



Self-rated health and mortality in individuals with diabetes mellitus: prospective cohort study

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4 **cohort study**
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Abstract

Background Self-rated health scores have shown to be predictors of vascular events and major complications in diabetes patients.

Objective To investigate whether low self-rated health is associated with increased mortality in patients with diabetes.

Design Self-rated health was assessed in self-administered questionnaires in 3,257 patients (mean \pm SD age was 55.8 \pm 7.6 years and 42% women) with confirmed diagnosis of diabetes mellitus. Enrolment took place between 1992 and 2000 in four centers (Bilthoven, Heidelberg, Potsdam, Umeå) in a sub-cohort nested in the European Prospective Investigation into Cancer and Nutrition. We used Cox proportional hazards modeling to estimate hazard ratios (HRs) for total mortality controlling for age, center, sex, educational level, BMI, physical inactivity, smoking, insulin treatment, hypertension, hyperlipidemia, history of myocardial infarction, stroke or cancer.

Results During follow-up (mean follow-up \pm SD was 8.6 \pm 2.3 years) 344 deaths (241 men/103 women) occurred. In a multivariate model, patients with low self-rated health were at higher risk of mortality (hazard ratio 1.38, 95% confidence interval 1.10 to 1.73) than patients with high self-rated health. The association was mainly driven by increased five-year mortality in men and was stronger among lean and normal-weight than obese patients. There was no indication of heterogeneity across centres.

Conclusions Low self-rated health was associated with increased mortality in patients with diabetes after controlling for established risk factors. In diabetes patients with low self-rated health, the physician should consider a more detailed consultation and intensified support.

Article summary

Article focus

- Is low self-rated health associated with increased mortality in diabetes patients?
- If so, is the association between self-rated health and mortality in diabetes patients moderated by socio-demographic and health-related variables?

Key messages

- Low self-rated health was associated with increased mortality in patients with diabetes after controlling for established risk factors. The association was homogeneous across the four EPIC centres situated in three different European countries.
- The association between low self-rated health and mortality was mainly driven by increased five-year mortality in men and was stronger among lean and normal-weight patients than obese patients.

Strength and limitations of this study

- To our knowledge, this is the first study that evaluates this research question in a population-based cohort of diabetes patients with long-term follow-up (up to a maximum of 14 years) in different European countries.
- The association between self-rated health and mortality remained robust after controlling for potential confounders including previous myocardial infarction, stroke or cancer, but we cannot rule out residual confounding from other co-morbidity that was not assessed at baseline.

Introduction

Patients with diabetes have a 1.5–2.5-fold higher risk of death compared to a non-diabetic population.[1-4] The excess mortality in diabetes patients is mainly caused by a higher risk of cardiovascular (CVD) mortality,[3-4] but mortality due to cancer is also increased.[5] It is of great importance to identify diabetes patients with high risk of CVD morbidity and mortality early on in the disease process in order to intervene with medication and lifestyle changes.[6] Hence, risk engines[7] or risk scores[8] have been developed to identify the subjects at highest risk of developing CVD. None of these tools have utilized subjective measures of health.

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 has been associated with future health outcomes such as cardiovascular events[9] and mortality both in representative community samples[10] and in defined patient cohorts.[11-13] Although there is no consensus on what SRH really represents, SRH is drawing increasingly attention as a key parameter in health care, including health policy evaluation, population surveys and research.[14] Previous research in different populations has suggested that the predictive strength of SRH for subsequent mortality may differ by sex,[15] age,[16] race,[17] education level,[18] and experience of chronic disease.[19] Studies evaluating SRH among diabetes patients are scarce. One previous study showed that SRH predicted vascular events and major complications.[20]

The primary aim of this study was to investigate whether low self-rated health is associated with increased mortality in patients with diabetes. Prospective studies investigating this research question have been restricted to short-term mortality (up to four years), whereas we can present data from a study with a mean follow-up of 8.6 years. As a secondary aim we investigated whether socio-demographic and health-related variables moderate the association between SRH and mortality in this cohort of diabetes patients.

