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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.

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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, Josefiën; 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
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Manuscripts

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3 1 **Ethnic differences in cardiovascular morbidity and mortality among breast cancer patients**  
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5 2 **in the Netherlands: a register-based cohort study.**  
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10 4 Laura Deen, MSC<sup>1,2</sup>; Josefiën Buddeke, MSC<sup>3</sup>; Ilonca Vaartjes, PhD<sup>3</sup>; Michiel L. Bots, MD  
11  
12 5 PhD<sup>3</sup>; Marie Norredam, MD PhD<sup>2,4</sup>; Charles Agyemang, MPH, PhD<sup>1</sup>  
13

14 6 <sup>1</sup>*Department of Public Health, Academic Medical Centre, University of Amsterdam, Amsterdam*  
15  
16  
17 7 *Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, The Netherlands*  
18

19 8 <sup>2</sup>*Section of Immigrant Medicine, Department of Infectious Diseases, Copenhagen University*  
20  
21 9 *Hospital, Kettegård allé 30, 2650 Hvidovre, Denmark*  
22

23  
24 10 <sup>3</sup>*Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht,*  
25  
26 11 *Heidelberglaan 100, 3584 CX Utrecht, The Netherlands*  
27

28 12 <sup>4</sup>*Danish Research Centre for Migration, Ethnicity and Health, Section of Health Services*  
29  
30 13 *Research, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, 1014*  
31  
32 14 *København K, Denmark*  
33  
34

35 15  
36  
37 16 Corresponding author:  
38  
39 17 Laura Deen, *Department of Public Health, Academic Medical Centre, University of Amsterdam,*  
40  
41 18 *Amsterdam Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, The Netherlands*  
42  
43

44 19 e-mail: [nhq382@alumni.ku.dk](mailto:nhq382@alumni.ku.dk), telephone.: +4527514559  
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## 25 **Abstract**

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

30  
31 **Methods:** A nationwide register-based cohort study comprising all women with a first admission  
32 for breast cancer (n=127,714) between 1996 and 2010 in the Netherlands was conducted.  
33 Differences in CVD admission, CVD mortality and overall CVD event, which comprised a CVD  
34 admission and/or CVD mortality, between the largest ethnic minority groups (Surinamese,  
35 Moroccan, Turkish, Antillean, and Indonesian) and the Dutch general population (henceforth,  
36 Dutch) were investigated using Cox proportional hazard models.

37  
38 **Results:** The incidence of cardiovascular outcomes varied by ethnic group. The incidence of an  
39 overall cardiovascular event was significantly higher for women with breast cancer from  
40 Suriname (HR=1.46;95% CI 1.29–1.64) and Turkey (HR=1.25;95% CI 1.03–1.51), compared  
41 with Dutch women with breast cancer. In contrast, Indonesian women with breast cancer had a  
42 significantly lower risk (HR=0.88; 95% CI 0.81–0.96) of a cardiovascular event compared with  
43 Dutch women with breast cancer. There were no significant differences between Moroccan and  
44 Antillean women, and Dutch women with breast cancer.

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46 **Conclusions:** Our findings suggest that Surinamese and Turkish women with breast cancer are  
47 disadvantaged in terms of cardiovascular outcomes compared with Dutch women with breast  
48 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.

### 73 1. Introduction

74 Due to earlier diagnosis and more effective treatment, the survival rate among breast cancer  
75 patients has now improved resulting in a growing population of breast cancer survivors. In The  
76 Netherlands, the 5-year-age-standardized survival rate has increased from 80% in 1995-99 to  
77 85% in 2005-09 [1]. With breast cancer becoming a curable disease, comorbidities and death  
78 from other conditions among breast cancer survivors are of increasing concern.

79  
80 One of the most important comorbidities to consider in women with breast cancer is  
81 cardiovascular disease (CVD), and with the growing number of breast cancer survivors, a better  
82 understanding of the risk of CVD in this group is crucial. Studies show that women surviving  
83 breast cancer have an increased risk of CVD morbidity and CVD-specific mortality compared  
84 with women without breast cancer [2,3]. Moreover, among breast cancer survivors, CVD-related  
85 mortality is becoming more common than breast cancer-specific mortality [4,5]. This is mainly  
86 attributable to cardiotoxic effects of breast cancer therapy [6,7]. Further, survivors are typically  
87 older than the general population and may be more likely to develop CVD because of risk factors  
88 common to both cancer and CVD [8].

89  
90 Evidence suggests ethnic inequalities in the prognosis of breast cancer with a higher risk of breast  
91 cancer-specific and overall mortality among some ethnic minority groups [9,10]. However,  
92 although ethnic variation in cardiovascular outcomes in the general population exists [11,12], the  
93 evidence among breast cancer patients is limited. Data from the US show that African American  
94 and Pacific Islander women with breast cancer had an increased risk of dying from CVD  
95 compared with White American breast cancer patients [4,13]. However, ethnic compositions and  
96 the national context vary across countries and, to our knowledge, no European study has

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3 97 examined the risk of CVD related outcomes in different ethnic groups among breast cancer  
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5 98 patients. Hence, the aim of this study was to explore differences in overall CVD event, CVD  
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7 99 admission and CVD mortality following a diagnosis of breast cancer between the largest ethnic  
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10 100 minority groups in the Netherlands compared with ethnic Dutch.  
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## 102 **2. Methods**

### 103 *Study sample*

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

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5 122 *Ethnic group*  
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8 123 Ethnic groups were constructed based on the country of birth of the resident and her parents,  
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10 124 according to the definition of Statistics Netherlands [15]. A woman was considered a migrant if  
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12 125 she was born abroad or at least one of the parents was born abroad. Women with both parents  
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14 126 born in the Netherlands were indicated as being Dutch. The major non-Western migrant groups  
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17 127 residing in the Netherlands were included, which are those born in Turkey, Suriname, Morocco,  
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19 128 Indonesia, and the Netherlands Antilles.  
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24 130 *Outcomes*  
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26 131 CVD admission after a diagnosis of breast cancer was defined as all admissions with either the  
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28 132 primary or secondary cause of admission coded as ICD-10: 017.2, 093, 228, 289.1–289.3, 390–  
29  
30 133 459, 557,745–747, 780.2, 782.3, 7825, 7826, 785, 786.50–786.59, 789.2, 794.30–794.39.  
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33 134 Cardiovascular mortality was defined as dying from a cardiovascular cause after a diagnosis of  
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35 135 breast cancer. Overall cardiovascular event combined the two outcomes and comprised a hospital  
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37 136 admission for CVD, and/or a dying from a cardiovascular cause.  
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42 138 *Data analyses*  
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45 139 We first presented baseline characteristics as absolute numbers and percentages according to  
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47 140 ethnic group. Continuous variables were summarized as mean and standard deviation or as  
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49 141 median and interquartile range where appropriate. Subsequently, we calculated hazard ratios  
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51 142 (HR) and corresponding 95% confidence intervals (95% CI) using cox proportional hazard  
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53 143 regression analyses to assess ethnic differences in overall cardiovascular events, and separately  
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55 144 for hospital admission for CVD and cardiovascular mortality between ethnic minority groups and  
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3 145 the Dutch (reference group) with adjustment for age, year of admission and type of breast cancer.  
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5 146 Cox proportional hazard assumptions were checked and met. All analyses were performed using  
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7 147 SPSS 22.0 (SPSS Inc., Chicago, IL, USA).  
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### 11 149 **3. Results**

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14 150 Table 1 presents the characteristics of the study population by ethnic group. In total, 127,714  
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16 151 women with a first admission for breast cancer between 01.01.1996 and 31.12.2010 were  
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18 152 included in the study, of which 5% belonged to an ethnic minority group (table 1). Dutch women  
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20 153 were in general followed for a longer period than the ethnic minority groups. Among migrants,  
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22 154 the Antilleans presented the smallest group and the Indonesians the largest group. In general, the  
23  
24 155 ethnic minority groups were younger than the Dutch population when diagnosed. During follow-  
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26 156 up, 19% of the Dutch population experienced a hospital admission due to CVD, whereas among  
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28 157 the ethnic minorities the proportion of CVD admission ranged from 9% for Moroccans to 19%  
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30 158 for Surinamese women. 31,203 women with breast cancer died during follow-up, of which 25%  
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32 159 were due to a cardiovascular cause.  
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40 161 Table 2 shows the incidence of a CVD event, which comprises a hospital admission for CVD,  
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42 162 and/or dying from a cardiovascular cause, among breast cancer patients by ethnic group.  
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44 163 Compared with Dutch women with breast cancer, both Surinamese (HR=1.46;95% CI 1.29–1.64)  
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46 164 and Turkish (HR=1.25;95% CI 1.03–1.51) women with breast cancer had a higher incidence of  
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48 165 CVD event after adjustment for breast cancer diagnosis, period of breast cancer diagnosis and  
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50 166 age. In contrast, Indonesian women with breast cancer had a significantly lower risk (HR=0.88;  
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52 167 95% CI 0.81–0.96) of cardiovascular event compared with Dutch women. For Moroccans and  
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54 168 Antilleans there were no significant differences from Dutch women.  
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3 169 Subsequently, we assessed cardiovascular admission and cardiovascular mortality separately.  
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5 170 Table 3 shows the unadjusted and adjusted hazard ratios for a cardiovascular admission. Only  
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7 171 women from Suriname had a significantly higher risk (HR=1.45; 95% CI 1.28–1.64) of  
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9 172 cardiovascular admission compared with Dutch women with breast cancer, whereas women from  
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11 173 Indonesia had a significantly lower risk of a cardiovascular admission (HR=0.85; 95% CI 0.78–  
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13 174 0.93). The unadjusted and adjusted hazard ratios for cardiovascular mortality for the different  
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15 175 ethnic groups are shown in table 4. The adjusted hazard ratios for cardiovascular mortality were  
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17 176 significantly higher for women from Suriname (HR=1.49; 95% CI 1.13-1.97) and Turkey  
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19 177 (HR=1.96; 95% CI 1.28-3.01), compared with Dutch women, whereas there were no significantly  
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21 178 differences between women from Indonesia and Dutch women. For Moroccan and Antillean  
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23 179 women the numbers of deaths due to cardiovascular disease were too small to perform analyses.  
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#### 181 **4. Discussion**

