (12.5)	230 (17.0)	104 (14.4)
1996-1999	32,196 (26.7)	121 (26.7)	912 (26.4)	201 (21.9)	326 (24.1)	187 (25.8)
2000-2003	33,385 (27.6)	139 (30.6)	990 (28.6)	289 (31.4)	420 (31.1)	222 (30.7)
2004-2007	26,359 (21.8)	128 (28.2)	812 (23.5)	314 (34.2)	375 (27.8)	211 (29.1)
2008-2010						
Marital status						
Single/ widowed/ divorced	53,860 (44.6)	268 (59.0)	1,701 (49.2)	301 (32.8)	820 (60.7)	277 (38.3)
Living with partner/ married	66,949 (55.4)	186 (41.0)	1,756 (50.8)	618 (67.2)	531 (39.3)	447 (61.7)
Hospital admissions						
CVD	23,431 (19.4)	68 (15.0)	515 (14.9)	85 (9.2)	259 (19.2)	101 (14.0)
- Heart failure	3,426 (2.8)	11 (2.4)	66 (1.9)	13 (1.4)	30 (2.2)	16 (2.2)
- Myocardial infarction	1,482 (1.2)	<10[a]	25 (0.7)	<10[a]	<10[a]	<10[a]
- Cerebrovascular disease	3,529 (2.9)	<10[a]	82 (2.4)	<10[a]	34 (2.5)	<10[a]
Death during follow-up						
Total deaths	29,966 (24.8)	101 (22.2)	665 (19.2)	124 (13.5)	251 (18.6)	96 (13.3)
Breast cancer cause	12,279 (10.2)	64 (14.1)	301 (8.7)	82 (8.9)	136 (10.1)	51 (7.0)
Cardiovascular cause	7,438 (6.2)	<10[a]	158 (4.6)	11 (1.2)	50 (3.7)	21 (2.9)
Other causes	10,249 (8.5)	<10	206 (6.0)	31 (3.4)	65 (4.8)	24 (3.3)

Abbreviations: CVD = cardiovascular disease, IQR = Interquartile range, y = years

[a] = Not given in line with the Dutch data protection guideline as the number of cases was less than 10

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Table 2 Unadjusted and adjusted hazard ratios (95% CI) for a cardiovascular event by ethnic group

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Ethnic group		
Dutch	1.00 (Ref.)	1.00 (Ref.)
Surinamese	1.03 (0.92-1.16)	1.46 (1.29-1.64)
Moroccans	0.51 (0.42-0.63)	1.01 (0.83-1.24)
Turkish	0.71 (0.59-0.86)	1.25 (1.03-1.51)
Antilleans	0.83 (0.66-1.04)	1.24 (0.98-1.56)
Indonesians	0.76 (0.70-0.82)	0.88 (0.81-0.96)

Adjusted for age, year of admission and type of breast cancer

Table 3 Unadjusted and adjusted hazard ratios [95% confidence interval] for a cardiovascular admission by ethnic group

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Ethnic group		
Dutch	1.00 (Ref.)	1.00 (Ref.)
Surinamese	1.09 (0.96-1.23)	1.45 (1.28-1.64)
Moroccans	0.53 (0.43-0.66)	0.92 (0.75 -1.14)
Turkish	0.76 (0.63-0.93)	1.21(0.99-1.47)
Antilleans	0.89 (0.70-1.13)	1.24 (0.98-1.57)
Indonesians	0.75 (0.69-0.82)	0.85 (0.78-0.93)

Adjusted for age, year of admission and type of breast cancer

Table 4 Unadjusted and adjusted hazard ratios for cardiovascular mortality by ethnic group

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Ethnic group		
Dutch	1.00 (Ref.)	1.00 (Ref.)
Surinamese	0.70 (0.53-0.93)	1.49 (1.13-1.97)
Turkish	0.55 (0.36-0.84)	1.96 (1.27-3.01)
Indonesians	0.76 (0.65-0.89)	0.99 (0.84-1.16)

