Self-rated health and type 2 diabetes risk in the European Prospective Investigation into Cancer and Nutrition-InterAct study: a case-cohort study

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ABSTRACT

Objectives: To investigate the association between self-rated health and risk of type 2 diabetes and whether the strength of this association is consistent across five European centres.

Design: Population-based prospective case-cohort study.

Setting: Enrolment took place between 1992 and 2000 in five European centres (Bilthoven, Cambridge, Heidelberg, Potsdam and Umeå).

Participants: Self-rated health was assessed by a baseline questionnaire in 3399 incident type 2 diabetic case participants and a centre-stratified subcohort of 4619 individuals from the European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct study which was drawn from a total cohort of 340 234 participants in the EPIC.

Primary outcome measure: Prentice-weighted Cox regression was used to estimate centre-specific HRs and 95% CIs for incident type 2 diabetes controlling for age, sex, centre, education, body mass index (BMI), smoking, alcohol consumption, energy intake, physical activity and hypertension. The centre-specific HRs were pooled across centres.

Results: Low self-rated health was associated with a higher hazard of type 2 diabetes after adjusting for age and sex (pooled HR 1.67, 95% CI 1.48 to 1.88). After additional adjustment for health-related variables including BMI, the association was attenuated but remained statistically significant (p = 0.33). We found no indication of heterogeneity in the association between SRH and T2DM across centres.

Conclusions: Low self-rated health was associated with a higher risk of type 2 diabetes. The association could be only partly explained by other health-related variables, of which obesity was the strongest. We found no indication of heterogeneity in the association between self-rated health and type 2 diabetes mellitus across the European centres.

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) worldwide has more than doubled since 1980. In 2010, it was estimated that over 250 million people suffered from T2DM. Several risk factors have been identified (eg, age, body mass index (BMI), family history and physical inactivity), but the aetiology of T2DM is complex and still largely
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unknown. Self-rated health (SRH) is a subjective measure of health usually defined by responses to a single question such as ‘How do you rate your health?’ SRH is suggested to capture physical, psychological and social aspects that may be difficult to assess by objective health measurements. Furthermore, SRH has been associated with ‘bodily sensations and symptoms that can reflect disease in clinical or pre-clinical stages’. Individuals with poor SRH tend to have higher mortality, poorer physical activity (PA) and higher healthcare utilisation. Disease in clinical or pre-clinical stages.

METHODS
Study population
The InterAct Project was initiated to investigate how genetic and lifestyle behavioural factors, particularly diet and PA, interact on the risk of developing diabetes and how knowledge about such interactions may be translated into preventive action. The EPIC-InterAct case-cohort study was nested in the EPIC, which in total consists of 519,978 men and women across Europe. Out of these, 340,234 participants were eligible for the EPIC-InterAct study, which includes centres from eight different European countries (Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden and the UK). A detailed description of the study design and methods can be found elsewhere. In the present analysis, we only included centres that had baseline data available on SRH (Germany: Heidelberg and Potsdam; the UK: Cambridge; the Netherlands: Bilthoven; Sweden: Umeå). Participants were enrolled between 1992 and 2000. An overview of the five centres is presented in table 1. Among the participants from the five centres included in this study, 3,399 incident T2DM cases and a subcohort of 4,619 individuals remained after exclusions (figure 1). Owing to the random nature of the case-cohort design applied in the present study, the subcohort also included 140 individuals who developed T2DM during follow-up. All participants gave written consent and the study was approved by the ethical review board of the International Agency for Research on Cancer and by the local review boards of the participating centres.

Ascertainment of T2DM cases
Incident cases of T2DM until 31 December 2007 were ascertained and verified at each EPIC centre participating in the EPIC-InterAct project using follow-up questionnaires (T2DM diagnosed by a medical doctor or antidiabetic drug use), linkage to primary and secondary care registers, medication use (prescription registers), hospital admission and mortality data and individual medical-record review at some centres. To increase the specificity of the case definition and to avoid inclusion in the study based on self-report of T2DM alone, further evidence was sought for all incident cases of T2DM. T2DM cases were included in the study only if confirmation of the diagnosis was secured from no less than two independent sources. Cases in Umeå were not ascertained by self-report, but