##### 182 *Key findings*

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

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3 193 *Discussion of key findings*  
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5 194 Evidence shows that ethnic minority and migrant groups in general have a lower risk of breast  
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7 195 cancer compared with the majority population [16,17]. However, the results of this study indicate  
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10 196 that among breast cancer patients, some ethnic minority groups are disadvantaged in terms of  
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12 197 cardiovascular outcomes compared with Dutch women. The results of this study are in line with  
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14 198 the sparse evidence on ethnic differences in CVD mortality among breast cancer patients in the  
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16 199 US, which also found some ethnic minority groups to be disadvantaged in terms of  
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18 200 cardiovascular mortality [4,13]. For example, African American women with ductal carcinoma in  
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20 201 situ of the breast were found to have a higher risk of CVD death compared with White American  
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22 202 women diagnosed with ductal carcinoma in situ of the breast [4]. However, even though CVD  
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24 203 have been shown to vary by ethnic group [11,18] data among breast cancer patients in Europe  
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26 204 have been lacking. Previous European studies on ethnic disparities in breast cancer prognosis  
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28 205 have mostly focused on mortality after breast cancer diagnosis, and found that some ethnic  
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30 206 minority groups have higher overall and breast cancer-specific mortality [9,10,19]. Our results  
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32 207 thereby add a great value to the existing literature by showing that women with breast cancer  
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34 208 from Suriname and Turkey are disadvantaged in terms of cardiovascular outcomes compared  
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36 209 with Dutch women with breast cancer. The higher incidence of CVD event among Surinamese  
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38 210 women with breast cancer reflects the pattern of CVD among Surinamese women in the general  
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40 211 Dutch population. Previous studies of the general population in the Netherlands showed that  
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42 212 Surinamese women have a higher risk of both AMI and stroke compared with Dutch women  
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44 213 [20,21], as well as a higher 5-year CVD mortality after initial admission for CVD [22]. Turkish  
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46 214 women with breast cancer were in the present study found to have a higher incidence of CVD  
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48 215 event, compared with Dutch women with breast cancer. However, this only partly reflects on the  
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50 216 pattern among Turkish women in the general population in the Netherlands. Previous studies of  
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3 217 the general population in the Netherlands did not find differences in the incidence of stroke or  
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5 218 AMI among Turkish women compared with the Dutch majority women [20,21]. However, when  
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7 219 stratifying on age, a higher incidence of AMI were observed in 50- to 70-year-old Turkish  
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10 220 women compared with the Dutch majority women [20].

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14 222 The relatively low risk of CVD outcomes among Indonesian women with breast cancer are in  
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16 223 contrast to previous studies of the general Dutch population that found no differences in  
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18 224 incidence of AMI and a slightly higher risk of stroke among Indonesians compared with Dutch  
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20 225 women [20,21]. The reasons for the better CVD prognosis among Indonesian breast cancer  
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22 226 patients are unclear. However, Indonesians are well integrated in the Dutch society with respect  
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24 227 to language and culture and have similar income levels and are employed at equal rates as the  
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26 228 Dutch general population [23]. This possibly results in better access to health care services than  
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28 229 other minority groups and may underlie the better cardiovascular health outcomes among  
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31 230 Indonesian women with breast cancer.

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36 232 Possible explanations for the higher risk of cardiovascular events among Surinamese and Turkish  
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38 233 breast cancer patients may include disparities in access to health care services and a high risk  
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40 234 factor burden among these ethnic minorities in the Netherlands. Regular health visits are  
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42 235 important for early diagnosis of risk factors that can lead to CVD progression and it is possible  
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44 236 that differences in health service utilisation may contribute to the observed ethnic differences in  
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46 237 CVD risk among breast cancer patients. Evidence on health care utilization among breast cancer  
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48 238 patients is scarce, but previous evidence of the general population in the Netherlands suggests  
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50 239 that some ethnic minority populations use more general practitioner care than Dutch people do,  
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52 240 but that they are less likely to use specialised care [24]. Moreover, ethnic differences in use of

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3 241 cardiac rehabilitation and lower adherence to medication therapy have been shown [25–28]. A  
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5 242 Danish study found that immigrants from Pakistan and Turkey did not receive adequate medical  
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7 243 treatment with beta-blockers after a first AMI compared with Danish-born residents [26]. In  
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9 244 addition, in the Netherlands, Surinamese people have been found to have poor blood pressure  
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11 245 control compared with their Dutch counterparts [28].  
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17 247 The relatively high incidence of CVD admission and mortality among Turkish and Surinamese  
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19 248 breast cancer women may be explained by the high prevalence of cardiovascular risk factors in  
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21 249 these populations. The current study lacked information on CVD risk factor and we were  
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23 250 therefore not able to address the possible contribution of these to the observed ethnic differences.  
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25 251 However, previous studies of Surinamese and Turkish populations in the Netherlands showed  
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27 252 that hypertension, diabetes mellitus and obesity are more common among these populations  
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29 253 compared with the Dutch general population [28–31]. As an example, a previous Dutch study  
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31 254 showed that the prevalence of hypertension, the leading risk factor for CVD worldwide, was  
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33 255 higher in both Turkish and Surinamese people than in Dutch people [28]. In addition, a study  
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35 256 from the US, found that African American breast cancer patients have higher prevalence of  
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37 257 certain CVD risk factors, such as hypertension, diabetes and obesity, prior to initiating aromatase  
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39 258 inhibitory therapy, compared with White American breast cancer patients of the same age [32].  
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41 259 Evidence suggests that the presence of CVD risk factors among breast cancer patients at  
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43 260 diagnosis is a strong predictive factor for the development of cardiovascular damage associated  
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45 261 with breast cancer therapy [33]. The higher risk factor burden in some ethnic minority groups  
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47 262 may therefore contribute to the higher incidence of CVD in these groups.  
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53 263 Additionally, since the risk of CVD has been shown to vary according to breast cancer therapy  
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55 264 [7,34], the observed differences may be explained by variation in the treatment received by  
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3 265 different ethnic groups. In the current study, data on treatment was not available. However,  
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5 266 studies from the US and UK have reported that ethnic minority women were more likely to  
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7 267 receive chemotherapy, which was largely explained by more advanced stage and higher grade  
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10 268 tumours [35,36].

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14 270 Our findings have important clinical and public health implications because identifying breast  
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16 271 cancer patients who are most vulnerable to cardiovascular outcomes is important in order to  
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18 272 guide strategies among breast cancer patients. The findings suggest the need to increase attention  
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20 273 for these women in the cardiovascular risk factor management guidelines in the Netherlands and  
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22 274 awareness of the observed ethnic differences in the risk of cardiovascular outcomes among breast  
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24 275 cancer patients should be raised among clinicians and incorporated into oncology practices. The  
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26 276 observed differences suggest the need for further studies to identify factors explaining these  
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28 277 differences. More specific, studies addressing the potential contribution of both CVD risk factors  
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30 278 and type of treatment to the observed ethnic differences found in this study are needed. This will  
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32 279 help to tailor appropriate public health and clinical interventions to improve outcomes among  
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34 280 breast cancer patients most at risk of adverse CVD outcomes.

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42 282 *Strength and limitations:*  
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44 283 The strength of the current study is the validity of the registries, the linkage methods, and the lack  
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46 284 of selection of the cohorts. A high validity of both the Dutch National Hospital Discharge  
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48 285 Register and the Dutch Population Register has been demonstrated. In a random sample of the  
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50 286 Hospital Discharge Register, 99% of the personal, admission and discharge data and 84% of the  
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52 287 principal diagnoses (validated through medical record review by medical specialists) were  
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54 288 correctly registered [37]. In addition, over 97% of the uniquely linked hospital admissions  
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3 289 resulting from linkage of the Hospital Discharge Register with the Population Register were  
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5 290 shown to be correctly linked [38].  
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10 292 Nonetheless, some limitations must be considered. First, although the study is based on a  
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12 293 nationwide cohort of breast cancer patients, absolute numbers are somewhat small when divided  
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14 294 into different ethnic groups. Consequently, the numbers were too small to investigate different  
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16 295 kinds of CVD, which could have afforded a more nuanced picture. Second, inherent to many  
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18 296 national-level databases, we lack detailed data on CVD risk factors, such as smoking, alcohol,  
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20 297 cholesterol and obesity, and therefore we were unable to do additional analyses to assess the  
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22 298 contribution of these to the observed ethnic differences. However, we were able to shed light on  
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24 299 the potential contributing risk factors to the observed differences due to previous studies on  
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26 300 ethnic differences in risk factors in the Netherlands [28–31]. Additionally, the study lack data on  
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28 301 treatment of breast cancer. Since, CVD risk has been shown to vary according to type of  
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30 302 treatment [7,34], adjustment for treatment would have been preferable in order to assess the  
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32 303 potential impact of differences in treatment to the observed ethnic differences in CVD. Finally, as  
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34 304 in numerous studies, the classifications of the various ethnic groups were based on country of  
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36 305 birth. Country of birth may reflect ethnicity reasonably well among some ethnic groups but is  
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38 306 likely to be an unreliable proxy measure of ethnicity for other groups such as Surinamese [15].  
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40 307 The results may be generalised to other European settings with similar health care services and  
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42 308 composition of ethnic groups.  
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51 310 **5. Conclusion**  
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53 311 The results of the current study suggest that the risk of CVD related outcomes among breast  
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55 312 cancer patients vary by ethnicity. Surinamese and Turkey breast cancer patients experienced a

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3 313 higher risk, whereas Indonesian patients had a slightly lower risk of CVD event compared with  
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5 314 their Dutch counterparts. More extensive cohort studies are needed to identify the forms of CVD  
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7 315 that are most common in these groups as well as the potential factors contributing to these  
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9 316 differences.

