Mortality and cancer incidence in the EPIC-NL cohort: impact of the healthy volunteer effect

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Background: Prospective cohort studies recruit relatively healthy population samples, resulting in lower morbidity and mortality rates than in the source population. This is known as the healthy volunteer effect. The aim of this study was to define the magnitude and the development over time of the healthy volunteer effect in the EPIC-NL cohort. Methods: We studied mortality rates in the EPIC-NL cohort, which comprises 37,551 men and women aged 20–70 years at recruitment in 1993–97. The date and cause of death of deceased participants until 2010 were obtained through linkage with the municipal registry and Statistics Netherlands. Standardized mortality ratios (SMRs) were computed by dividing the observed number of deaths by the number of deaths expected from the general Dutch population. Additionally, standardized incidence ratios were calculated to compare cancer incidence. Results: After an average follow-up of 14.9 years, 3029 deaths were documented. Overall mortality in men [SMR 73.5%, 95% confidence interval (CI): 68.1–79.3] and women [SMR 65.9%, 95% CI: 63.2–68.6] was lower compared with the general population for the whole follow-up period. Among women, the SMR was lower for death due to cardiovascular diseases than death due to cancer. Cancer incidence was also lower in EPIC-NL than in the general population (SMR 78.3 and 82.7% for men and women, respectively). Conclusion: The results show a healthy volunteer effect in the EPIC-NL cohort, which tapers off with longer follow-up. Therefore, in the first years of follow-up, power might not be sufficient to detect small associations.

Introduction

Participants of cohort studies tend to be healthier than the overall population they are sampled from.1,2 This is known as the healthy volunteer effect. Self-selection of healthy and usually higher-educated persons, together with self-exclusion of persons in poor health who meet the study criteria, are most likely causes of the healthy volunteer effect in cohort studies.3 Furthermore, persons might not feel well long before death and may, therefore, be less likely to participate.

Because of the healthy volunteer effect, morbidity and mortality rates in the first years after the study entry might be much lower than the morbidity and mortality rates from the general population.1 This leads to selection bias when comparisons are made with an external population. When associations are made between different exposure groups and the outcome of interest within a cohort, the result is less affected. However, follow-up needs to be long enough to generate sufficient endpoints and power. Moreover, the healthy volunteer effect might result in less variation in the exposure status of cohort members, resulting in small effects that remain undetected.

The extent of the healthy volunteer effect can be evaluated by comparing the mortality and morbidity with that of the general population using standardized mortality ratios (SMRs) and standardized incidence ratios (SIRs). Previous studies that showed a healthy volunteer effect by calculating SMRs were mostly screening trials1–6 and cohorts of vegetarian populations.7,8 Having a better insight into the healthy volunteer effect might be helpful in interpreting results from epidemiological cohort studies. The aim of this study was, therefore, to define the magnitude and the development over time of the healthy volunteer effect by calculating SMRs and SIRs in a cohort study with a large sample size, including a substantial general population sample of men and women, and a long follow-up.

Methods

The EPIC-NL cohort

The EPIC-NL study consists of the two Dutch contributions to the European Prospective Investigation into Cancer and Nutrition (EPIC), Prospect-EPIC and MORGEN-EPIC.9 EPIC is an ongoing multicentre prospective cohort study, designed to investigate the relationship of nutrition and lifestyle with the development of cancer and other chronic diseases. Prospect-EPIC and MORGEN-EPIC were set up simultaneously between 1993 and 1997. For Prospect-EPIC, 50,313 Dutch women aged 49–70 years living in the city of Utrecht and vicinity who were scheduled for the nationwide Dutch breast cancer screening, received a mailed invitation to join the Prospect-EPIC study, along with their
invitations for a routine mammography. Of them, 17,357 (34.5%) agreed to participate. The participation rate was somewhat higher for the younger women and for women from less urbanized areas. Those who agreed to participate in the Prospect-EPIC project received questionnaires by mail.\textsuperscript{10} For MORGEN-EPIC, a random sample of 50,766 men and women aged 20–64 years was drawn from the general Dutch population in three different towns (Doetinchem, Amsterdam and Maastricht), stratified for age and sex. This sample received an invitation to participate in the MORGEN cohort. Those who returned a reply card received questionnaires by mail and were asked to visit the local public health service for a physical examination. From the general sample, 22,654 (45%) individuals participated in the study. The response percentages were higher among women and among older persons.\textsuperscript{11}