Adjusted for age, year of admission and type of breast cancer
The number of cardiovascular mortality for the Antilleans and Moroccan women were too low.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 and 6
Bias	9	Describe any efforts to address potential sources of bias	6 and 7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6 and 7
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	-

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 and 21 (table 1)
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	21 (table 1)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7 and 21 (table 1)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8, and 22 (table 2, 3,4)
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12 - 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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BMJ Open

Ethnic differences in cardiovascular morbidity and mortality among breast cancer patients in The Netherlands: a register-based cohort study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-021509.R2
Article Type:	Research
Date Submitted by the Author:	11-May-2018
Complete List of Authors:	Deen, Laura; University of Amsterdam, Department of Public Health, Academic Medical Centre; Copenhagen University Hospital, Section of Immigrant Medicine, Department of Infectious Diseases Buddeke, Josefien; University Medical Centre Utrecht, Julius Centre for Health Sciences and Primary Care Vaartjes, Ilonca; University Medical Centre Utrecht, Julius Centre for Health Sciences and Primary Care Bots, Michiel; University Medical Center Utrecht, Julius Centre for Health Sciences and Primary Care Nørredam, Marie; University of Copenhagen, Danish Research Centre for Migration, Ethnicity and Health, Section of Health Services Research, Department of Public Health; Copenhagen University Hospital, Section of Immigrant Medicine, Department of Infectious Diseases Agyemang, Charles; University of Amsterdam, Department of Public Health, Academic Medical Center
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Oncology, Cardiovascular medicine
Keywords:	Ethnicity, breast cancer, migrant, cardiovascular disease, cardiovascular mortality

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Ethnic differences in cardiovascular morbidity and mortality among breast cancer patients in The Netherlands: a register-based cohort study.

Laura Deen, MSC[1,2]; Josefien Buddeke, MSC[3]; Ilonca Vaartjes, PhD[3]; Michiel L. Bots, MD PhD[3]; Marie Norredam, MD PhD[2,4]; Charles Agyemang, MPH, PhD[1]

[1]Department of Public Health, Academic Medical Centre, University of Amsterdam, Amsterdam Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, The Netherlands

[2]Section of Immigrant Medicine, Department of Infectious Diseases, Copenhagen University Hospital, Kettegård allé 30, 2650 Hvidovre, Denmark

[3]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

[4]Danish Research Centre for Migration, Ethnicity and Health, Section of Health Services Research, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, 1014 København K, Denmark

Corresponding author:

Charles Agyemang, Department of Public Health, Amsterdam Public Health Research Institute Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands.

e-mail: c.o.agyemang@amc.uva.nl, telephone.: +31205664885

Word count:

Abstract: 250.

Total manuscript (excluding references, tables and figures): 3221.

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Abstract

Objectives: Cardiovascular disease (CVD) is of increasing concern among breast cancer survivors. However, evidence on ethnic differences in CVD among women with breast cancer is sparse. We assessed ethnic differences in cardiovascular morbidity and mortality among breast cancer patients in The Netherlands.

Methods: A nationwide register-based cohort study comprising all women with a first admission for breast cancer (n=127,714) between 1996 and 2010 in The Netherlands was conducted. Differences in CVD admission, CVD mortality and overall CVD event, which comprised a CVD admission and/or CVD mortality, between the largest ethnic minority groups (Surinamese, Moroccan, Turkish, Antillean, and Indonesian) and the Dutch general population (henceforth, Dutch) were investigated using Cox proportional hazard models.

Results: The incidence of cardiovascular outcomes varied by ethnic group. The incidence of an overall cardiovascular event was significantly higher for women with breast cancer from Suriname (HR=1.46;95% CI 1.29–1.64) and Turkey (HR=1.25;95% CI 1.03–1.51), compared with Dutch women with breast cancer. In contrast, Indonesian women with breast cancer had a significantly lower risk (HR=0.88; 95% CI 0.81–0.96) of a cardiovascular event compared with Dutch women with breast cancer. The risk of a cardiovascular event did not differ between Moroccan and Dutch women with breast cancer, whereas for Antillean women the risk was not significantly higher.