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14 318 **Competing interest:** None declared.

15  
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18  
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20  
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25 323 **Contributor ship statement**

26  
27 324 LD, JB, IV, MLB, MN, CA were involved in the study design. LD and CA wrote the paper. JB  
28  
29 325 analysed the data. JB, IV, MLB and MN critically revised the manuscript. All Authors approved  
30  
31 326 the final version of the manuscript.

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35 328 **Data sharing statement**

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37 329 No additional data are available.

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481 **Table 1** Demographic and disease characteristics of women admitted for breast cancer between  
 482 1996 and 2010 in the Netherlands according to ethnic group

	<b>Ethnic Dutch</b> N %	<b>Antillean</b> N %	<b>Indonesian</b> N %	<b>Moroccan</b> N %	<b>Surinamese</b> N %	<b>Turkish</b> N %
<b>No. of patients</b>	120,809 (100)	454 (100)	3,457 (100)	919 (100)	1,351 (100)	724 (100)
<b>Mean age at diagnosis (y), sd</b>	60.4 (13.3)	52.8 (11.8)	57.0 (13.1)	47.0 (10.7)	52.8 (12.7)	49.5 (11.4)
<b>Attained age (y) end of follow-up</b>						
≤ 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)
<b>Follow-up time (y), median (IQR)</b>	5.7 (6.8)	4.1 (5.4)	5.6 (6.6)	4.1 (5.0)	4.61 (6.1)	4.7 (5.7)
<b>Breast cancer diagnosis</b>						
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)
<b>Period of breast cancer diagnosis (y)</b>						
1996-1999	28,869 (23.9)	66 (14.5)	743 (21.5)	115 (12.5)	230 (17.0)	104 (14.4)
2000-2003	32,196 (26.7)	121 (26.7)	912 (26.4)	201 (21.9)	326 (24.1)	187 (25.8)
2004-2007	33,385 (27.6)	139 (30.6)	990 (28.6)	289 (31.4)	420 (31.1)	222 (30.7)
2008-2010	26,359 (21.8)	128 (28.2)	812 (23.5)	314 (34.2)	375 (27.8)	211 (29.1)
<b>Marital status</b>						
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)
<b>Hospital admissions</b>						
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 <sup>a</sup>	25 (0.7)	<10 <sup>a</sup>	<10 <sup>a</sup>	<10 <sup>a</sup>
- Cerebrovascular disease	3,529 (2.9)	<10 <sup>a</sup>	82 (2.4)	<10 <sup>a</sup>	34 (2.5)	<10 <sup>a</sup>
<b>Death during follow-up</b>						
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 <sup>a</sup>	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

<sup>a</sup> = Not given in line with the Dutch data protection guideline as the number of cases was less than 10

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

	<b>Unadjusted HR (95% CI)</b>	<b>Adjusted HR (95% CI)</b>
<b>Ethnic group</b>		
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)

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

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

	<b>Unadjusted HR (95% CI)</b>	<b>Adjusted HR (95% CI)</b>
<b>Ethnic group</b>		
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)

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

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

	<b>Unadjusted HR (95% CI)</b>	<b>Adjusted HR (95% CI)</b>
<b>Ethnic group</b>		
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)

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

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



**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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	-

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	-
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	21 (table 1)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7 and 21 (table 1)
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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	-
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://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.

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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, Josefiën; 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
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Manuscripts

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3 1 **Ethnic differences in cardiovascular morbidity and mortality among breast cancer patients**  
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5 2 **in the Netherlands: a register-based cohort study.**  
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10 4 Laura Deen, MSC<sup>1,2</sup>; Josefiën Buddeke, MSC<sup>3</sup>; Ilonca Vaartjes, PhD<sup>3</sup>; Michiel L. Bots, MD  
11  
12 5 PhD<sup>3</sup>; Marie Norredam, MD PhD<sup>2,4</sup>; Charles Agyemang, MPH, PhD<sup>1</sup>  
13

14 6 <sup>1</sup>*Department of Public Health, Academic Medical Centre, University of Amsterdam, Amsterdam*  
15  
16  
17 7 *Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, The Netherlands*  
18

19 8 <sup>2</sup>*Section of Immigrant Medicine, Department of Infectious Diseases, Copenhagen University*  
20  
21 9 *Hospital, Kettegård allé 30, 2650 Hvidovre, Denmark*  
22

23  
24 10 <sup>3</sup>*Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht,*  
25  
26 11 *Heidelberglaan 100, 3584 CX Utrecht, The Netherlands*  
27

28 12 <sup>4</sup>*Danish Research Centre for Migration, Ethnicity and Health, Section of Health Services*  
29  
30 13 *Research, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, 1014*  
31  
32 14 *København K, Denmark*  
33  
34

35 15  
36  
37 16 Corresponding author:  
38  
39 17 Laura Deen, *Department of Public Health, Academic Medical Centre, University of Amsterdam,*  
40  
41 18 *Amsterdam Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, The Netherlands*  
42  
43

44 19 e-mail: [nhq382@alumni.ku.dk](mailto:nhq382@alumni.ku.dk), telephone.: +4527514559  
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3 **Abstract**  
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5 **Objectives:** Cardiovascular disease (CVD) is of increasing concern among breast cancer  
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7 survivors. However, evidence on ethnic differences in CVD among women with breast cancer is  
8  
9 sparse. We assessed ethnic differences in cardiovascular morbidity and mortality among breast  
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11 cancer patients in the Netherlands.  
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17 **Methods:** A nationwide register-based cohort study comprising all women with a first admission  
18  
19 for breast cancer (n=127,714) between 1996 and 2010 in the Netherlands was conducted.  
20  
21 Differences in CVD admission, CVD mortality and overall CVD event, which comprised a CVD  
22  
23 admission and/or CVD mortality, between the largest ethnic minority groups (Surinamese,  
24  
25 Moroccan, Turkish, Antillean, and Indonesian) and the Dutch general population (henceforth,  
26  
27 Dutch) were investigated using Cox proportional hazard models.  
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33 **Results:** The incidence of cardiovascular outcomes varied by ethnic group. The incidence of an  
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35 overall cardiovascular event was significantly higher for women with breast cancer from  
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37 Suriname (HR=1.46;95% CI 1.29–1.64) and Turkey (HR=1.25;95% CI 1.03–1.51), compared  
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39 with Dutch women with breast cancer. In contrast, Indonesian women with breast cancer had a  
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41 significantly lower risk (HR=0.88; 95% CI 0.81–0.96) of a cardiovascular event compared with  
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43 Dutch women with breast cancer. The risk of a cardiovascular event did not differ between  
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45 Moroccan and Dutch women with breast cancer, whereas for Antillean women the risk was not  
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47 significantly higher.  
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3 47 **Conclusions:** Our findings suggest that Surinamese and Turkish women with breast cancer are  
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5 48 disadvantaged in terms of cardiovascular outcomes compared with Dutch women with breast  
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7 49 cancer. More work is needed to unravel the potential factors contributing to these differences.  
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12 51 **Strengths and limitations of this study:**

- 13 52 • The study builds on data from nationwide registries which resulted in a large sample size.  
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16 53 • The validity of the linkage of the included registries has proved to be high.  
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18 54 • Although the study is based on a nationwide cohort of breast cancer patients, absolute  
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20 55 numbers are somewhat small when divided into different ethnic groups.  
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23 56 • Data on CVD risk factors, such as smoking, alcohol and obesity were not available since the  
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25 57 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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3 95 compared with White American breast cancer patients [4,15]. However, ethnic compositions and  
4  
5 96 the national context vary across countries and, to our knowledge, no European study has  
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7 97 examined the risk of CVD related outcomes in different ethnic groups among breast cancer  
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9 98 patients. Hence, the aim of this study was to explore differences in overall CVD event, CVD  
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11 99 admission and CVD mortality following a diagnosis of breast cancer between the largest ethnic  
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14 100 minority groups in the Netherlands compared with ethnic Dutch.  
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## 19 102 **2. Methods**