Methods

Study population

The study was nested in the European Prospective Investigation into Cancer and Nutrition (EPIC). EPIC is an ongoing cohort study, which consists of 519,978 men and women from ten European countries. A detailed description of the study design and methods can be found elsewhere.[21] Participants were 35 to 70 years at enrolment between 1992 and 2000 and were recruited predominantly from the general population residing in a given geographic area. Participants gave their written consent and the study was approved by the ethical review boards of the International Agency for Research on Cancer and by the review boards at the local centres where participants had been recruited for the EPIC study. Originally, the EPIC centres in Denmark, Germany, Italy, Spain, Sweden and the Netherlands contributed 7,048 cases of self-reported diabetes at baseline. Self-reports of diabetes obtained at baseline were confirmed by additional information sources, which include the following depending on the available options in the different countries: contact with a medical practitioner, use of diabetes-related medication (e.g. insulin and blood glucose lowering drugs), repeated self-report during follow-up, linkage to diabetes registries, or a measure of glycated haemoglobin (HbA1c) above 6%.[22] A total of 5,542 cases of diabetes mellitus could be confirmed. We also included 870 participants whose diabetes diagnosis was confirmed within another project in EPIC, leading to a sub-cohort of 6,412 individuals with confirmed diabetes at baseline.[23] For the current study, only EPIC study centres which could provide data on SRH were included (Germany: Heidelberg and Potsdam; the Netherlands: Bilthoven; Sweden: Umeå). For this reason, 3,155 participants (from the centres in Denmark, Italy and Spain) were excluded. The final dataset therefore comprised 3,257 participants from four EPIC study centres with a confirmed diagnosis of diabetes mellitus at baseline. No clear separation between type 1 and type 2 diabetes could be made.

Assessment of self-rated health

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 standardized (described in **Appendix**). Given the low frequency of responses in the extreme categories (n=316 in the highest and n=241 in the lowest), we dichotomized the SRH variable by combining the two highest categories (high SRH) and the two lowest categories (low SRH).

Covariates and outcome

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.[24] Body mass index (BMI) was calculated after measurement of body weight and height, as weight (kilograms) divided by height (metres squared). For the blood pressure measurements, uniform procedures were recommended. Hypertension was defined by a hypertension diagnosis or use of hypertensive medication or blood pressure $\geq 140/90$ mmHg. Further health-related variables were collected using questionnaires including questions on educational level, smoking status (current smoker versus non-smoker or ex-smoker), physical activity level, and medical history including history of myocardial infarction, stroke and cancer. Hyperlipidaemia was defined by use of medication for hyperlipidaemia.

Participants were followed from study entry until death, emigration, withdrawal, or end of follow-up period. Causes and dates of deaths were ascertained using record linkages with central cancer registries, death indexes or by follow-up mailings and subsequent inquiries to municipality registries, regional health departments, physicians or hospitals. Mortality data were coded following the 10th revision of the International Classification of Diseases, Injuries and Causes of Death (ICD-10). ICD-10 codes I00–I99 were used to calculate proportions of cardiovascular mortality. Hazard ratios were calculated for all-

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3 cause mortality only, since we did not have statistical power for analyses of specified
4 mortality.
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7 *Statistical analyses*