| Centre    | Description of source population                                      | Baseline collection |
|-----------|------------------------------------------------------------------------|---------------------|
|           |                                                                      | N     | Women (%) | 5th and 95th age percentiles |
| Bilthoven | Participants were invited as an age-stratified and sex-stratified     | 22715 | 55        | 23–58                       |
|           | random sample of the general population                               |        |           |                             |
| Cambridge | Volunteers were invited as a random sample of the population listed    | 30441 | 55        | 45–74                       |
|           | at general practitioners                                              |        |           |                             |
| Heidelberg| Volunteers were invited from the general population                   | 25540 | 53        | 37–63                       |
|           |                                                                      |        |           |                             |
| Potsdam  | Volunteers were invited from the general population                   | 27548 | 60        | 36–64                       |
|           |                                                                      |        |           |                             |
| Umeå      | Participants were invited as a random sample of the population        | 25728 | 52        | 30–60                       |

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identified via local and national diabetes and pharmaceutical registers, and hence all ascertained cases were considered to be verified.16

Assessment of SRH
SRH was assessed at baseline using self-administered questionnaires in the native language. The questionnaires were somewhat differently formulated at each centre and were therefore standardised (described in the appendix). Given the low frequency of responses in the extreme categories (n=305 in the lowest category), we dichotomised the SRH variable in the analysis by combining the two highest categories (high SRH) and the two lowest categories (low SRH) in order to increase statistical power. This is also in conformity with previous research.17–19

Assessment of covariates
Weight and height were measured with participants not wearing shoes. Each participant’s body weight was corrected for clothing worn during measurement in order to reduce heterogeneity due to protocol differences among centres.20 BMI was calculated as weight (kilograms) divided by height (metres) squared. Hypertension was defined as self-reported medical history of hypertension or hypertension (based on measurements or drug use) at baseline. Further health-related variables were collected using questionnaires including questions on educational level, smoking status (current smoker vs non-smoker or exsmoker), diet, PA level, alcohol consumption and previous myocardial infarction. PA was assessed using the Cambridge index, a Validated Categorical Global Index of activity derived from simple questions assessing recreational and occupational activity.21

Statistical analysis
The association between SRH and various baseline characteristics within the subcohort was tested using a χ² test (for categorical variables) and a Kruskal-Wallis test (for continuous variables). Cox proportional hazards regression, modified for the case-cohort design according to the Prentice method,22 was used to estimate centre-specific HRs and 95% CI for the association between SRH and T2DM.

Age was used as the primary time variable, with entry time defined as the participant’s age in years at recruitment and exit time as the participant’s age in years at date of diagnosis, death or censoring. The centre-specific HRs were then pooled across centres by random effects meta-analysis.

It is not clear whether SRH mechanistically operates as an indicator of some unmeasured process or as a summary of a large number of other measures.3 23 Therefore, a large set of covariates were considered as potential confounders and included in models to determine pooled HRs at different levels of adjustment. All models were adjusted for age and sex. Each model was then further adjusted for the other health-related variables, one at a time, and finally, all potential confounders in the same model. Education level, smoking status, PA and hypertension were included as categorical variables, whereas BMI, alcohol consumption and energy intake were included as continuous variables.1—the percentage of variation between centres due to heterogeneity—was calculated. A possible interaction between SRH and sex on T2DM incidence was tested by introducing an interaction term in the regression analysis. We conducted a sensitivity analysis by excluding participants who were diagnosed with T2DM within 2 years of follow-up. In a second sensitivity analysis, we excluded all participants with a history of myocardial infarction at baseline. To investigate the impact of excluding 323 T2DM cases and 405 members of the subcohort with missing data on covariates, a third sensitivity analysis was conducted by multiple imputation of missing data considered missing at random (based on 5, 10 and 50 imputations) in cases and non-cases. For each variable with missing data, a predictive model was created among participants with no missing data; that model was then used to predict values for participants who were missing those
data. All analyses were performed using Stata V.11.2, except for the random effects meta-analysis, which was performed using Comprehensive Meta-Analysis V.2.

RESULTS
The mean follow-up time was 9.1 years (±3.8). SRH by centre in incident cases of T2DM and subcohort individuals is presented in table 2. Table 3 shows the baseline characteristics of individuals in the subcohort by categories of SRH. Participants with low SRH were younger, had a lower educational level and a higher BMI than participants with high SRH. Moreover, participants with low SRH were more often smokers, less physically active, had lower alcohol consumption and estimated reported energy intake, and more frequently had hypertension and a history of myocardial infarction than persons with high SRH.