### 21 103 *Study sample*

23 104 This register-based cohort study builds on data from different Dutch nationwide registers. The  
24  
25 105 registries and linkage procedures used in this cohort study have previously been described in  
26  
27 106 detail [16]. In brief, we linked data between the national Dutch hospital discharge register, the  
28  
29 107 population register and the cause of death register using a record identification number. This  
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31 108 number is assigned to each resident in the Netherlands with a unique combination of birth date,  
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33 109 sex and postal code (84% of the Dutch population). The Dutch national hospital discharge  
34  
35 110 register and cause of death register were linked to identify all women with a first admission for  
36  
37 111 breast cancer between 1996 and 2010, using the International Classification of Diseases (ICD) 9<sup>th</sup>  
38  
39 112 revision and ICD 10<sup>th</sup> revision. Both patients with invasive (ICD-9: 174 and ICD-10: C50) and in  
40  
41 113 situ breast cancer (ICD-9: 233 and ICD-10: D05) were identified and men were excluded. Data  
42  
43 114 from the population register and the cause of death register were available until 2012 and data  
44  
45 115 from the Dutch hospital discharge register were available until 2010. Individuals were followed  
46  
47 116 from the date of their first breast cancer admission until (a) CVD admission, (b) CVD death, (c)  
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49 117 death due to other causes, (d) first emigration or (d) study end (31.12.2012), whichever came  
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51 118 first. Linkage of data from the different registries was performed in agreement with the privacy  
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3 119 legislation in The Netherlands. All linkages and analysis were performed in a secured  
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5 120 environment of Statistics Netherlands. The data set was made available and analysed in an  
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7 121 anonymous form in a secured environment of Statistics Netherlands. Prior to publication,  
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9 122 Statistics Netherlands made sure that none of the analysis results showed potential reducibility to  
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11 123 the individual level.  
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19 125 *Ethnic group*  
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21 126 Ethnic groups were constructed based on the country of birth of the resident and her parents,  
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23 127 according to the definition of Statistics Netherlands [17]. A woman was considered a migrant if  
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25 128 she was born abroad or at least one of the parents was born abroad. Women with both parents  
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27 129 born in the Netherlands were indicated as being Dutch. The major migrant groups residing in the  
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29 130 Netherlands were included, which are those born in Turkey, Suriname, Morocco, Indonesia, and  
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31 131 the Netherlands Antilles.  
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35 132  
36 133 *Outcomes*  
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38 134 CVD admission after a diagnosis of breast cancer was defined as all admissions with either the  
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40 135 primary or secondary cause of admission coded as ICD-9: 017.2, 093, 228, 289.1–289.3, 390–  
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42 136 459, 557,745–747, 780.2, 782.3, 7825, 7826, 785, 786.50–786.59, 789.2, 794.30–794.39.  
43  
44 137 Cardiovascular mortality was defined as dying from a cardiovascular cause after a diagnosis of  
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46 138 breast cancer.  
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49 139 Overall cardiovascular event combined the two outcomes and comprised a hospital admission for  
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51 140 CVD, and/or a dying from a cardiovascular cause.  
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56 142 *Data analyses*  
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3 143 We first presented baseline characteristics as absolute numbers and percentages according to  
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5 144 ethnic group. Continuous variables were summarized as mean and standard deviation or as  
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7 145 median and interquartile range where appropriate. Subsequently, we calculated hazard ratios  
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9 146 (HR) and corresponding 95% confidence intervals (95% CI) using cox proportional hazard  
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11 147 regression analyses to assess ethnic differences in overall cardiovascular events, and separately  
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13 148 for hospital admission for CVD and cardiovascular mortality between ethnic minority groups and  
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15 149 the Dutch (reference group) with adjustment for age as a continuous variable, year of admission  
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17 150 and type of breast cancer. Cox proportional hazard assumptions were tested by plotting the log  
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19 151 minus log functions for the continuous variable age. The assumptions were met in all analyses.  
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23 152 All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).  
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#### 27 28 154 *Patient and Public Involvement*

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31 155 No patient or public were involved in this study.  
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### 34 35 157 **3. Results**

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37 158 Table 1 presents the characteristics of the study population by ethnic group. In total, 127,714  
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39 159 women with a first admission for breast cancer between 01.01.1996 and 31.12.2010 were  
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41 160 included in the study, of which 5% belonged to an ethnic minority group (table 1). Women with  
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43 161 more adverse outcomes were in general followed for a shorter period. Among migrants, the  
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45 162 Antilleans presented the smallest group and the Indonesians the largest group. In general, the  
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47 163 ethnic minority groups were younger than the Dutch population when diagnosed. During follow-  
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49 164 up, 19% of the Dutch population experienced a hospital admission due to CVD, whereas among  
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53 165 the ethnic minorities the proportion of CVD admission ranged from 9% for Moroccans to 19%

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3 166 for Surinamese women. 31,203 women with breast cancer died during follow-up, of which 25%  
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5 167 were due to a cardiovascular cause.

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7 168 Table 2 shows the incidence of a CVD event, which comprises a hospital admission for CVD,  
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10 169 and/or dying from a cardiovascular cause, among breast cancer patients by ethnic group.  
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12 170 Compared with Dutch women with breast cancer, both Surinamese (HR=1.46;95% CI 1.29–1.64)  
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14 171 and Turkish (HR=1.25;95% CI 1.03–1.51) women with breast cancer had a higher incidence of  
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16 172 CVD event after adjustment for breast cancer diagnosis, period of breast cancer diagnosis and  
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18 173 age. In contrast, Indonesian women with breast cancer had a significantly lower risk (HR=0.88;  
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20 174 95% CI 0.81–0.96) of cardiovascular event compared with Dutch women. Although not  
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22 175 significant, the Antillean women had a higher incidence of CVD event compared with Dutch  
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24 176 women. For Moroccans, there were no significant differences from Dutch women.

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27 177 Subsequently, we assessed cardiovascular admission and cardiovascular mortality separately.  
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29 178 Table 3 shows the unadjusted and adjusted hazard ratios for a cardiovascular admission. Only  
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31 179 women from Suriname had a significantly higher risk (HR=1.45; 95% CI 1.28–1.64) of  
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33 180 cardiovascular admission compared with Dutch women with breast cancer, whereas women from  
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35 181 Indonesia had a significantly lower risk of a cardiovascular admission (HR=0.85; 95% CI 0.78–  
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37 182 0.93). The unadjusted and adjusted hazard ratios for cardiovascular mortality for the different  
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39 183 ethnic groups are shown in table 4. The adjusted hazard ratios for cardiovascular mortality were  
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41 184 significantly higher for women from Suriname (HR=1.49; 95% CI 1.13–1.97) and Turkey  
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43 185 (HR=1.96; 95% CI 1.28–3.01), compared with Dutch women, whereas there were no significant  
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45 186 differences between women from Indonesia and Dutch women. For Moroccan and Antillean  
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47 187 women the numbers of deaths due to CVD were too small to perform analyses. In order to  
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49 188 determine the impact of breast cancer treatment on the observed differences in CVD outcomes a  
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51 189 sensitivity analysis was performed excluding all women with in situ breast cancer. This did not  
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3 190 change the results significantly, suggesting that cancer status and treatment of cancer is not strongly  
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5 191 related to CVD outcomes in our study.  
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#### 9 193 **4. Discussion**

##### 10 194 *Key findings*

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14 195 In this population-based cohort study of women with breast cancer in the Netherlands, the risk of  
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16 196 cardiovascular outcomes varied by ethnic group. Women from Suriname and Turkey had a higher  
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18 197 risk of a CVD event compared with Dutch women with breast cancer. When separating  
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20 198 cardiovascular admission and cardiovascular mortality, Surinamese and Turkish women had a  
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22 199 higher risk of both cardiovascular admission and cardiovascular mortality compared with Dutch  
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24 200 women, though in Turkish women the results for CVD admission was not significant. In contrast,  
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26 201 women from Indonesia with breast cancer had a lower risk of cardiovascular event, and  
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28 202 cardiovascular admission, but similar risk of cardiovascular mortality compared with ethnic  
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30 203 Dutch women with breast cancer. For Moroccan women, the risk of a cardiovascular event did  
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32 204 not differ from Dutch women with breast cancer, whereas for Antillean women the risk was not  
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34 205 significantly higher.  
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##### 41 207 *Discussion of key findings*