At baseline, a general questionnaire was administered containing questions on lifestyle such as smoking status. A physical examination was performed for anthropometry and blood pressure measurements. All 40,011 participants provided informed consents before study inclusion. The study complies with the Declaration of Helsinki and was approved by the institutional review board of the University Medical Center Utrecht (Prospect-EPIC) and the medical ethical committee of TNO Nutrition and Food Research (MORGEN-EPIC). Further details of the study design have previously been published.\textsuperscript{9}

EPIC-NL participants are followed for vital status, cause of death and disease occurrence by regular linkage to several disease registries. Vital status of all EPIC-NL participants is obtained through linkage with the municipal registries. Subsequently, causes of death for the deceased persons are obtained through linkage with Statistics Netherlands. Information on vital status and causes of death is complete until 31 December 2010. Information on cancer incidence (overall, breast, prostate, colorectal and lung cancer) was available through the Dutch cancer registration and was complete until 31 December 2007.

For comparing mortality rates, subjects who did not give permission for linkage with the municipal registry and Statistics Netherlands (n = 2460) were excluded, leaving 37,551 men and women for analysis. For comparing cancer morbidity, we excluded participants who did not give permission for linkage with municipal registries and the Dutch cancer registration (n = 2306), leaving 37,705 participants for analysis.

**Risk factors**

Baseline characteristics, i.e. age, high educational level (those with vocational education or university), current smoking status, average number of cigarettes a day and overweight [body mass index (BMI) \( \geq 25 \text{ kg/m}^2 \)], are presented as means with standard deviations or percentages and stratified by age and sex. The distribution of educational level and risk factors in EPIC-NL is compared with the distribution in the general reference population, which is obtained from the Permanent Onderzoek LeefSituatie (POLS) questionnaire from Statistics Netherlands.\textsuperscript{12,13} We used the chi-square test to test whether this difference is significant. The POLS questionnaires are yearly questionnaires filled out by a random sample of \( \sim 10,000 \) persons of the general Dutch population (response rate 35–40%). The goal of POLS is to gather information on living conditions in the Netherlands.\textsuperscript{14} The health survey of POLS aims to give an overview of developments in health, medical consumption, lifestyle and preventive behaviour of the Dutch population.\textsuperscript{15} We used the data from 2001 as a reference because data from 1993 to 1997 were not available.

**Standardized Mortality Ratios**

To compare mortality in EPIC-NL with mortality in the general Dutch population, we calculated SMRs for overall mortality and for the two most frequent causes of death, i.e. cardiovascular diseases (CVDs; ICD-10 I00-I99) and cancer (ICD-10 C00-C97). The SMR is the ratio between observed and expected deaths, expressed as a percentage. Expected deaths were calculated by multiplying the sex-, age- and calendar year-specific national mortality rates by the number of person-years in EPIC-NL in the same category. Information on national mortality rates of the reference population was retrieved from Statistics Netherlands.\textsuperscript{16} EPIC-NL person-years at risk is the time between recruitment and the censor date (date of death, loss to follow-up or end of follow-up). To compute person-years for each category, numbers of living participants were calculated by counting the number of living participants per age and sex on July first of every calendar year, assuming the enrolment as well as the number of deaths was evenly distributed over the calendar year. For women from Prospect-EPIC who entered the study in 1993, ages were determined on 1 October because the recruitment started in July 1993. Thus, for example, we multiplied the mortality rate for 40-year-old persons in 2000 with the number of persons in the study who were 40-year-old in the year 2000, etc. Observed deaths were also categorized according to sex, age at death and calendar year. Observed and expected deaths were summed into specific age and calendar year groups and subsequently divided by each other to obtain the SMRs. To compare cancer incidence in the EPIC-NL study with cancer incidence in the general population, we additionally calculated SIRs in the same way as we did for SMRs. Information on national cancer incidence rates of the reference population was retrieved from the Dutch cancer registration.\textsuperscript{17} Reference CVD incidence rates were unfortunately not available.

SMRs and SIRs were calculated for the total follow-up period and additionally for three subsequent calendar years of the study follow-up. Because of the different recruitment years, the number of follow-up years of participants at a given moment in time can vary 5 years. Therefore, we additionally calculated the SMRs and SIRs per 3-year person-time on the study to assess whether the healthy volunteer effect changes over time. The calculations were done for the total population and per 10-year age groups. All analyses were stratified by sex. We additionally stratified the analysis by cohort. CIs were computed assuming a Poisson’s distribution when the number of observed deaths was below 100. Above 100 observed deaths, Byar’s approximation was used.\textsuperscript{1}

**Results**

During a median follow-up of 14.9 years, 3029 EPIC-NL participants died. The baseline table shows that EPIC-NL consists of \( \sim 75\% \) women who were older than the men in the cohort (table 1). Compared with the general population, EPIC-NL participants did not seem to smoke less in all age categories. Compared with the general population, EPIC-NL participants were not only more often overweight but also more often highly educated in all age categories.