In a model with adjustment for age and centre, low SRH was associated with a higher hazard of T2DM (HR 1.67, 95% CI 1.48 to 1.88; table 4). We found no significant interaction between SRH and sex on T2DM incidence (p=0.54) and the analyses were therefore not stratified by sex. The strength of the association between SRH and T2DM was mainly unaffected by adjustment for smoking, alcohol consumption and estimated reported energy intake. Adjustment for other health-related variables, BMI in particular, led to attenuation of the association (adding BMI to the model attenuated the pooled HR to 1.38, 95% CI 1.19 to 1.60). In a final model with adjustment for age, sex, education, BMI, smoking, PA, alcohol consumption, estimated reported energy intake and hypertension, the association was attenuated but remained significant (HR 1.29, 95% CI 1.09 to 1.53). The centre-specific HRs and the pooled HR, based on the final model, are presented in figure 2. We found no indication of heterogeneity in the association between SRH and T2DM across centres (I² index 13.3%, p=0.33).

In a first sensitivity analysis, we excluded participants who were diagnosed with T2DM within 2 years of follow-up (n=398). These exclusions had only a minor effect on the pooled HR (1.29, 95% CI 1.08 to 1.55, adjusted for the variables in the final model). The number of participants with a history of myocardial infarction was low (n=202) and the multivariate model did not fit when this covariate was included. Thus, in the second sensitivity analysis, we excluded all participants with a history of myocardial infarction at baseline. This did not change the conclusions (pooled HR 1.27, 95% CI 1.08 to 1.50, adjusted for the variables in the final model). Owing to missing data on covariates, 323 T2DM cases and 405 members of the subcohort were excluded from the analyses. As a third sensitivity analysis, multiple imputations of these data, assuming missingness at random, were conducted. No significant differences in results were found in datasets based on 5, 10 or 50 imputations, compared with the original dataset. Therefore, it seems unlikely that the results are biased due to missing data.

DISCUSSION
In this prospective case-cohort study, we found that low SRH was associated with a higher risk of T2DM. The association was partly explained by other health-related variables, particularly BMI. A somewhat unexpected finding was that the association between SRH and T2DM was mainly unaffected by adjustment for smoking, alcohol consumption and estimated reported

| Centre     | Self-rated health | Low          |
|------------|------------------|--------------|
|            | High             | Moderate     |
|            |                  | Poor         |
| Bilthoven  |                  |              |
| Cases      | 13 (4.3)         | 73 (24.4)    |
| Subcohort  | 52 (9.0)         | 101 (17.5)   |
| Cambridge  |                  |              |
| Cases      | 92 (12.3)        | 206 (27.5)   |
| Subcohort  | 159 (16.2)       | 23 (2.3)     |
| Heidelberg |                  |              |
| Cases      | 173 (23.1)       | 156 (20.9)   |
| Subcohort  | 286 (32.9)       | 125 (14.4)   |
| Potsdam    |                  |              |
| Cases      | 118 (15.2)       | 171 (22.1)   |
| Subcohort  | 274 (23.1)       | 164 (13.9)   |
| Umeå       |                  |              |
| Cases      | 155 (18.7)       | 236 (28.5)   |
| Subcohort  | 265 (26.2)       | 215 (21.2)   |

Data shown are numbers of individuals (percentage).
energy intake. We found no indication of heterogeneity in the association between SRH and T2DM across the European centres.

SRH has been widely used as a global health measure. Previous studies on general populations have shown that there is a strong relationship between SRH and mortality, even after controlling for sociodemographic factors, objective measures of health status and health behaviours.62 5 A few studies have investigated the association between SRH and mortality in populations of diabetes patients with results similar to those of general populations.18 26 27 SRH and prevalent diabetes have been associated in several cross-sectional studies.9–12 28 However, cross-sectional studies are limited by their inability to study the temporal sequence of exposure and disease. Furthermore, these studies have not separated types 2 and 1 diabetes.