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44 208 Evidence shows that ethnic minority and migrant groups in general have a lower risk of breast  
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46 209 cancer compared with the majority population [18,19]. However, the results of this study indicate  
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48 210 that among breast cancer patients, some ethnic minority groups are disadvantaged in terms of  
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50 211 cardiovascular outcomes compared with Dutch women. The results of this study are in line with  
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52 212 the sparse evidence on ethnic differences in CVD mortality among breast cancer patients in the  
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54 213 US, which also found some ethnic minority groups to be disadvantaged in terms of  
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3 214 cardiovascular mortality [4,15]. For example, African America women with ductal carcinoma in  
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5 215 situ of the breast were found to have a higher risk of CVD death compared with White American  
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7 216 women diagnosed with ductal carcinoma in situ of the breast [4]. However, even though CVD  
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10 217 have been shown to vary by ethnic group [13,20] data among breast cancer patients in Europe  
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12 218 have been lacking. Previous European studies on ethnic disparities in breast cancer prognosis  
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14 219 have mostly focused on mortality after breast cancer diagnosis, and found that some ethnic  
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16 220 minority groups have higher overall and breast cancer-specific mortality [11,12,21]. Our results  
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18 221 thereby add a great value to the existing literature by showing that women with breast cancer  
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20 222 from Suriname and Turkey are disadvantaged in terms of cardiovascular outcomes compared  
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22 223 with Dutch women with breast cancer. The higher incidence of CVD event among Surinamese  
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24 224 women with breast cancer reflects the pattern of CVD among Surinamese women in the general  
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26 225 Dutch population. Previous studies of the general population in the Netherlands showed that  
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28 226 Surinamese women have a higher risk of both AMI and stroke compared with Dutch women  
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30 227 [22,23], as well as a higher 5-year CVD mortality after initial admission for CVD [24]. Turkish  
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32 228 women with breast cancer were in the present study found to have a higher incidence of CVD  
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34 229 event, compared with Dutch women with breast cancer. However, this only partly reflects on the  
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36 230 pattern among Turkish women in the general population in the Netherlands. Previous studies of  
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38 231 the general population in the Netherlands did not find differences in the incidence of stroke or  
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40 232 AMI among Turkish women compared with the Dutch majority women [22,23]. However, when  
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42 233 stratifying on age, a higher incidence of AMI were observed in 50- to 70-year-old Turkish  
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44 234 women compared with the Dutch majority women [22].  
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53 236 The relatively low risk of CVD outcomes among Indonesian women with breast cancer are in  
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55 237 contrast to previous studies of the general Dutch population that found no differences in  
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3 238 incidence of AMI and a slightly higher risk of stroke among Indonesians compared with Dutch  
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5 239 women [22,23]. The reasons for the better CVD prognosis among Indonesian breast cancer  
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7 240 patients are unclear. However, Indonesians are well integrated in the Dutch society with respect  
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10 241 to language and culture and have similar income levels and are employed at equal rates as the  
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12 242 Dutch general population [25]. This possibly results in better access to health care services than  
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14 243 other minority groups and may underlie the better cardiovascular health outcomes among  
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17 244 Indonesian women with breast cancer.  
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19 245  
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21 246 Possible explanations for the higher risk of cardiovascular events among Surinamese and Turkish  
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23 247 breast cancer patients may include disparities in access to health care services and a high risk  
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26 248 factor burden among these ethnic minorities in the Netherlands. Regular health visits are  
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28 249 important for early diagnosis of risk factors that can lead to CVD progression and it is possible  
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30 250 that differences in health service utilisation may contribute to the observed ethnic differences in  
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33 251 CVD risk among breast cancer patients. Evidence on health care utilization among breast cancer  
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35 252 patients is scarce, but previous evidence of the general population in the Netherlands suggests  
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37 253 that some ethnic minority populations use more general practitioner care than Dutch people do,  
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39 254 but that they are less likely to use specialised care [26]. Moreover, ethnic differences in use of  
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42 255 cardiac rehabilitation and lower adherence to medication therapy have been shown [27–30]. A  
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44 256 Danish study found that immigrants from Pakistan and Turkey did not receive adequate medical  
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46 257 treatment with beta-blockers after a first AMI compared with Danish-born residents [28]. In  
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48 258 addition, in the Netherlands, Surinamese people have been found to have poor blood pressure  
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50 259 control compared with their Dutch counterparts [30].  
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53 260 The relatively high incidence of CVD admission and mortality among Turkish and Surinamese  
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55 261 breast cancer women may be explained by the high prevalence of cardiovascular risk factors in  
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3 262 these populations. The current study lacked information on CVD risk factor and we were  
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5 263 therefore not able to address the possible contribution of these to the observed ethnic differences.  
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7 264 However, previous studies of Surinamese and Turkish populations in the Netherlands showed  
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9 265 that hypertension, diabetes mellitus and obesity are more common among these populations  
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11 266 compared with the Dutch general population [30–33]. As an example, a previous Dutch study  
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13 267 showed that the prevalence of hypertension, the leading risk factor for CVD worldwide, was  
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15 268 higher in both Turkish and Surinamese people than in Dutch people [30]. A previous study found  
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17 269 that Antillean women have higher risk of certain CVD risk factors than Dutch women [34].  
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19 270 Further, since Antilleans resemble other ethnic groups who have been found to have higher risk  
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21 271 of some CVD risk factors, such as Surinamese women with African background, this might be  
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23 272 the case for Antillean women as well and suggests the need for further study among this  
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25 273 population in the Netherlands. In addition, a study from the US, found that African American  
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27 274 breast cancer patients have higher prevalence of certain CVD risk factors, such as hypertension,  
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29 275 diabetes and obesity, prior to initiating aromatase inhibitory therapy, compared with White  
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31 276 American breast cancer patients of the same age [35]. Although the ethnic groups are not directly  
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33 277 comparable, this may also be the case for some of the ethnic groups in the current study, such as  
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35 278 the African Surinamese and Antillean women. Evidence suggests that the presence of CVD risk  
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37 279 factors among breast cancer patients at diagnosis is a strong predictive factor for the development  
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39 280 of cardiovascular damage associated with breast cancer therapy [36]. The higher risk factor  
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41 281 burden in some ethnic minority groups may therefore contribute to the higher incidence of CVD  
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43 282 in these groups.  
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51 283 Additionally, since the risk of CVD has been shown to vary according to breast cancer therapy  
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53 284 [9,37], the observed differences may be explained by variation in the treatment received by  
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55 285 different ethnic groups. In the current study, data on treatment was not available. However,  
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3 286 studies from the US and UK have reported that ethnic minority women were more likely to  
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5 287 receive chemotherapy, which was largely explained by more advanced stage and higher grade  
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7 288 tumours [38,39].  
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12 290 Our findings have important clinical and public health implications because identifying breast  
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14 291 cancer patients who are most vulnerable to cardiovascular outcomes is important in order to  
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16 292 guide strategies among breast cancer patients. The findings suggest the need to increase attention  
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18 293 for these women in the cardiovascular risk factor management guidelines in the Netherlands and  
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20 294 awareness of the observed ethnic differences in the risk of cardiovascular outcomes among breast  
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22 295 cancer patients should be raised among clinicians and incorporated into oncology practices. The  
23  
24 296 observed differences suggest the need for further studies to identify factors explaining these  
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26 297 differences. More specific, studies addressing the potential contribution of both CVD risk factors  
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28 298 and type of treatment to the observed ethnic differences found in this study are needed. This will  
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30 299 help to tailor appropriate public health and clinical interventions to improve outcomes among  
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32 300 breast cancer patients most at risk of adverse CVD outcomes.  
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40 302 *Strength and limitations:*

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42 303 The strength of the current study is the validity of the registries, the linkage methods, and the lack  
43  
44 304 of selection of the cohorts. A high validity of both the Dutch National Hospital Discharge  
45  
46 305 Register and the Dutch Population Register has been demonstrated. In a random sample of the  
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48 306 Hospital Discharge Register, 99% of the personal, admission and discharge data and 84% of the  
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50 307 principal diagnoses (validated through medical record review by medical specialists) were  
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52 308 correctly registered [40]. In addition, over 97% of the uniquely linked hospital admissions  
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3 309 resulting from linkage of the Hospital Discharge Register with the Population Register were  
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5 310 shown to be correctly linked [41].  
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7 311 Nonetheless, some limitations must be considered. First, although the study is based on a  
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9 312 nationwide cohort of breast cancer patients, absolute numbers are somewhat small when divided  
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11 313 into different ethnic groups. Consequently, the numbers were too small to investigate different  
12  
13 314 kinds of CVD, which could have afforded a more nuanced picture. Second, inherent to many  
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15 315 national-level databases, we lack detailed data on CVD risk factors, such as smoking, alcohol,  
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17 316 cholesterol and obesity, and therefore we were unable to do additional analyses to assess the  
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19 317 contribution of these to the observed ethnic differences. However, we were able to shed light on  
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21 318 the potential contributing risk factors to the observed differences due to previous studies on  
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23 319 ethnic differences in risk factors in the Netherlands [30–33]. Additionally, the study lack data on  
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25 320 treatment of breast cancer. Since, CVD risk has been shown to vary according to type of  
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27 321 treatment [9,37], adjustment for treatment would have been preferable in order to assess the  
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29 322 potential impact of differences in treatment to the observed ethnic differences in CVD. Finally, as  
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31 323 in numerous studies, the classifications of the various ethnic groups were based on country of  
32  
33 324 birth. Country of birth may reflect ethnicity reasonably well among some ethnic groups but is  
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35 325 likely to be an unreliable proxy measure of ethnicity for other groups such as Surinamese [17].  
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37 326 The results may be generalised to other European settings with similar health care services and  
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39 327 composition of ethnic groups.  
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## 49 329 **5. Conclusion**

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51 330 The results of the current study suggest that the risk of CVD related outcomes among breast  
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53 331 cancer patients vary by ethnicity. Surinamese and Turkey breast cancer patients experienced a  
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55 332 higher risk, whereas Indonesian patients had a slightly lower risk of CVD event compared with  
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3 333 their Dutch counterparts. More extensive cohort studies are needed to identify the forms of CVD  
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5 334 that are most common in these groups as well as the potential factors contributing to these  
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8 335 differences.

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11  
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18  
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21 341 **Contributor ship statement**

22  
23 342 LD, JB, IV, MLB, MN, CA were involved in the study design. LD and CA wrote the paper. JB  
24  
25 343 analysed the data. JB, IV, MLB and MN critically revised the manuscript. All Authors approved  
26  
27  
28 344 the final version of the manuscript.

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32 346 **Data sharing statement**

33  
34 347 No additional data are available.