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10 Chi-square test was used for testing proportions in categorical variables. Kruskal-Wallis
11 test was used for significance testing in continuous variables. Hazard ratios (HRs) and
12 95% confidence intervals (CI) were estimated using Cox proportional hazards models.
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14 Age was used as the primary time variable, with entry time defined as the subject's age
15 in years at recruitment and exit time defined as the subject's age in years at death or
16 censoring. Multivariate models were constructed to determine HRs adjusted for
17 covariates. Age, centre, sex, BMI, physical inactivity, insulin treatment, hypertension and
18 history of myocardial infarction, stroke or cancer were tested as covariates and included
19 in the multivariate model since they met the criteria of being significantly associated with
20 both SRH and mortality during follow-up in men or in women. Given the low frequencies
21 of previous myocardial infarction, stroke and cancer, these covariates were combined in
22 one variable in the multivariate analysis to ensure a good model fit. Interaction was
23 tested by including interaction terms in the Cox proportional hazards analysis. The
24 hazard ratios were combined across centres using random effects meta-analysis, and I^2 –
25 the percentage of variation between centres due to real heterogeneity – was calculated.
26 The first sensitivity analysis was performed to see if the strength of the association
27 between SRH and mortality differed for short-term mortality and long-term mortality. For
28 this reason we dichotomized the decedents in two categories, participants who died
29 before the median follow-up time (5.4 years) and participants who died after the median
30 follow-up time. The second sensitivity analysis was performed by excluding participants
31 with low weight ($BMI \leq 20$). A *P*-value under 0.05 was considered significant. All analyses
32 were performed using SPSS Statistics 19.0 except for the I^2 index test which was
33 performed using Comprehensive Meta-Analysis version 2.
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Missing values

There was no information on history of stroke and cancer from the centre in Umeå (n=427) and these missing values were assigned to a separate category in multivariate analysis. The proportions of missing values for other variables were all less than 2.5% and coded as missing in multivariate analysis. Consequently, 85 persons including eight decedents were lost in the multivariate analysis.

Results

The mean follow-up time was 8.6 years (\pm 2.3). Baseline characteristics for the 1,903 men and 1,354 women are presented in **Table 1**. Mean age at baseline was 56.2 years (\pm 7.1) for men and 55.4 years (\pm 8.2) for women. Among the 3,257 persons included in the study there were 241 deaths (13%) in men and 103 deaths (8%) in women. Of the 344 persons who died, 40% were cardiovascular deaths, 52% were non-cardiovascular deaths and in 8% the cause of death was unknown.

Table 2 shows the baseline characteristics in relation to categories of SRH. Persons with low SRH were younger, more frequently women, had higher BMI and had more frequently a history of myocardial infarction or stroke compared to persons with high SRH. Moreover, in men with low SRH, insulin treatment was more common and in women with low SRH, hypertension and a history of cancer were more common.

In a model adjusted for age and centre, low SRH was associated with increased mortality (**Table 3**). In sex-specific analyses, this association was significant in men but not in women. After further adjustments for potential confounders, the association between low SRH and mortality was attenuated but remained significant in men and in both sexes combined. The fully adjusted HR for both sexes was 1.38 (95% confidence interval 1.10 to 1.73). In a sensitivity analyses we calculated HRs for low SRH for short-term mortality (participants who died before median follow-up time among the

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3 decedents, 5.4 years) and long-term mortality (participants who died after median
4 follow-up time among the decedents). HR of low SRH for short-term mortality was 1.89
5 (1.31 to 2.73) for men and 1.23 (0.68 to 2.22) for women in the fully adjusted model.
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8 HR of low SRH for long-term mortality was 1.20 (0.81 to 1.77) for men and 1.03 (0.57 to
9 1.87) for women in the same multivariate model.
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14 Interaction analyses were performed between SRH and covariates in relation to
15 mortality. We found a significant interaction between SRH and BMI with $P_{\text{interaction}}$ value
16 0.03. When analysing HRs for SRH in different strata of BMI we found stronger
17 associations between SRH and mortality at lower levels of BMI, indicating an
18 antagonistic interaction (**Table 4**). For example, fully adjusted HR for both sexes
19 combined in the 1st tertile of BMI was 1.89 (1.27 to 2.82), compared to 1.06 (0.72 to
20 1.54) in the 3rd tertile. Consequently, we performed a second sensitivity analysis by
21 excluding persons with low weight ($\text{BMI} \leq 20$, 43 persons) from the main analysis of SRH
22 and mortality, which attenuated the fully adjusted HR from 1.38 to 1.35 (1.08 to 1.70)
23 in both sexes combined. We found no statistical interaction between SRH and sex
24 ($P_{\text{interaction}}$ value 0.30), age ($P_{\text{interaction}}$ value 0.22), education level ($P_{\text{interaction}}$ value 0.14),
25 smoking ($P_{\text{interaction}}$ value 0.13), physical inactivity ($P_{\text{interaction}}$ value 0.24), insulin
26 treatment ($P_{\text{interaction}}$ value 0.18), hypertension ($P_{\text{interaction}}$ value 0.23), hyperlipidaemia
27 ($P_{\text{interaction}}$ value 0.16) and history of myocardial infarction, stroke or cancer ($P_{\text{interaction}}$
28 value 0.29).
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46 **Figure 1** shows a forest plot with adjusted HRs for low SRH by sex and in both sexes
47 combined for each centre. We found no clear indication of heterogeneity in the
48 association between SRH and mortality across centres (I^2 index=0).
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52 Discussion