Any causality cannot be established by an observational study, but the findings in this prospective study imply that there is a dominant direction of this

| Table 3  | Baseline characteristics of subcohort individuals in the European Prospective Investigation into Cancer and Nutrition-InterAct study by categories of self-rated health |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Self-rated health** | **High** | **Low** | **p Value for overall difference*** |
| | **Excellent** | **Good** | **Moderate** | **Poor** | **Mean%/SD/N** | **Mean%/SD/N** | **Mean%/SD/N** | **Mean%/SD/N** |
| **Age (years)** | 48.8 ± 10.3 | 50.5 ± 11.1 | 51.7 ± 10.9 | 50.3 ± 10.2 | <0.001 |
| **Sex (% men)** | 42.8 ± 443 | 45.2 ± 1208 | 44.8 ± 347 | 37.8 ± 51 | 0.24 |
| **Educational level (%)** | | | | | <0.001 |
| Primary school or none | 19.2 ± 194 | 24.4 ± 635 | 37.9 ± 287 | 30.8 ± 40 | <0.001 |
| Technical/professional school | 34.6 ± 351 | 35.0 ± 910 | 29.6 ± 224 | 32.3 ± 42 | <0.001 |
| Secondary school | 14.9 ± 151 | 14.2 ± 369 | 14.4 ± 109 | 18.5 ± 24 | <0.001 |
| Higher (incl. university degree) | 31.3 ± 317 | 26.4 ± 688 | 18.1 ± 137 | 18.5 ± 24 | <0.001 |
| **BMI (kg/m²)** | 24.8 ± 3.4 | 25.5 ± 4.0 | 26.2 ± 4.5 | 25.6 ± 5.4 | <0.001 |
| **Smoking status (%)** | | | | | <0.001 |
| Never | 52.1 ± 540 | 46.6 ± 1246 | 41.7 ± 323 | 40.7 ± 55 | <0.001 |
| Former | 27.5 ± 285 | 30.1 ± 804 | 30.1 ± 233 | 23.7 ± 32 | <0.001 |
| Current | 18.8 ± 195 | 21.0 ± 561 | 26.1 ± 202 | 32.6 ± 44 | <0.001 |
| Unknown | 1.5 ± 16 | 2.3 ± 62 | 2.2 ± 17 | 3.0 ± 4 | <0.001 |
| **Physical activity (%)** | 15.9 ± 160 | 21.3 ± 548 | 31.1 ± 231 | 43.3 ± 52 | <0.001 |
| Inactive | 33.2 ± 335 | 31.7 ± 818 | 28.8 ± 214 | 29.2 ± 35 | <0.001 |
| Moderately inactive | 25.5 ± 257 | 26.8 ± 689 | 21.8 ± 162 | 15.0 ± 18 | <0.001 |
| Active | 25.5 ± 257 | 20.2 ± 521 | 18.2 ± 135 | 12.5 ± 15 | <0.001 |
| **Alcohol consumption (g/day)** | 11.5 ± 16.2 | 10.8 ± 15.2 | 9.2 ± 15.4 | 5.6 ± 9.8 | <0.001 |
| Total energy intake (kcal) | 2016.6 ± 649.7 | 2056.7 ± 618.3 | 2009.4 ± 617.3 | 1928.3 ± 617.9 | 0.007 |
| Hypertension (%) | 16.0 ± 165 | 22.8 ± 600 | 32.7 ± 245 | 33.3 ± 44 | <0.001 |
| History of myocardial infarction (%) | 0.4 ± 4 | 1.5 ± 40 | 3.6 ± 28 | 3.7 ± 5 | <0.001 |

Data are presented as mean and SD for continuous variables and percentages and frequencies for categorical variables.

*Comparing excellent, good, moderate and poor self-rated health.

BMI, body mass index.

| Table 4  | Pooled HRs of incident T2DM comparing low (moderate or poor) versus high (excellent or good) self-related health |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Model 1: Adjusted for age and sex** | 1.00 (referent) | 1.67 (1.48 to 1.88) |
| **Model 1+education** | 1.00 (referent) | 1.60 (1.42 to 1.81) |
| **Model 1+BMI** | 1.00 (referent) | 1.38 (1.19 to 1.60) |
| **Model 1+smoking** | 1.00 (referent) | 1.67 (1.48 to 1.89) |
| **Model 1+physical activity** | 1.00 (referent) | 1.67 (1.48 to 1.89) |
| **Model 1+alcohol consumption** | 1.00 (referent) | 1.67 (1.48 to 1.89) |
| **Model 1+energy intake** | 1.00 (referent) | 1.67 (1.48 to 1.89) |
| **Model 1+hypertension** | 1.00 (referent) | 1.48 (1.31 to 1.69) |
| **Model 1+all covariates above** | 1.00 (referent) | 1.29 (1.09 to 1.53) |

*Pooled HRs calculated using a centre-stratified approach in combination with a random-effect meta-analysis.