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Conclusions: Our findings suggest that Surinamese and Turkish women with breast cancer are disadvantaged in terms of cardiovascular outcomes compared with Dutch women with breast cancer. More work is needed to unravel the potential factors contributing to these differences.

Strengths and limitations of this study:

- The study builds on data from nationwide registries which resulted in a large sample size.
- The validity of the linkage of the included registries has proved to be high.
- Although the study is based on a nationwide cohort of breast cancer patients, absolute numbers are somewhat small when divided into different ethnic groups.
- Data on CVD risk factors, such as smoking, alcohol and obesity were not available since the study builds on registry data.

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1. Introduction

Due to earlier diagnosis and more effective treatment, the survival rate among breast cancer patients has now improved resulting in a growing population of breast cancer survivors. In The Netherlands, the 5-year-age-standardized survival rate has increased from 80% in 1995-99 to 85% in 2005-09 [1]. With breast cancer becoming a curable disease, comorbidities and death from other conditions among breast cancer survivors are of increasing concern.

One of the most important comorbidities to consider in women with breast cancer is cardiovascular disease (CVD), and with the growing number of breast cancer survivors, a better understanding of the risk of CVD in this group is crucial. Studies show that women surviving breast cancer have an increased risk of CVD morbidity and CVD-specific mortality compared with women without breast cancer [2,3]. Moreover, among breast cancer survivors, CVD-related mortality is becoming more common than breast cancer-specific mortality [4,5]. This is attributable to improvements in breast cancer survival due to early detection by screening programs and improved treatments [6,7]. Additionally, cardiotoxic effects of breast cancer therapy play a role [8,9]. Further, survivors are typically older than the general population and may be more likely to develop CVD because of risk factors common to both cancer and CVD [10].

Evidence suggests ethnic inequalities in the prognosis of breast cancer with a higher risk of breast cancer-specific and overall mortality among some ethnic minority groups [11,12]. However, although ethnic variation in cardiovascular outcomes in the general population exists [13,14], the evidence among breast cancer patients is limited. Data from the US show that African American women with breast cancer had an increased risk of dying from CVD compared with White

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American breast cancer patients [4]. However, ethnic compositions and the national context vary across countries and, to our knowledge, no European study has examined the risk of CVD related outcomes in different ethnic groups among breast cancer patients. Hence, the aim of this study was to explore differences in overall CVD event, CVD admission and CVD mortality following a diagnosis of breast cancer between the largest ethnic minority groups in The Netherlands compared with ethnic Dutch.

2. Methods

Study sample

This register-based cohort study builds on data from different Dutch nationwide registers. The registries and linkage procedures used in this cohort study have previously been described in detail [15]. In brief, we linked data between the national Dutch hospital discharge register, the population register and the cause of death register using a record identification number. This number is assigned to each resident in The Netherlands with a unique combination of birth date, sex and postal code (84% of the Dutch population). The Dutch national hospital discharge register and cause of death register were linked to identify all women with a first admission for breast cancer between 1996 and 2010, using the International Classification of Diseases (ICD) 9th revision and ICD 10th revision. Both patients with invasive (ICD-9: 174 and ICD-10: C50) and in situ breast cancer (ICD-9: 233 and ICD-10: D05) were identified and men were excluded. Data from the population register and the cause of death register were available until 2012 and data from the Dutch hospital discharge register were available until 2010. Individuals were followed from the date of their first breast cancer admission until (a) CVD admission, (b) CVD death, (c) death due to other causes, (d) first emigration or (d) study end (31.12.2012), whichever came first. Linkage of data from the different registries was performed in agreement with the privacy

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legislation in The Netherlands. All linkages and analysis were performed in a secured environment of Statistics Netherlands. The data set was made available and analysed in an anonymous form in a secured environment of Statistics Netherlands. Prior to publication, Statistics Netherlands made sure that none of the analysis results showed potential reducibility to the individual level.