For women, the total SMR calculated over total follow-up until 2010 was 65.9 (95% CI: 63.2–68.6) (table 2). This means that the mortality of female EPIC-NL participants was \( \sim 34\% \) lower than the mortality in the general female population. With increasing study follow-up, this healthy volunteer effect decreased from an SMR of 28.4% (95% CI: 19.2–40.6) in follow-up years 1993–95 to an SMR of 78.1% (95% CI: 72.7–83.7) for the period 2008–10, but all SMRs remained statistically significantly at <100%. Also with increasing participants’ follow-up time on the study, the healthy volunteer effect decreases from an SMR of 39.9% (95% CI: 33.4–47.2) for a follow-up of 3 years to an SMR of 65.9% (95% CI: 63.2–68.6) after a maximum follow-up of 18 years. For men, the observed healthy cohort effect was somewhat smaller (SMR 73.5%, 95% CI: 68.1–79.3). A similar trend with follow-up time was observed starting at an SMR of 52.8% (95% CI: 31.8–82.5) in 1993–95 and ending at 87.0% (95% CI: 75.8–99.4) in the period 2008–10. The healthy volunteer effect per
The healthy volunteer effect was more pronounced in younger participants compared with older participants, both in men and women. When the analyses for women were stratified for cohort, we observed a somewhat lower SMR for the women from Prospect-EPIC (64.7%, 95% CI: 61.9–67.7) than for the women from the MORGEN-EPIC cohort (70.9%, 95% CI: 64.6–77.6) (data not shown in tables).
The healthy volunteer effect among women was stronger for mortality due to CVD (SMR 53.9%, 95% CI: 49.4–58.6) than for mortality due to cancer (SMR 76.7%, 95% CI: 72.4–81.1). In men, the healthy volunteer effect was approximately the same for CVD and cancer mortality (SMR CVD 71.3%, 95% CI: 61.8–81.9, SMR cancer 73.7%, 95% CI: 65.5–82.6) and comparable with the SMR of overall mortality.

Cancer incidence rates in EPIC-NL were also lower than that in the reference population. The SIR for women was 82.7% (95% CI: 79.5–86.1) and 78.3% (95% CI: 71.8–85.2) for men (table 3). Although the SMRs clearly decrease over follow-up time, this is not observed for SIRs. Additionally, for cancer incidence, the healthy volunteer effect was not more pronounced in younger participants as was the case for the SMRs.

We also stratified for different cancer types. Especially, lung cancer incidence was much lower than expected in the EPIC-NL cohort for both men and women (table 3). Compared with the general population, the incidence of breast cancer in women was also lower. Colorectal cancer incidence and prostate cancer incidence among men did not differ significantly compared with the general population.

### Discussion

The results demonstrate a healthy volunteer effect for men and women at all ages of the EPIC-NL cohort. After a median follow-up of 15 years, overall mortality among men and women was 26 and 34% lower, respectively, compared with the general population (SMR 73.5 and 65.9%, respectively). The healthy volunteer effect was strongest during the first years of follow-up and declined over time but was still observable after 15 years of follow-up. Cancer incidence was somewhat less affected by the healthy cohort effect (SMR 78.3 and 82.7% for men and women, respectively) and remained stable over time. The results indicate that when causal relationships are of interest, the power in the first years of follow-up is lower than expected from the general population. Together with a possible lower degree of variation in the exposure of interest among the more healthy population, this might lead to small effects remaining undetected. When cohorts like EPIC-NL, where a healthy volunteer effect is present, are used, for example, for the estimation of absolute risks or prediction models, it is important to realize that the cohort is not completely representative of the target population.