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55 We found that low SRH was associated with an increased risk of mortality in diabetes
56 patients after adjusting for major established risk factors. This association was
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3 homogeneous across the four EPIC centres situated in three different European countries.
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5 The strength of the association between SRH and mortality in this study was similar to
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7 results in general populations.[25] In sex-specific analyses we found that the association
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9 between SRH and mortality was significant in men but not in women. However, the HR in
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11 women pointed in the same direction as in men, and we cannot rule out that the lack of
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13 significance was due to the lower statistical power to detect an association in women.
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15 Interestingly, the association between SRH and mortality was stronger among lean and
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17 normal-weight patients than among obese patients in both men and women. This finding
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19 could possibly be explained by the presence of other chronic diseases leading to low body
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21 weight, low SRH and higher risk of premature death. However, the association between
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23 low SRH and mortality remained significant even after the exclusion of persons with
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25 BMI \leq 20. Therefore, there are likely other factors contributing to the weaker association
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27 between SRH and overall mortality in obese diabetes patients. First, we found that the
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29 proportion of cardiovascular mortality was highest in the tertile with the highest BMI in
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31 both men and women, suggesting that the mortality pattern may be different at
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33 different levels of BMI. Previous research has shown that the link between SRH and
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35 mortality may be weaker for cardiovascular mortality than for cancer mortality or
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37 mortality from other causes.[26] Second, we found that the obese diabetes patients
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39 rated their health lower than patients with normal weight, which is in line with studies
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41 on general populations.[27] Previous studies have shown that obese patients may
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43 experience discrimination, stigmatization and major limitations in daily life linked to their
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45 obesity.[28-29] These factors will likely have a considerable impact on their health
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47 perception. We hypothesize that these factors related to obesity may overshadow other
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49 important health problems or health behaviours in the perception of health and possibly
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51 weaken the association between SRH and mortality in obese patients.