Ethnic group

Ethnic groups were constructed based on the country of birth of the resident and her parents, according to the definition of Statistics Netherlands [16]. A woman was considered a migrant if she was born abroad or at least one of the parents was born abroad. Women with both parents born in The Netherlands were indicated as being Dutch. The major migrant groups residing in The Netherlands were included, which are those born in Turkey, Suriname, Morocco, Indonesia, and The Netherlands Antilles.

Outcomes

CVD admission after a diagnosis of breast cancer was defined as all admissions with either the primary or secondary cause of admission coded as ICD-9: 017.2, 093, 228, 289.1–289.3, 390–459, 557,745–747, 780.2, 782.3, 7825, 7826, 785, 786.50–786.59, 789.2, 794.30–794.39. Cardiovascular mortality was defined as dying from a cardiovascular cause after a diagnosis of breast cancer.

Overall cardiovascular event combined the two outcomes and comprised a hospital admission for CVD, and/or a dying from a cardiovascular cause.

Data analyses

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We first presented baseline characteristics as absolute numbers and percentages according to ethnic group. Continuous variables were summarized as mean and standard deviation or as median and interquartile range where appropriate. Subsequently, we calculated hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) using cox proportional hazard regression analyses to assess ethnic differences in overall cardiovascular events, and separately for hospital admission for CVD and cardiovascular mortality between ethnic minority groups and the Dutch (reference group) with adjustment for age as a continuous variable, year of admission and type of breast cancer. Cox proportional hazard assumptions were tested by plotting the log minus log functions for the continuous variable age. The assumptions were met in all analyses. All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Patient and Public Involvement

No patient or public were involved in this study.

3. Results

Table 1 presents the characteristics of the study population by ethnic group. In total, 127,714 women with a first admission for breast cancer between 01.01.1996 and 31.12.2010 were included in the study, of which 5% belonged to an ethnic minority group (table 1). Women with more adverse outcomes were in general followed for a shorter period. Among migrants, the Antilleans presented the smallest group and the Indonesians the largest group. In general, the ethnic minority groups were younger than the Dutch population when diagnosed. During follow-up, 19% of the Dutch population experienced a hospital admission due to CVD, whereas among the ethnic minorities the proportion of CVD admission ranged from 9% for Moroccans to 19%

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for Surinamese women. 31,203 women with breast cancer died during follow-up, of which around 25% were due to a cardiovascular cause.

Table 2 shows the incidence of a CVD event, which comprises a hospital admission for CVD, and/or dying from a cardiovascular cause, among breast cancer patients by ethnic group. Compared with Dutch women with breast cancer, both Surinamese (HR=1.46;95% CI 1.29–1.64) and Turkish (HR=1.25;95% CI 1.03–1.51) women with breast cancer had a higher incidence of CVD event after adjustment for breast cancer diagnosis, period of breast cancer diagnosis and age. In contrast, Indonesian women with breast cancer had a significantly lower risk (HR=0.88; 95% CI 0.81–0.96) of cardiovascular event compared with Dutch women. Although not significant, the Antillean women had a higher incidence of CVD event compared with Dutch women. For Moroccans, there were no differences from Dutch women.

Subsequently, we assessed cardiovascular admission and cardiovascular mortality separately. Table 3 shows the unadjusted and adjusted hazard ratios for a cardiovascular admission. Only women from Suriname had a significantly higher risk (HR=1.45;95% CI 1.28–1.64) of cardiovascular admission compared with Dutch women with breast cancer, whereas women from Indonesia had a significantly lower risk of a cardiovascular admission (HR=0.85;95% CI 0.78–0.93). The unadjusted and adjusted hazard ratios for cardiovascular mortality for the different ethnic groups are shown in table 4. The adjusted hazard ratios for cardiovascular mortality were significantly higher for women from Suriname (HR=1.49;95% CI 1.13-1.97) and Turkey (HR=1.96; 95% CI 1.27-3.01), compared with Dutch women, whereas there were no significantly differences between women from Indonesia and Dutch women. For Moroccan and Antillean women the numbers of deaths due to CVD were too small to perform analyses. In order to determine the impact of breast cancer treatment on the observed differences in CVD outcomes a sensitivity analysis was performed excluding all women with in situ breast cancer. This did not

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change the results significantly, suggesting that cancer status and treatment of cancer is not strongly related to CVD outcomes in our study.