Other studies reported similar healthy volunteer effects. Froom et al. reported an SIR among male volunteers of 71% after 8 years of follow-up. In the EPIC-Oxford cohort, the SIR was lower (52%). Two other prospective cohorts also reported low SMRs of 59 and 52%. Participants from the latter three studies were mainly vegetarians who were selected via vegetarian societies, health food shops and magazines. This has likely resulted in an even more health-conscious study population and might explain the lower SMRs. Screening trials also seem to attract more health-conscious participants. Among volunteers of a US cancer screening trial, SMRs of 46% for men and 38% for women were observed over 7 years of follow-up. This strong healthy volunteer effect in this screening trial might also be caused by the fact that persons who were already diagnosed with prostate, lung, colorectal or ovarian cancer were excluded from the trial, leaving a healthier group for analysis. A similar effect was reported in an ovarian cancer screening trial that reported an overall SIR of 37% after an average of 5.6 years of follow-up. However, in the Rotterdam part of the European Randomized Study of Screening for Prostate Cancer, the SIR was 86.7% after an average follow-up of only 2.8 years. When we stratified our analysis for women recruited via breast cancer screening, the healthy volunteer effect among women was higher for mortality than for incidence due to the more pronounced selection effect. The healthy volunteer effect among women was stronger for mortality due to CVD (SMR 53.9%, 95% CI: 49.4–58.6) than for mortality due to cancer (SMR 76.7%, 95% CI: 72.4–81.1). In men, the healthy volunteer effect was approximately the same for CVD and cancer mortality (SMR CVD 71.3%, 95% CI: 61.8–81.9, SMR cancer 73.7%, 95% CI: 65.5–82.6) and comparable with the SMR of overall mortality.

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### Table 3 SIRs of cancer incidence among 37705 participants of the EPIC-NL cohort stratified for sex

<table>
<thead>
<tr>
<th>Categories</th>
<th>Women</th>
<th>Men</th>
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<tr>
<td>Overall cancer</td>
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<td>1999–2001</td>
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<td>2002–4</td>
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<td>91</td>
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<td>2005–7</td>
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<td>101</td>
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<td>21–30</td>
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<td>30–39</td>
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<td>Colorectal cancer</td>
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</tr>
<tr>
<td>Prostate cancer</td>
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</tbody>
</table>

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a: The incidence rate (cases/1000) is the average age- and calendar year-specific incidence rate of the reference population in that category.

b: The number of expected deaths cannot be recalculated from this table because it has been calculated from age- and calendar year-specific rates.

c: The follow-up period represents the maximum period participants are on the study.
screening (Prospect-EPIC) and those recruited from the general population (MORGEN-EPIC), we observed a somewhat stronger reduced overall mortality among the women from Prospect-EPIC, i.e. 64.7 vs. 70.9%, respectively, suggesting that the healthy cohort effect might be stronger for cohorts based on the screening. However, it should be taken into account that the woman from the MORGEN cohort are on average much younger, and morbidity and mortality are still lower compared with the Prospect cohort.

Another way of exploring the healthy volunteer effect is by comparing the mortality of study participants with non-participants. However, in many situations, like in our cohort follow-up of non-participants, it is not feasible because of the absence of informed consent. The response rate was 34.5% for the Prospect-EPIC cohort and 45% for the MORGEN-EPIC cohort, resulting in an overall response rate of 40% for the whole EPIC-NL cohort. Van Loon et al. compared characteristics of MORGEN-EPIC participants with those of non-responders who gave limited information, showing only minor differences in the level of education and proportion of smokers. However, ~34% of the invitees did not respond at all, and it cannot be excluded that those non-responders have different educational level or smoking habits. In addition, we compared the characteristics of participants who are included in the EPIC-NL study but did not give informed consent for linkage (n = 2460; 6.2%) with the municipal registry and Statistics Netherlands with those who gave permission. Participants who did not give informed consent were on average younger, more often current smokers and less active than those who gave permission (data not shown). Exclusion of these participants might contribute to the healthy volunteer effect.

In women, the healthy volunteer effect was stronger for mortality due to CVD than for mortality due to cancer. This was also observed in other studies. It is possible that a healthier lifestyle reduces CVD mortality more than cancer mortality. It might also indicate that people who eventually die from CVD experience more complaints of their disease long before, which reduces willingness to participate in studies. Why we did not observe a similar healthy cohort effect in men and women is unclear. Possibly, the number of deaths was still too low.

Over time, the healthy volunteer effect was fading, which has also been observed in other studies. This seems intuitive, as persons with a disease are less likely to participate and lifestyle takes decades before impacting on major chronic diseases. Thus, the effect of a healthy selection at start is likely to slowly disappear over time, although not completely, as after even >10 years of follow-up a lower mortality is observed in the EPIC-NL cohort. The SIRs for cancer incidence remained more stable over time in our study because participants are probably more health conscious and less likely to develop cancer and remain more health conscious, resulting in lower cancer incidence in all years of the study. This has also been observed in the cancer screening trial of Pinsky et al.