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501 **Table 1** Demographic and disease characteristics of women admitted for breast cancer between  
 502 1996 and 2010 in the Netherlands according to ethnic group

	<b>Ethnic Dutch</b> N %	<b>Antillean</b> N %	<b>Indonesian</b> N %	<b>Moroccan</b> N %	<b>Surinamese</b> N %	<b>Turkish</b> N %
<b>No. of patients</b>	120,809 (100)	454 (100)	3,457 (100)	919 (100)	1,351 (100)	724 (100)
<b>Mean age at diagnosis (y), sd</b>	60.4 (13.3)	52.8 (11.8)	57.0 (13.1)	47.0 (10.7)	52.8 (12.7)	49.5 (11.4)
<b>Attained age (y) end of follow-up</b>						
≤ 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)
<b>Follow-up time (y), median (IQR)</b>	4.5 (6.5)	3.6 (5.8)	4.6 (5.5)	3.6 (6.0)	3.8 (??)	4.0 (6.0)
<b>Breast cancer diagnosis</b>						
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)
<b>Period of breast cancer diagnosis (y)</b>						
1996-1999	28,869 (23.9)	66 (14.5)	743 (21.5)	115 (12.5)	230 (17.0)	104 (14.4)
2000-2003	32,196 (26.7)	121 (26.7)	912 (26.4)	201 (21.9)	326 (24.1)	187 (25.8)
2004-2007	33,385 (27.6)	139 (30.6)	990 (28.6)	289 (31.4)	420 (31.1)	222 (30.7)
2008-2010	26,359 (21.8)	128 (28.2)	812 (23.5)	314 (34.2)	375 (27.8)	211 (29.1)
<b>Marital status</b>						
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)
<b>Hospital admissions</b>						
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 <sup>a</sup>	25 (0.7)	<10 <sup>a</sup>	<10 <sup>a</sup>	<10 <sup>a</sup>
- Cerebrovascular disease	3,529 (2.9)	<10 <sup>a</sup>	82 (2.4)	<10 <sup>a</sup>	34 (2.5)	<10 <sup>a</sup>
<b>Death during follow-up</b>						
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 <sup>a</sup>	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

<sup>a</sup> = Not given in line with the Dutch data protection guideline as the number of cases was less than 10

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

	<b>Unadjusted HR (95% CI)</b>	<b>Adjusted HR (95% CI)</b>
<b>Ethnic group</b>		
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)

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

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

	<b>Unadjusted HR (95% CI)</b>	<b>Adjusted HR (95% CI)</b>
<b>Ethnic group</b>		
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)

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

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516  
517 **Table 4** Unadjusted and adjusted hazard ratios for cardiovascular mortality by ethnic group

	<b>Unadjusted HR (95% CI)</b>	<b>Adjusted HR (95% CI)</b>
<b>Ethnic group</b>		
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)

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

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

**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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	-

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	-
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	21 (table 1)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7 and 21 (table 1)
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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	-
<b>Discussion</b>			
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
<b>Other information</b>			
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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4 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE  
5 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  
6 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://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.

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<b>Primary Subject Heading</b>:	Public health
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Manuscripts

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3 1 **Ethnic differences in cardiovascular morbidity and mortality among breast cancer patients**  
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5 2 **in The Netherlands: a register-based cohort study.**  
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10 4 Laura Deen, MSC<sup>1,2</sup>; Josefiën Buddeke, MSC<sup>3</sup>; Ilonca Vaartjes, PhD<sup>3</sup>; Michiel L. Bots, MD  
11  
12 5 PhD<sup>3</sup>; Marie Norredam, MD PhD<sup>2,4</sup>; Charles Agyemang, MPH, PhD<sup>1</sup>  
13

14 6 <sup>1</sup>*Department of Public Health, Academic Medical Centre, University of Amsterdam, Amsterdam*  
15  
16  
17 7 *Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, The Netherlands*  
18

19 8 <sup>2</sup>*Section of Immigrant Medicine, Department of Infectious Diseases, Copenhagen University*  
20  
21 9 *Hospital, Kettegård allé 30, 2650 Hvidovre, Denmark*  
22

23  
24 10 <sup>3</sup>*Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht,*  
25  
26 11 *Heidelberglaan 100, 3584 CX Utrecht, The Netherlands*  
27

28 12 <sup>4</sup>*Danish Research Centre for Migration, Ethnicity and Health, Section of Health Services*  
29  
30 13 *Research, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, 1014*  
31  
32 14 *København K, Denmark*  
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36  
37 16 Corresponding author:  
38  
39 17 Charles Agyemang, *Department of Public Health, Amsterdam Public Health Research Institute*  
40  
41 18 *Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The*  
42  
43 19 *Netherlands.*  
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46 20 e-mail: [c.o.agyemang@amc.uva.nl](mailto:c.o.agyemang@amc.uva.nl), telephone.: +31205664885  
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1  
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45 26 **Abstract**

7 27 **Objectives:** Cardiovascular disease (CVD) is of increasing concern among breast cancer  
8 28 survivors. However, evidence on ethnic differences in CVD among women with breast cancer is  
9  
10 29 sparse. We assessed ethnic differences in cardiovascular morbidity and mortality among breast  
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12 30 cancer patients in The Netherlands.  
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19 32 **Methods:** A nationwide register-based cohort study comprising all women with a first admission  
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21 33 for breast cancer (n=127,714) between 1996 and 2010 in The Netherlands was conducted.  
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23 34 Differences in CVD admission, CVD mortality and overall CVD event, which comprised a CVD  
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25 35 admission and/or CVD mortality, between the largest ethnic minority groups (Surinamese,  
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27 36 Moroccan, Turkish, Antillean, and Indonesian) and the Dutch general population (henceforth,  
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29 37 Dutch) were investigated using Cox proportional hazard models.  
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35 39 **Results:** The incidence of cardiovascular outcomes varied by ethnic group. The incidence of an  
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37 40 overall cardiovascular event was significantly higher for women with breast cancer from  
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39 41 Suriname (HR=1.46;95% CI 1.29–1.64) and Turkey (HR=1.25;95% CI 1.03–1.51), compared  
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41 42 with Dutch women with breast cancer. In contrast, Indonesian women with breast cancer had a  
42  
43 43 significantly lower risk (HR=0.88; 95% CI 0.81–0.96) of a cardiovascular event compared with  
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45 44 Dutch women with breast cancer. The risk of a cardiovascular event did not differ between  
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47 45 Moroccan and Dutch women with breast cancer, whereas for Antillean women the risk was not  
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49 46 significantly higher.  
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3 48 **Conclusions:** Our findings suggest that Surinamese and Turkish women with breast cancer are  
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5 49 disadvantaged in terms of cardiovascular outcomes compared with Dutch women with breast  
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7 50 cancer. More work is needed to unravel the potential factors contributing to these differences.  
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12 52 **Strengths and limitations of this study:**

- 13 53 • The study builds on data from nationwide registries which resulted in a large sample size.  
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15  
16 54 • The validity of the linkage of the included registries has proved to be high.  
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18 55 • Although the study is based on a nationwide cohort of breast cancer patients, absolute  
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20 56 numbers are somewhat small when divided into different ethnic groups.  
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23 57 • Data on CVD risk factors, such as smoking, alcohol and obesity were not available since the  
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25 58 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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3 96 American breast cancer patients [4]. However, ethnic compositions and the national context vary  
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5 97 across countries and, to our knowledge, no European study has examined the risk of CVD related  
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7 98 outcomes in different ethnic groups among breast cancer patients. Hence, the aim of this study  
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10 99 was to explore differences in overall CVD event, CVD admission and CVD mortality following a  
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12 100 diagnosis of breast cancer between the largest ethnic minority groups in The Netherlands  
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14 101 compared with ethnic Dutch.  
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## 19 103 **2. Methods**

### 21 104 *Study sample*

23 105 This register-based cohort study builds on data from different Dutch nationwide registers. The  
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25 106 registries and linkage procedures used in this cohort study have previously been described in  
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27 107 detail [15]. In brief, we linked data between the national Dutch hospital discharge register, the  
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29 108 population register and the cause of death register using a record identification number. This  
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31 109 number is assigned to each resident in The Netherlands with a unique combination of birth date,  
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33 110 sex and postal code (84% of the Dutch population). The Dutch national hospital discharge  
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35 111 register and cause of death register were linked to identify all women with a first admission for  
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37 112 breast cancer between 1996 and 2010, using the International Classification of Diseases (ICD) 9<sup>th</sup>  
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39 113 revision and ICD 10<sup>th</sup> revision. Both patients with invasive (ICD-9: 174 and ICD-10: C50) and in  
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41 114 situ breast cancer (ICD-9: 233 and ICD-10: D05) were identified and men were excluded. Data  
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43 115 from the population register and the cause of death register were available until 2012 and data  
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45 116 from the Dutch hospital discharge register were available until 2010. Individuals were followed  
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47 117 from the date of their first breast cancer admission until (a) CVD admission, (b) CVD death, (c)  
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49 118 death due to other causes, (d) first emigration or (d) study end (31.12.2012), whichever came  
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51 119 first. Linkage of data from the different registries was performed in agreement with the privacy  
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3 120 legislation in The Netherlands. All linkages and analysis were performed in a secured  
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5 121 environment of Statistics Netherlands. The data set was made available and analysed in an  
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7 122 anonymous form in a secured environment of Statistics Netherlands. Prior to publication,  
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10 123 Statistics Netherlands made sure that none of the analysis results showed potential reducibility to  
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12 124 the individual level.

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17 126 *Ethnic group*  
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19 127 Ethnic groups were constructed based on the country of birth of the resident and her parents,  
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21 128 according to the definition of Statistics Netherlands [16]. A woman was considered a migrant if  
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23 129 she was born abroad or at least one of the parents was born abroad. Women with both parents  
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26 130 born in The Netherlands were indicated as being Dutch. The major migrant groups residing in  
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28 131 The Netherlands were included, which are those born in Turkey, Suriname, Morocco, Indonesia,  
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30 132 and The Netherlands Antilles.

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35 134 *Outcomes*  
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37 135 CVD admission after a diagnosis of breast cancer was defined as all admissions with either the  
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39 136 primary or secondary cause of admission coded as ICD-9: 017.2, 093, 228, 289.1–289.3, 390–  
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41 137 459, 557,745–747, 780.2, 782.3, 7825, 7826, 785, 786.50–786.59, 789.2, 794.30–794.39.  
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43 138 Cardiovascular mortality was defined as dying from a cardiovascular cause after a diagnosis of  
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45 139 breast cancer.