BMI, body mass index; T2DM, type 2 diabetes mellitus.
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**Figure 2** Centre-specific and pooled HRs of incident type 2 diabetes mellitus adjusted for the variables in the final model (age, sex, education, body mass index, smoking, physical activity, alcohol consumption, energy intake and hypertension).

| Centre         | Hazard ratio | Lower limit | Upper limit | p-value |
|----------------|--------------|-------------|-------------|---------|
| Bilthoven      | 1.87         | 1.13        | 3.09        | 0.015   |
| Cambridge      | 1.34         | 0.95        | 1.89        | 0.092   |
| Heidelberg     | 1.37         | 0.96        | 1.97        | 0.083   |
| Potsdam        | 1.32         | 0.96        | 1.81        | 0.085   |
| Umeå           | 1.03         | 0.77        | 1.37        | 0.852   |
| Pooled         | 1.29         | 1.09        | 1.53        | 0.003   |

*p-value for heterogeneity 0.33, I² index 13.3%*

association from low SRH to T2DM (ie, a temporal relationship). We have found only two previous prospective studies showing the association between SRH and T2DM in large general populations. In the Australian Diabetes Obesity and Lifestyle study, Tapp et al. found that participants with newly diagnosed diabetes had reported impaired general health before the onset of T2DM. The study was limited by a shorter follow-up (5 years) and did not present any sensitivity analysis excluding participants, who were diagnosed with T2DM shortly after baseline, which makes a bidirectional association more likely. In our study, with a mean follow-up of over 9 years, the association between SRH and T2DM remained when we excluded participants who were diagnosed with T2DM within 2 years of follow-up. Recently, Latham and Peek published a report from the Health and Retirement Study, a longitudinal survey of a US midlife cohort. They found that SRH predicted diabetes as well as coronary heart disease, stroke, lung disease and arthritis but not cancer. A weakness in the study was that the outcome measurement was based on self-reports. Our study supports this previous prospective research by also showing an association between SRH and T2DM when a strict verification procedure for outcome measurement is applied.

In the present study, low SRH was associated with a higher BMI, which is in line with previous research. In a study investigating the relationship between SRH and obesity, Prosper et al. found that obese individuals had threefold greater odds of reporting reduced health compared with individuals with normal weight or overweight. As obesity is also considered to be a major risk factor for diabetes, it is likely to explain a substantial part of the association between low SRH and T2DM. Thus, it is not surprising that BMI may act as an important confounder in the association between SRH and T2DM in this study—or as a mediator since SRH and obesity might be on the same causal pathway. More surprising was the fact that participants with low SRH had lower alcohol consumption and estimated reported energy intake. These findings are not easily explained and raise questions regarding the criteria for self-assessment. Previous research on occupational cohorts has suggested that SRH principally reflects physical and mental health problems and, to a lesser extent, age, early life factors, family history, sociodemographic variables, psychosocial factors and health behaviours. One study that used in-depth interviews found that the same frame of reference is not used by all respondents in answering this question. Some study participants think about specific health problems when asked to rate their health, whereas others think in terms of either general physical functioning or health behaviours. In our study, the question for SRH referred to different time frames (eg, satisfaction with health today in Germany and perception of health over the last year in Sweden). SRH has been shown to be stable over time in population-based studies, suggesting that a considerable component of SRH reflects an aspect of one’s enduring self-concept and, to a lesser extent, a spontaneous assessment of one’s health status. Thus, the impact of different time frames on SRH assessment is likely to be small.

Compared with studies of SRH with mortality outcomes in individuals with diabetes, the strength of the SRH association (with T2DM incidence) found in the present study was weak. There may be several explanations for this. It has been shown that diabetes patients have higher death rates from several causes, including cancer. It is likely that the comparatively strong association between SRH and mortality is due to the higher ability of SRH to summarise global health risk among diabetes patients than specifically metabolic risk in a general population. It is also possible that SRH is more susceptible to ‘reporting behaviour’ (ie, how optimistic or pessimistic people are about their health) in a generally healthier population compared with subjective health ratings later on in the disease process.