4. Discussion

Key findings

In this population-based cohort study of women with breast cancer in The Netherlands, the risk of cardiovascular outcomes varied by ethnic group. Women from Suriname and Turkey had a higher risk of a CVD event compared with Dutch women with breast cancer. When separating cardiovascular admission and cardiovascular mortality, Surinamese and Turkish women had a higher risk of both cardiovascular admission and cardiovascular mortality compared with Dutch women, though in Turkish women the results for CVD admission was not significant. In contrast, women from Indonesia with breast cancer had a lower risk of cardiovascular event, and cardiovascular admission, but similar risk of cardiovascular mortality compared with ethnic Dutch women with breast cancer. For Moroccan women, the risk of a cardiovascular event did not differ from Dutch women with breast cancer, whereas for Antillean women the risk was not significantly higher.

Discussion of key findings

Evidence shows that ethnic minority and migrant groups in general have a lower risk of breast cancer compared with the majority population [17,18]. However, the results of this study indicate that among breast cancer patients, some ethnic minority groups are disadvantaged in terms of cardiovascular outcomes compared with Dutch women. The results of this study are in line with the sparse evidence on ethnic differences in CVD mortality among breast cancer patients in the US, which also found some ethnic minority groups to be disadvantaged in terms of

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cardiovascular mortality [4,19]. For example, African America women with ductal carcinoma in situ of the breast were found to have a higher risk of CVD death compared with White American women diagnosed with ductal carcinoma in situ of the breast [4]. However, even though CVD have been shown to vary by ethnic group [13,20] data among breast cancer patients in Europe have been lacking. Previous European studies on ethnic disparities in breast cancer prognosis have mostly focused on mortality after breast cancer diagnosis, and found that some ethnic minority groups have higher overall and breast cancer-specific mortality [11,12,21]. Our results thereby add a great value to the existing literature by showing that women with breast cancer from Suriname and Turkey are disadvantaged in terms of cardiovascular outcomes compared with Dutch women with breast cancer. The higher incidence of CVD event among Surinamese women with breast cancer reflects the pattern of CVD among Surinamese women in the general Dutch population. Previous studies of the general population in The Netherlands showed that Surinamese women have a higher risk of both AMI and stroke compared with Dutch women [22,23], as well as a higher 5-year CVD mortality after initial admission for CVD [24]. Turkish women with breast cancer were in the present study found to have a higher incidence of CVD event, compared with Dutch women with breast cancer. However, this only partly reflects on the pattern among Turkish women in the general population in The Netherlands. Previous studies of the general population in The Netherlands did not find differences in the incidence of stroke or AMI among Turkish women compared with the Dutch majority women [22,23]. However, when stratifying on age, a higher incidence of AMI were observed in 50- to 70-year-old Turkish women compared with the Dutch majority women [22].

The relatively low risk of CVD outcomes among Indonesian women with breast cancer are in contrast to previous studies of the general Dutch population that found no differences in

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incidence of AMI and a slightly higher risk of stroke among Indonesians compared with Dutch women [22,23]. The reasons for the better CVD prognosis among Indonesian breast cancer patients are unclear. However, Indonesians are well integrated in the Dutch society with respect to language and culture and have similar income levels and are employed at equal rates as the Dutch general population [25]. This possibly results in better access to health care services than other minority groups and may underlie the better cardiovascular health outcomes among Indonesian women with breast cancer.