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48 140 Overall cardiovascular event combined the two outcomes and comprised a hospital admission for  
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50 141 CVD, and/or a dying from a cardiovascular cause.

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55 143 *Data analyses*

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3 144 We first presented baseline characteristics as absolute numbers and percentages according to  
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5 145 ethnic group. Continuous variables were summarized as mean and standard deviation or as  
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7 146 median and interquartile range where appropriate. Subsequently, we calculated hazard ratios  
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10 147 (HR) and corresponding 95% confidence intervals (95% CI) using cox proportional hazard  
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12 148 regression analyses to assess ethnic differences in overall cardiovascular events, and separately  
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14 149 for hospital admission for CVD and cardiovascular mortality between ethnic minority groups and  
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16 the Dutch (reference group) with adjustment for age as a continuous variable, year of admission  
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18 150 and type of breast cancer. Cox proportional hazard assumptions were tested by plotting the log  
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20 151 minus log functions for the continuous variable age. The assumptions were met in all analyses.  
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24 153 All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).  
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### 27 28 155 *Patient and Public Involvement*

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30 156 No patient or public were involved in this study.  
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## 34 35 158 **3. Results**

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37 159 Table 1 presents the characteristics of the study population by ethnic group. In total, 127,714  
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39 160 women with a first admission for breast cancer between 01.01.1996 and 31.12.2010 were  
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41 161 included in the study, of which 5% belonged to an ethnic minority group (table 1). Women with  
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43 162 more adverse outcomes were in general followed for a shorter period. Among migrants, the  
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45 163 Antilleans presented the smallest group and the Indonesians the largest group. In general, the  
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47 164 ethnic minority groups were younger than the Dutch population when diagnosed. During follow-  
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49 165 up, 19% of the Dutch population experienced a hospital admission due to CVD, whereas among  
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51 166 the ethnic minorities the proportion of CVD admission ranged from 9% for Moroccans to 19%  
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3 167 for Surinamese women. 31,203 women with breast cancer died during follow-up, of which  
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5 168 around 25% were due to a cardiovascular cause.

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7 169 Table 2 shows the incidence of a CVD event, which comprises a hospital admission for CVD,  
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9 and/or dying from a cardiovascular cause, among breast cancer patients by ethnic group.  
10 170 Compared with Dutch women with breast cancer, both Surinamese (HR=1.46;95% CI 1.29–1.64)  
11 171 and Turkish (HR=1.25;95% CI 1.03–1.51) women with breast cancer had a higher incidence of  
12 172 CVD event after adjustment for breast cancer diagnosis, period of breast cancer diagnosis and  
13 173 age. In contrast, Indonesian women with breast cancer had a significantly lower risk (HR=0.88;  
14 174 95% CI 0.81–0.96) of cardiovascular event compared with Dutch women. Although not  
15 175 significant, the Antillean women had a higher incidence of CVD event compared with Dutch  
16 176 women. For Moroccans, there were no differences from Dutch women.

17 178 Subsequently, we assessed cardiovascular admission and cardiovascular mortality separately.  
18 179 Table 3 shows the unadjusted and adjusted hazard ratios for a cardiovascular admission. Only  
19 180 women from Suriname had a significantly higher risk (HR=1.45;95% CI 1.28–1.64) of  
20 181 cardiovascular admission compared with Dutch women with breast cancer, whereas women from  
21 182 Indonesia had a significantly lower risk of a cardiovascular admission (HR=0.85;95% CI 0.78–  
22 183 0.93). The unadjusted and adjusted hazard ratios for cardiovascular mortality for the different  
23 184 ethnic groups are shown in table 4. The adjusted hazard ratios for cardiovascular mortality were  
24 185 significantly higher for women from Suriname (HR=1.49;95% CI 1.13–1.97) and Turkey  
25 186 (HR=1.96; 95% CI 1.27–3.01), compared with Dutch women, whereas there were no significantly  
26 187 differences between women from Indonesia and Dutch women. For Moroccan and Antillean  
27 188 women the numbers of deaths due to CVD were too small to perform analyses. In order to  
28 189 determine the impact of breast cancer treatment on the observed differences in CVD outcomes a  
29 190 sensitivity analysis was performed excluding all women with in situ breast cancer. This did not

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3 191 change the results significantly, suggesting that cancer status and treatment of cancer is not strongly  
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5 192 related to CVD outcomes in our study.  
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#### 9 194 **4. Discussion**

##### 10 195 *Key findings*

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12 196 In this population-based cohort study of women with breast cancer in The Netherlands, the risk of  
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14 197 cardiovascular outcomes varied by ethnic group. Women from Suriname and Turkey had a higher  
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16 198 risk of a CVD event compared with Dutch women with breast cancer. When separating  
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18 199 cardiovascular admission and cardiovascular mortality, Surinamese and Turkish women had a  
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20 200 higher risk of both cardiovascular admission and cardiovascular mortality compared with Dutch  
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22 201 women, though in Turkish women the results for CVD admission was not significant. In contrast,  
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24 202 women from Indonesia with breast cancer had a lower risk of cardiovascular event, and  
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26 203 cardiovascular admission, but similar risk of cardiovascular mortality compared with ethnic  
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28 204 Dutch women with breast cancer. For Moroccan women, the risk of a cardiovascular event did  
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30 205 not differ from Dutch women with breast cancer, whereas for Antillean women the risk was not  
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32 206 significantly higher.  
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##### 41 208 *Discussion of key findings*

42 209 Evidence shows that ethnic minority and migrant groups in general have a lower risk of breast  
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44 210 cancer compared with the majority population [17,18]. However, the results of this study indicate  
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46 211 that among breast cancer patients, some ethnic minority groups are disadvantaged in terms of  
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48 212 cardiovascular outcomes compared with Dutch women. The results of this study are in line with  
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50 213 the sparse evidence on ethnic differences in CVD mortality among breast cancer patients in the  
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52 214 US, which also found some ethnic minority groups to be disadvantaged in terms of  
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3 215 cardiovascular mortality [4,19]. For example, African America women with ductal carcinoma in  
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5 216 situ of the breast were found to have a higher risk of CVD death compared with White American  
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7 217 women diagnosed with ductal carcinoma in situ of the breast [4]. However, even though CVD  
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9 218 have been shown to vary by ethnic group [13,20] data among breast cancer patients in Europe  
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11 219 have been lacking. Previous European studies on ethnic disparities in breast cancer prognosis  
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13 220 have mostly focused on mortality after breast cancer diagnosis, and found that some ethnic  
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15 221 minority groups have higher overall and breast cancer-specific mortality [11,12,21]. Our results  
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17 222 thereby add a great value to the existing literature by showing that women with breast cancer  
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19 223 from Suriname and Turkey are disadvantaged in terms of cardiovascular outcomes compared  
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21 224 with Dutch women with breast cancer. The higher incidence of CVD event among Surinamese  
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23 225 women with breast cancer reflects the pattern of CVD among Surinamese women in the general  
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25 226 Dutch population. Previous studies of the general population in The Netherlands showed that  
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27 227 Surinamese women have a higher risk of both AMI and stroke compared with Dutch women  
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29 228 [22,23], as well as a higher 5-year CVD mortality after initial admission for CVD [24]. Turkish  
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31 229 women with breast cancer were in the present study found to have a higher incidence of CVD  
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33 230 event, compared with Dutch women with breast cancer. However, this only partly reflects on the  
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35 231 pattern among Turkish women in the general population in The Netherlands. Previous studies of  
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37 232 the general population in The Netherlands did not find differences in the incidence of stroke or  
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39 233 AMI among Turkish women compared with the Dutch majority women [22,23]. However, when  
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41 234 stratifying on age, a higher incidence of AMI were observed in 50- to 70-year-old Turkish  
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43 235 women compared with the Dutch majority women [22].  
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53 237 The relatively low risk of CVD outcomes among Indonesian women with breast cancer are in  
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55 238 contrast to previous studies of the general Dutch population that found no differences in  
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3 239 incidence of AMI and a slightly higher risk of stroke among Indonesians compared with Dutch  
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5 240 women [22,23]. The reasons for the better CVD prognosis among Indonesian breast cancer  
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7 241 patients are unclear. However, Indonesians are well integrated in the Dutch society with respect  
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10 242 to language and culture and have similar income levels and are employed at equal rates as the  
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12 243 Dutch general population [25]. This possibly results in better access to health care services than  
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14 244 other minority groups and may underlie the better cardiovascular health outcomes among  
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16 245 Indonesian women with breast cancer.  
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21 247 Possible explanations for the higher risk of cardiovascular events among Surinamese and Turkish  
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23 248 breast cancer patients may include disparities in access to health care services and a high risk  
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25 249 factor burden among these ethnic minorities in The Netherlands. Regular health visits are  
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27 250 important for early diagnosis of risk factors that can lead to CVD progression and it is possible  
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29 251 that differences in health service utilisation may contribute to the observed ethnic differences in  
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31 252 CVD risk among breast cancer patients. Evidence on health care utilization among breast cancer  
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33 253 patients is scarce, but previous evidence of the general population in The Netherlands suggests  
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35 254 that some ethnic minority populations use more general practitioner care than Dutch people do,  
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37 255 but that they are less likely to use specialised care [26]. Moreover, ethnic differences in use of  
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39 256 cardiac rehabilitation and lower adherence to medication therapy have been shown [27–30]. A  
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41 257 Danish study found that immigrants from Pakistan and Turkey did not receive adequate medical  
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43 258 treatment with beta-blockers after a first AMI compared with Danish-born residents [28]. In  
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45 259 addition, in The Netherlands, Surinamese people have been found to have poor blood pressure  
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47 260 control compared with their Dutch counterparts [30].  
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53 261 The relatively high incidence of CVD admission and mortality among Turkish and Surinamese  
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55 262 breast cancer women may be explained by the high prevalence of cardiovascular risk factors in  
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3 263 these populations. The current study lacked information on CVD risk factor and we were  
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5 264 therefore not able to address the possible contribution of these to the observed ethnic differences.  
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7 265 However, previous studies of Surinamese and Turkish populations in The Netherlands showed  
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9 266 that hypertension, diabetes mellitus and obesity are more common among these populations  
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11 267 compared with the Dutch general population [30–33]. As an example, a previous Dutch study  
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13 268 showed that the prevalence of hypertension, the leading risk factor for CVD worldwide, was  
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15 269 higher in both Turkish and Surinamese people than in Dutch people [30]. A previous study found  
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17 270 that Antillean women have higher risk of certain CVD risk factors than Dutch women [34].  
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19 271 Further, since Antilleans resemble other ethnic groups who have been found to have higher risk  
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21 272 of some CVD risk factors, such as Surinamese women with African background, this might be  
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23 273 the case for Antillean women as well and suggests the need for further study among this  
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25 274 population in The Netherlands. In addition, a study from the US, found that African American  
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27 275 breast cancer patients have higher prevalence of certain CVD risk factors, such as hypertension,  
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29 276 diabetes and obesity, prior to initiating aromatase inhibitory therapy, compared with White  
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31 277 American breast cancer patients of the same age [35]. Although the ethnic groups are not directly  
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33 278 comparable, this may also be the case for some of the ethnic groups in the current study, such as  
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35 279 the African Surinamese and Antillean women. Evidence suggests that the presence of CVD risk  
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37 280 factors among breast cancer patients at diagnosis is a strong predictive factor for the development  
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39 281 of cardiovascular damage associated with breast cancer therapy [36]. The higher risk factor  
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41 282 burden in some ethnic minority groups may therefore contribute to the higher incidence of CVD  
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43 283 in these groups.  
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51 284 Additionally, since the risk of CVD has been shown to vary according to breast cancer therapy  
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53 285 [9,37], the observed differences may be explained by variation in the treatment received by  
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55 286 different ethnic groups. In the current study, data on treatment was not available. However,  
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3 287 studies from the US and UK have reported that ethnic minority women were more likely to  
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5 288 receive chemotherapy, which was largely explained by more advanced stage and higher grade  
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7 289 tumours [38,39].  
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12 291 Our findings have important clinical and public health implications because identifying breast  
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14 292 cancer patients who are most vulnerable to cardiovascular outcomes is important in order to  
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16 293 guide strategies among breast cancer patients. The findings suggest the need to increase attention  
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18 294 for these women in the cardiovascular risk factor management guidelines in The Netherlands and  
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20 295 awareness of the observed ethnic differences in the risk of cardiovascular outcomes among breast  
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22 296 cancer patients should be raised among clinicians and incorporated into oncology practices. The  
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24 297 observed differences suggest the need for further studies to identify factors explaining these  
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26 298 differences. More specific, studies addressing the potential contribution of both CVD risk factors  
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28 299 and type of treatment to the observed ethnic differences found in this study are needed. This will  
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31 300 help to tailor appropriate public health and clinical interventions to improve outcomes among  
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33 301 breast cancer patients most at risk of adverse CVD outcomes.  
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40 303 *Strength and limitations:*