Previous findings suggest that there may be sex differences in the SRH-mortality association, but we found no sex difference in the association between SRH and T2DM. SRH may also vary across countries. In the present study, it is likely that the differences in SRH across centres can, to some extent, be explained by different sampling strategies and age distributions at different centres. We did not find support for heterogeneity in the association between SRH and T2DM across centres in this study. However, the study was restricted to countries in northern Europe. It is, therefore, not clear how these findings are generalisable to other populations. Moreover, in Heidelberg and Potsdam, the SRH question was assessed in terms of satisfaction with health.
and in the other centres in terms of perception of health, which may have had an influence on the distribution of responses. There were also some differences in response alternatives between centres. To some extent, these differences were handled by standardisation, but the differences in the construct of the SRH question between centres are limitations to this study, particularly to the analysis of heterogeneity.

The strengths of the present study include the thorough ascertainment and verification of T2DM cases. Moreover, cultural differences may also have an impact on SRH, even within Europe, and we included populations from four different European countries. Several limitations of the study have already been listed, such as different constructs of the SRH question and the restrictions from four different European countries. Several different constructs of the SRH question and the restrictions from four different European countries. The strengths of the present study include the thorough ascertainment and verification of T2DM cases. Moreover, cultural differences may also have an impact on SRH, even within Europe, and we included populations from four different European countries. Several limitations of the study have already been listed, such as different constructs of the SRH question and the restrictions from four different European countries. The strengths of the present study include the thorough ascertainment and verification of T2DM cases. Moreover, cultural differences may also have an impact on SRH, even within Europe, and we included populations from four different European countries. Several limitations of the study have already been listed, such as different constructs of the SRH question and the restrictions from four different European countries. The strengths of the present study include the thorough ascertainment and verification of T2DM cases. Moreover, cultural differences may also have an impact on SRH, even within Europe, and we included populations from four different European countries. Several limitations of the study have already been listed, such as different constructs of the SRH question and the restrictions from four different European countries. The strengths of the present study include the thorough ascertainment and verification of T2DM cases. Moreover, cultural differences may also have an impact on SRH, even within Europe, and we included populations from four different European countries. Several limitations of the study have already been listed, such as different constructs of the SRH question and the restrictions from four different European countries. The strengths of the present study include the thorough ascertainment and verification of T2DM cases. Moreover, cultural differences may also have an impact on SRH, even within Europe, and we included populations from four different European countries. Several limitations of the study have already been listed, such as different constructs of the SRH question and the restrictions from four different European countries. The strengths of the present study include the thorough ascertainment and verification of T2DM cases. Moreover, cultural differences may also have an impact on SRH, even within Europe, and we included populations from four different European countries. Several limitations of the study have already been listed, such as different constructs of the SRH question and the restrictions from four different European countries.

In conclusion, results from this prospective case-cohort study provide some evidence that low SRH is associated with a higher risk of T2DM. The association could be only partly explained by other health-related variables, of which obesity was the strongest.

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Acknowledgements We thank all EPIC participants and staff for their contribution to the study. We also thank Nicola Kerrison (MRC Epidemiology Unit, Cambridge) for managing the data for the InterAct Project.

Contributors OR and PW conceived the idea of the study. PW analysed the data and produced the tables and graphs. OR, SJS, CL, NF and NW provided input into the data analysis. The initial draft of the manuscript was prepared by PW and OR and then circulated repeatedly among all authors for critical revision. All authors contributed to either EPIC or EPIC-InterAct data collection, study management or coordination. All authors contributed to the interpretation and review of the manuscript. All authors approved the manuscript.

Funding Funding for the InterAct project was provided by the EU FP6 programme (grant number Integrated Project LSHM_CT_2006_037197). In addition, InterAct investigators acknowledge funding from the following agencies: Dlvda and AMWS: Dutch Ministry of Public Health, Welfare and Sports (WVS), Netherlands Cancer Registry (NKR), LR Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); RK: Deutsche Krebshilfe.

Competing interests None.

Ethics approval The study was approved by the IARC Institutional Review Board and by the local review boards of the participating centres.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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