Possible explanations for the higher risk of cardiovascular events among Surinamese and Turkish breast cancer patients may include disparities in access to health care services and a high risk factor burden among these ethnic minorities in The Netherlands. Regular health visits are important for early diagnosis of risk factors that can lead to CVD progression and it is possible that differences in health service utilisation may contribute to the observed ethnic differences in CVD risk among breast cancer patients. Evidence on health care utilization among breast cancer patients is scarce, but previous evidence of the general population in The Netherlands suggests that some ethnic minority populations use more general practitioner care than Dutch people do, but that they are less likely to use specialised care [26]. Moreover, ethnic differences in use of cardiac rehabilitation and lower adherence to medication therapy have been shown [27–30]. A Danish study found that immigrants from Pakistan and Turkey did not receive adequate medical treatment with beta-blockers after a first AMI compared with Danish-born residents [28]. In addition, in The Netherlands, Surinamese people have been found to have poor blood pressure control compared with their Dutch counterparts [30].

The relatively high incidence of CVD admission and mortality among Turkish and Surinamese breast cancer women may be explained by the high prevalence of cardiovascular risk factors in

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these populations. The current study lacked information on CVD risk factor and we were therefore not able to address the possible contribution of these to the observed ethnic differences. However, previous studies of Surinamese and Turkish populations in The Netherlands showed that hypertension, diabetes mellitus and obesity are more common among these populations compared with the Dutch general population [30–33]. As an example, a previous Dutch study showed that the prevalence of hypertension, the leading risk factor for CVD worldwide, was higher in both Turkish and Surinamese people than in Dutch people [30]. A previous study found that Antillean women have higher risk of certain CVD risk factors then Dutch women [34]. Further, since Antilleans resemble other ethnic groups who have been found to have higher risk of some CVD risk factors, such as Surinamese women with African background, this might be the case for Antillean women as well and suggests the need for further study among this population in The Netherlands. In addition, a study from the US, found that African American breast cancer patients have higher prevalence of certain CVD risk factors, such as hypertension, diabetes and obesity, prior to initiating aromatase inhibitory therapy, compared with White American breast cancer patients of the same age [35]. Although the ethnic groups are not directly comparable, this may also be the case for some of the ethnic groups in the current study, such as the African Surinamese and Antillean women. Evidence suggests that the presence of CVD risk factors among breast cancer patients at diagnosis is a strong predictive factor for the development of cardiovascular damage associated with breast cancer therapy [36]. The higher risk factor burden in some ethnic minority groups may therefore contribute to the higher incidence of CVD in these groups.

Additionally, since the risk of CVD has been shown to vary according to breast cancer therapy [9,37], the observed differences may be explained by variation in the treatment received by different ethnic groups. In the current study, data on treatment was not available. However,

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studies from the US and UK have reported that ethnic minority women were more likely to receive chemotherapy, which was largely explained by more advanced stage and higher grade tumours [38,39].

Our findings have important clinical and public health implications because identifying breast cancer patients who are most vulnerable to cardiovascular outcomes is important in order to guide strategies among breast cancer patients. The findings suggest the need to increase attention for these women in the cardiovascular risk factor management guidelines in The Netherlands and awareness of the observed ethnic differences in the risk of cardiovascular outcomes among breast cancer patients should be raised among clinicians and incorporated into oncology practices. The observed differences suggest the need for further studies to identify factors explaining these differences. More specific, studies addressing the potential contribution of both CVD risk factors and type of treatment to the observed ethnic differences found in this study are needed. This will help to tailor appropriate public health and clinical interventions to improve outcomes among breast cancer patients most at risk of adverse CVD outcomes.

Strength and limitations:

The strength of the current study is the validity of the registries, the linkage methods, and the lack of selection of the cohorts. A high validity of both the Dutch National Hospital Discharge Register and the Dutch Population Register has been demonstrated. In a random sample of the Hospital Discharge Register, 99% of the personal, admission and discharge data and 84% of the principal diagnoses (validated through medical record review by medical specialists) were correctly registered [40]. In addition, over 97% of the uniquely linked hospital admissions

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resulting from linkage of the Hospital Discharge Register with the Population Register were shown to be correctly linked [41].