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54 The association between SRH and mortality has been of interest in medical research for
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56 several decades. Already in 1973, Maddox, one of the pioneers in this research field
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58 stated that SRH "clearly measure something more—and something less—than objective
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3 medical ratings".[30] It is still debated what information individuals rely on when rating
4 their health. Qualitative research has suggested that SRH reflects a combination of
5 specific health problems, general physical functioning and health behaviours.[31] Cultural
6 differences may also have an impact on SRH, even within Europe.[32] A previous
7 quantitative study from NHANES found that low SRH is particularly predictive for
8 respondents with self-reported history of circulatory system diagnoses and perception of
9 symptoms, but not for respondents without symptoms or diagnoses.[19]
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19 Only a few studies have evaluated the association between SRH and mortality in well-
20 defined cohorts of diabetes patients.[33-35] In 1994, Dasbach and colleagues found
21 increased mortality in 987 patients with older onset of diabetes who rated their health
22 as worse than other people of similar age. The average age in their study was 64.7
23 years (± 11.0) compared to 55.8 years (± 7.6) in our study. More recently, McEwen and
24 co-workers found that SRH predicted mortality in an American multi-ethnic cohort of
25 over 7,000 diabetes patients.[34] However, their study was restricted to patients with
26 longer duration of diabetes (diagnosed at least 18 months before survey) in managed
27 care and a relatively short follow-up (the average length was 3.7 years). In the FIELD
28 study, a controlled trial of fenofibrate performed in Australia, New Zealand and Finland,
29 the mean duration of follow-up was even shorter, only 2.4 years. In this study involving
30 7348 diabetes patients, Clarke and colleagues found that low SRH was associated with
31 vascular events, diabetes complications and all-cause mortality.[33] In our study, which
32 was population-based, the participants were younger and followed for an average of 8.6
33 years. We found that the association between SRH and mortality was weaker and no
34 longer statistically significant when we restricted the analysis to long-term mortality.
35 These findings raise questions about the long-term predictiveness of a single self-rating
36 of health and we therefore suggest that future research in diabetes patients should
37 include repeated self-ratings and follow-up for long-term mortality.
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3 There are some limitations to our study. Even if the association between SRH and
4 mortality was robust when individuals with low BMI were excluded, we cannot rule out
5 other potential residual confounding from co-morbidity other than MI, stroke or cancer
6 that was not assessed at baseline health examinations. Moreover, the sample size in the
7 present study did not allow any clear conclusions in relation to sex-specific analyses. The
8 questions and the response alternatives on SRH were formulated somewhat differently
9 and in the native language at each centre. The questions and answers were translated
10 and standardized in four response alternatives, which may have led to some degree of
11 misclassification, particularly for the centres in Bilthoven and Umeå (which had five
12 response alternatives). However, the forest plot gave no indication that the
13 standardization in four response alternatives had a major impact on the risk estimates.
14 The multivariate models used in this study were similar but not identical with equations
15 used in risk engines[7] and risk scores.[8] Whether SRH adds predictive value over and
16 above these models needs to be further analysed in future studies using adequate
17 methods.[36]

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24 Although more research is needed to gain a more complete understanding of the
25 relationship between SRH and mortality in diabetes patients, we find that self-ratings of
26 health are an inexpensive and time-efficient way to obtain subjective prognostic
27 information that may be difficult to assess by objective health measurements. In
28 diabetes patients with low SRH the physician should consider a more detailed
29 consultation and intensified support.

30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 *Conclusions*

49 This is the first study investigating the association between self-rated health and
50 mortality in diabetes patients with a long-term follow-up in different European countries.
51 We found that low self-rated health was associated with increased mortality in patients
52 with diabetes after controlling for established risk factors. The association was mainly
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3 driven by increased five-year mortality in men and was stronger among lean and
4 normal-weight patients than obese patients.
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Table 1 Baseline characteristics of 3257 diabetes patients participating in the European Prospective Investigation into Cancer and Nutrition. Data are presented as percent or mean (standard deviation).

	Men N=1903	Women N=1354
Age (years)	56.2 (7.1)	55.4 (8.2)
Self-rated health (%)		
High		
<i>Excellent</i>	10.5	8.6
<i>Good</i>	54.1	49.9
Low		
<i>Moderate</i>	28.4	33.5
<i>Poor</i>	7.0	8.0
Education (%)		
<i>None</i>	0.6	1.8
<i>Primary school</i>	35.0	43.9
<i>Technical/professional school</i>	29.1	33.7
<i>Secondary school</i>	6.8	7.6
<i>Longer (incl. university degree)</i>	28.6	13.1
BMI (kg/m ²)	28.6 (4.3)	29.5 (5.6)
Current smoking (%)	24.0	16.2
Physical inactivity (%)	26.8	33.0
Insulin treatment (%)	22.8	24.3
Hypertension (%)	70.0	71.3
Hyperlipidaemia (%)	21.8	18.5
History of myocardial infarction (%)	9.2	3.8
History of stroke (%)	3.5	3.0
History of cancer (%)	4.1	6.4

Table 2 Baseline characteristics in relation to categories of self-rated health. Data are presented as percent or mean.