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42 304 The strength of the current study is the validity of the registries, the linkage methods, and the lack  
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44 305 of selection of the cohorts. A high validity of both the Dutch National Hospital Discharge  
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46 306 Register and the Dutch Population Register has been demonstrated. In a random sample of the  
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48 307 Hospital Discharge Register, 99% of the personal, admission and discharge data and 84% of the  
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50 308 principal diagnoses (validated through medical record review by medical specialists) were  
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52 309 correctly registered [40]. In addition, over 97% of the uniquely linked hospital admissions  
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3 310 resulting from linkage of the Hospital Discharge Register with the Population Register were  
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5 311 shown to be correctly linked [41].  
6

7 312 Nonetheless, some limitations must be considered. First, although the study is based on a  
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9 313 nationwide cohort of breast cancer patients, absolute numbers are somewhat small when divided  
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11 314 into different ethnic groups. Consequently, the numbers were too small to investigate different  
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13 315 kinds of CVD, which could have afforded a more nuanced picture. Second, inherent to many  
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15 316 national-level databases, we lack detailed data on CVD risk factors, such as smoking, alcohol,  
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17 317 cholesterol and obesity, and therefore we were unable to do additional analyses to assess the  
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19 318 contribution of these to the observed ethnic differences. However, we were able to shed light on  
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21 319 the potential contributing risk factors to the observed differences due to previous studies on  
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23 320 ethnic differences in risk factors in The Netherlands [30–33]. Additionally, the study lack data on  
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25 321 treatment of breast cancer. Since, CVD risk has been shown to vary according to type of  
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27 322 treatment [9,37], adjustment for treatment would have been preferable in order to assess the  
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29 323 potential impact of differences in treatment to the observed ethnic differences in CVD. Finally, as  
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31 324 in numerous studies, the classifications of the various ethnic groups were based on country of  
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33 325 birth. Country of birth may reflect ethnicity reasonably well among some ethnic groups but is  
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35 326 likely to be an unreliable proxy measure of ethnicity for other groups such as Surinamese [16].  
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37 327 The results may be generalised to other European settings with similar health care services and  
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39 328 composition of ethnic groups.  
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## 48 330 **5. Conclusion**

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51 331 The results of the current study suggest that the risk of CVD related outcomes among breast  
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53 332 cancer patients vary by ethnicity. Surinamese and Turkey breast cancer patients experienced a  
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55 333 higher risk, whereas Indonesian patients had a slightly lower risk of CVD event compared with  
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3 334 their Dutch counterparts. More extensive cohort studies are needed to identify the forms of CVD  
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5 335 that are most common in these groups as well as the potential factors contributing to these  
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7 336 differences.  
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11  
12 338 **Competing interest:** None declared.  
13

14 339

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19 342

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21 343

### 22 344 **Contributor ship statement**

23  
24 345 LD, JB, IV, MLB, MN, CA were involved in the study design. LD and CA wrote the paper. JB  
25  
26 346 analysed the data. JB, IV, MLB and MN critically revised the manuscript. All Authors approved  
27  
28 347 the final version of the manuscript.  
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31 348

### 32 349 **Data sharing statement**

33 350 No additional data are available.  
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502 **Table 1** Demographic and disease characteristics of women admitted for breast cancer between  
 503 1996 and 2010 in The Netherlands according to ethnic group

	<b>Ethnic Dutch</b> N %	<b>Antillean</b> N %	<b>Indonesian</b> N %	<b>Moroccan</b> N %	<b>Surinamese</b> N %	<b>Turkish</b> N %
<b>No. of patients</b>	120,809 (100)	454 (100)	3,457 (100)	919 (100)	1,351 (100)	724 (100)
<b>Mean age at diagnosis (y), sd</b>	60.4 (13.3)	52.8 (11.8)	57.0 (13.1)	47.0 (10.7)	52.8 (12.7)	49.5 (11.4)
<b>Attained age (y) end of follow-up</b>						
≤ 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)
<b>Follow-up time (y), median (IQR)</b>	4.5 (6.5)	3.6 (5.8)	4.6 (5.5)	3.6 (6.0)	3.8 (6.0)	4.0 (6.0)
<b>Breast cancer diagnosis</b>						
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)
<b>Period of breast cancer diagnosis (y)</b>						
1996-1999	28,869 (23.9)	66 (14.5)	743 (21.5)	115 (12.5)	230 (17.0)	104 (14.4)
2000-2003	32,196 (26.7)	121 (26.7)	912 (26.4)	201 (21.9)	326 (24.1)	187 (25.8)
2004-2007	33,385 (27.6)	139 (30.6)	990 (28.6)	289 (31.4)	420 (31.1)	222 (30.7)
2008-2010	26,359 (21.8)	128 (28.2)	812 (23.5)	314 (34.2)	375 (27.8)	211 (29.1)
<b>Marital status</b>						
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)
<b>Hospital admissions</b>						
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 <sup>a</sup>	25 (0.7)	<10 <sup>a</sup>	<10 <sup>a</sup>	<10 <sup>a</sup>
- Cerebrovascular disease	3,529 (2.9)	<10 <sup>a</sup>	82 (2.4)	<10 <sup>a</sup>	34 (2.5)	<10 <sup>a</sup>
<b>Death during follow-up</b>						
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 <sup>a</sup>	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

<sup>a</sup> = Not given in line with the Dutch data protection guideline as the number of cases was less than 10

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

	<b>Unadjusted HR (95% CI)</b>	<b>Adjusted HR (95% CI)</b>
<b>Ethnic group</b>		
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)

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

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

	<b>Unadjusted HR (95% CI)</b>	<b>Adjusted HR (95% CI)</b>
<b>Ethnic group</b>		
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)

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

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

	<b>Unadjusted HR (95% CI)</b>	<b>Adjusted HR (95% CI)</b>
<b>Ethnic group</b>		
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)

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

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

**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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	-

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	-
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	21 (table 1)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7 and 21 (table 1)
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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	-
<b>Discussion</b>			
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
<b>Other information</b>			
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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4 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE  
5 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  
6 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).  
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