Nonetheless, some limitations must be considered. First, although the study is based on a nationwide cohort of breast cancer patients, absolute numbers are somewhat small when divided into different ethnic groups. Consequently, the numbers were too small to investigate different kinds of CVD, which could have afforded a more nuanced picture. Second, inherent to many national-level databases, we lack detailed data on CVD risk factors, such as smoking, alcohol, cholesterol and obesity, and therefore we were unable to do additional analyses to assess the contribution of these to the observed ethnic differences. However, we were able to shed light on the potential contributing risk factors to the observed differences due to previous studies on ethnic differences in risk factors in The Netherlands [30–33]. Additionally, the study lack data on treatment of breast cancer. Since, CVD risk has been shown to vary according to type of treatment [9,37], adjustment for treatment would have been preferable in order to assess the potential impact of differences in treatment to the observed ethnic differences in CVD. Finally, as in numerous studies, the classifications of the various ethnic groups were based on country of birth. Country of birth may reflect ethnicity reasonably well among some ethnic groups but is likely to be an unreliable proxy measure of ethnicity for other groups such as Surinamese [16]. The results may be generalised to other European settings with similar health care services and composition of ethnic groups.

5. Conclusion

The results of the current study suggest that the risk of CVD related outcomes among breast cancer patients vary by ethnicity. Surinamese and Turkey breast cancer patients experienced a higher risk, whereas Indonesian patients had a slightly lower risk of CVD event compared with

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their Dutch counterparts. More extensive cohort studies are needed to identify the forms of CVD that are most common in these groups as well as the potential factors contributing to these differences.

Competing interest: None declared.

Funding

This work was supported by the Dutch Heart Foundation (grant number 2010B296).

Contributor ship statement

LD, JB, IV, MLB, MN, CA were involved in the study design. LD and CA wrote the paper. JB analysed the data. JB, IV, MLB and MN critically revised the manuscript. All Authors approved the final version of the manuscript.

Data sharing statement

No additional data are available.

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Table 1 Demographic and disease characteristics of women admitted for breast cancer between 1996 and 2010 in The Netherlands according to ethnic group

	Ethnic Dutch N %	Antillean N %	Indonesian N %	Moroccan N %	Surinamese N %	Turkish N %
No. of patients	120,809 (100)	454 (100)	3,457 (100)	919 (100)	1,351 (100)	724 (100)
Mean age at diagnosis (y), sd	60.4 (13.3)	52.8 (11.8)	57.0 (13.1)	47.0 (10.7)	52.8 (12.7)	49.5 (11.4)
Attained age (y) end of follow-up						
≤ 44	5,029 (4.2)	53 (11.7)	206 (6.0)	230 (25.0)	172 (12.7)	125 (17.3)
45-59	31,731 (26.3)	197 (43.4)	1,262 (36.5)	476 (51.8)	582 (43.1)	336 (46.4)
60-74	46,671 (38.6)	169 (37.2)	1,199 (34.7)	185 (20.1)	421 (31.2)	225 (31.1)
≥ 75	37,378 (30.9)	35 (7.7)	790 (22.9)	28 (3.0)	176 (13.0)	38 (5.2)
Follow-up time (y), median (IQR)	4.5 (6.5)	3.6 (5.8)	4.6 (5.5)	3.6 (6.0)	3.8 (6.0)	4.0 (6.0)
Breast cancer diagnosis						
In situ	9,774 (8.1)	45 (9.9)	336 (9.7)	91 (9.9)	131 (9.7)	62 (8.6)
Invasive	111,035 (91.9)	409 (90.1)	3,121 (90.3)	828 (90.1)	1,220 (90.3)	662 (91.4)
Period of breast cancer diagnosis (y)	28,869 (23.9)	66 (14.5)	743 (21.5)	115 (12.5)	230 (17.0)	104 (14.4)
1996-1999	32,196 (26.7)	121 (26.7)	912 (26.4)	201 (21.9)	326 (24.1)	187 (25.8)
2000-2003	33,385 (27.6)	139 (30.6)	990 (28.6)	289 (31.4)	420 (31.1)	222 (30.7)
2004-2007	26,359 (21.8)	128 (28.2)	812 (23.5)	314 (34.2)	375 (27.8)	211 (29.1)
2008-2010						
Marital status						
Single/ widowed/ divorced	53,860 (44.6)	268 (59.0)	1,701 (49.2)	301 (32.8)	820 (60.7)	277 (38.3)
Living with partner/ married	66,949 (55.4)	186 (41.0)	1,756 (50.8)	618 (67.2)	531 (39.3)	447 (61.7)
Hospital admissions						
CVD	23,431 (19.4)	68 (15.0)	515 (14.9)	85 (9.2)	259 (19.2)	101 (14.0)
- Heart failure	3,426 (2.8)	11 (2.4)	66 (1.9)	13 (1.4)	30 (2.2)	16 (2.2)
- Myocardial infarction	1,482 (1.2)	<10[a]	25 (0.7)	<10[a]	<10[a]	<10[a]
- Cerebrovascular disease	3,529 (2.9)	<10[a]	82 (2.4)	<10[a]	34 (2.5)	<10[a]
Death during follow-up						
Total deaths	29,966 (24.8)	101 (22.2)	665 (19.2)	124 (13.5)	251 (18.6)	96 (13.3)
Breast cancer cause	12,279 (10.2)	64 (14.1)	301 (8.7)	82 (8.9)	136 (10.1)	51 (7.0)
Cardiovascular cause	7,438 (6.2)	<10[a]	158 (4.6)	11 (1.2)	50 (3.7)	21 (2.9)
Other causes	10,249 (8.5)	<10	206 (6.0)	31 (3.4)	65 (4.8)	24 (3.3)