In the paper of Burnell et al., the SIR increased over time, but follow-up of non-participants, it is not feasible because of the absence of informed consent. The response rate was 34.5% for the Prospect-EPIC cohort and 45% for the MORGEN-EPIC cohort, resulting in an overall response rate of 40% for the whole EPIC-NL cohort. Van Loon et al. compared characteristics of MORGEN-EPIC participants with those of non-responders who gave limited information, showing only minor differences in the level of education and proportion of smokers. However, ~34% of the invitees did not respond at all, and it cannot be excluded that those non-responders have different educational level or smoking habits. In addition, we compared the characteristics of participants who are included in the EPIC-NL study but did not give informed consent for linkage (n = 2460; 6.2%) with the municipal registry and Statistics Netherlands with those who gave permission. Participants who did not give informed consent were on average younger, more often current smokers and less active than those who gave permission (data not shown). Exclusion of these participants might contribute to the healthy volunteer effect.

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Participants of the EPIC-NL cohort are higher educated compared with the general population. A higher socio-economic status has been associated with earlier cancer treatment and therefore better survival and lower mortality. Furthermore, higher-educated persons tend to have a healthier lifestyle; this might partly explain the healthy volunteer effect. However, the significantly lower mortality and cancer incidence in our study cannot be easily explained by more favourable distributions of the risk factors—overweight and smoking. The percentage of overweight was higher in EPIC-NL participants than in the reference population. However, unlike the measured EPIC-NL data, the reference data for overweight were based on self-report. The proportion of overweight in the general reference population might therefore be underestimated; it is known that people tend to underestimate their weight and that the level of underreporting increases with increasing overweight. EPIC-NL women did not seem to smoke less often than the general population. The reference data used to compare the lifestyle of the participants were available for 2001, whereas the information on smoking status for the EPIC-NL participants is from 1993–97. Therefore, the percentage of smokers in the reference data may have been too low because the percentage of smokers has decreased over this time. Moreover, the reference data on smoking were also based on surveys among the general population. Respondents to these surveys might also be more health conscious and have a more favourable distribution of risk factors than the total population. Therefore, we cannot exclude the possibility that smoking and overweight explains some of the healthy volunteer effect in our cohort. Unfortunately, there were no good reference data available to compare physical activity and diet.

We conclude that there is a healthy volunteer effect in the EPIC-NL study causing lower mortality rates compared with the general population, which tapers off during follow-up. Also, cancer incidences are lower compared with the general population. When the cohort is used to obtain absolute risks or information for prediction models, it is important to realize that cohort studies like EPIC-NL comprise a subgroup of the population with some different characteristics than the general population where the results are used for. The consequence of the healthy volunteer effect when studying etiological associations is that small effects might remain undetected when comparisons are made within the cohort, especially in the first years of follow-up. Therefore, follow-up needs to be long enough to generate sufficient power.

Acknowledgements

The authors thank the National Cancer registry and Statistics Netherlands for follow-up data. None of the study sponsors had a role in the study design, data collection, analysis or interpretation, report writing or the decision to submit the report for publication. This work has previously been presented orally at the following conference: WEON 2012, Rotterdam, 14 June. The authors' responsibilities were as follows: E.A.S. conducted the statistical analyses and drafted the article; A.M.M., J.W.J.B. and P.H.M.P. supervised data analysis and provided critical review of the article; C.H.G., E.M.M., J.M.A.B., W.M.M.V., H.B.B.-M. and Y.T.S. provided critical review of the article. J.W.J.B., H.B.B.-M. and P.H.M.P. shared responsibility for data collection. All authors read and approved the final article.

Funding

Dutch research council (NWO-ZonMW; grant no 40-00812-98-10040). The EPIC-NL study was funded by the 'Europe against Cancer' Program of the European Commission (SANCO), the Dutch Ministry of Health, the Dutch Cancer Society, the Netherlands Organisation for Health research and Development (ZonMW) and World Cancer Research Fund (WCRF).

Conflict of interest: None declared.

Key points

- Our results show a healthy volunteer effect in the EPIC-NL cohort, which is strongest during the first years of follow-up and declined over time but was still observable after 15 years of follow-up.
- Cancer incidence was also lower than expected from the general population, but this effect remained stable over time.
- Especially in the first years of follow-up, the power of the study is lower than expected from the general population with the consequence that when studying etiological associations, small effects might remain undetected.
References