Abbreviations: CVD = cardiovascular disease, IQR = Interquartile range, y = years

[a] = Not given in line with the Dutch data protection guideline as the number of cases was less than 10

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Table 2 Unadjusted and adjusted hazard ratios (95% CI) for a cardiovascular event by ethnic group

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Ethnic group		
Dutch	1.00 (Ref.)	1.00 (Ref.)
Surinamese	1.03 (0.92-1.16)	1.46 (1.29-1.64)
Moroccans	0.51 (0.42-0.63)	1.01 (0.83-1.24)
Turkish	0.71 (0.59-0.86)	1.25 (1.03-1.51)
Antilleans	0.83 (0.66-1.04)	1.24 (0.98-1.56)
Indonesians	0.76 (0.70-0.82)	0.88 (0.81-0.96)

Adjusted for age, year of admission and type of breast cancer

Table 3 Unadjusted and adjusted hazard ratios (95% CI) for a cardiovascular admission by ethnic group

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Ethnic group		
Dutch	1.00 (Ref.)	1.00 (Ref.)
Surinamese	1.09 (0.96-1.23)	1.45 (1.28-1.64)
Moroccans	0.53 (0.43-0.66)	0.92 (0.75 -1.14)
Turkish	0.76 (0.63-0.93)	1.21(0.99-1.47)
Antilleans	0.89 (0.70-1.13)	1.24 (0.98-1.57)
Indonesians	0.75 (0.69-0.82)	0.85 (0.78-0.93)

Adjusted for age, year of admission and type of breast cancer

Table 4 Unadjusted and adjusted hazard ratios (95% CI) for cardiovascular mortality by ethnic group

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Ethnic group		
Dutch	1.00 (Ref.)	1.00 (Ref.)
Surinamese	0.70 (0.53-0.93)	1.49 (1.13-1.97)
Turkish	0.55 (0.36-0.84)	1.96 (1.27-3.01)
Indonesians	0.76 (0.65-0.89)	0.99 (0.84-1.16)

Adjusted for age, year of admission and type of breast cancer
The number of cardiovascular mortality for the Antilleans and Moroccan women were too low.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 and 6
Bias	9	Describe any efforts to address potential sources of bias	6 and 7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6 and 7
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	-

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 and 21 (table 1)
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	21 (table 1)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7 and 21 (table 1)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8, and 22 (table 2, 3,4)
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12 - 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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