	Men					Women				
	Self-rated health				P	Self-rated health				P
	High		Low			High		Low		
	Excellent	Good	Moderate	Poor		Excellent	Good	Moderate	Poor	
Age (years)	57.1	56.6	55.2	55.4	<0.001	53.8	55.8	55.4	54.1	0.001
Education (%)										
None	0.5	0.5	0.7	0.8	0.42	1.7	1.5	2.0	2.9	0.40
Primary school	35.9	33.1	36.8	42.4		35.3	44.6	44.5	44.8	
Technical/ professional school	31.8	28.4	29.3	28.8		41.4	33.2	32.3	34.3	
Secondary school	6.6	6.7	7.5	4.5		8.6	6.3	9.8	5.7	
Longer (incl. university degree)	25.3	31.3	25.7	23.5		12.9	14.5	11.4	12.4	
BMI (kg/m ²)	28.6	28.4	28.9	29.0	0.05	28.1	29.2	30.0	31.1	<0.001
Current smoking (%)	25.5	23.4	24.8	23.7	0.89	16.4	15.6	15.4	21.3	0.49
Physical inactivity (%)	20.6	26.3	26.6	41.1	0.001	18.3	32.8	35.8	39.8	0.002
Insulin treatment (%)	15.2	20.8	27.4	29.2	0.002	18.1	23.0	28.0	24.1	0.15
Hypertension (%)	67.5	68.5	74.0	70.7	0.11	56.9	72.4	72.3	75.0	0.004
Hyperlipidaemia (%)	22.0	20.4	24.1	21.8	0.42	14.7	18.6	19.0	20.4	0.69
History of myocardial infarction (%)	9.0	6.9	11.5	17.3	<0.001	1.7	2.4	6.0	4.6	0.009
History of stroke (%)	2.8	2.4	4.5	9.5	0.001	1.0	2.1	4.7	3.3	0.07
History of cancer (%)	5.1	5.1	3.6	5.7	0.61	4.9	5.8	6.1	14.3	0.02

Table 3 Hazard ratios (HRs) of low (moderate or poor) versus high (excellent or good) self-rated health for all-cause mortality during follow-up.

	Model 1*	Model 2†	Model 3‡
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Both sexes	1.56 (1.25 to 1.94)	1.49 (1.19 to 1.86)	1.38 (1.10 to 1.73)
Men	1.75 (1.35 to 2.27)	1.63 (1.25 to 2.12)	1.52 (1.16 to 1.98)
Women	1.35 (0.90 to 2.03)	1.21 (0.80 to 1.83)	1.11 (0.73 to 1.69)

*Adjusted for age and centre.

†Adjusted for age, centre, sex, BMI, physical inactivity, insulin treatment and hypertension.

‡Adjusted for age, centre, sex, BMI, physical inactivity, insulin treatment, hypertension and history of myocardial infarction, stroke or cancer.

Table 4 Hazard ratios (HRs) of low versus high self-rated health for all-cause mortality by tertiles of body mass index.

		BMI	CV	Model 1*	Model 2†	Model 3‡
		(kg/m ²)	mortality (%)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Both sexes	<i>1st tertile</i>	<26.73	41.3	2.10 (1.42 to 3.10)	2.09 (1.41 to 3.10)	1.89 (1.27 to 2.82)
	<i>2nd tertile</i>	26.73-30.49	33.3	1.54 (1.05 to 2.25)	1.38 (0.93 to 2.05)	1.24 (0.83 to 1.86)
	<i>3rd tertile</i>	>30.49	46.0	1.18 (0.82 to 1.71)	1.10 (0.76 to 1.61)	1.06 (0.72 to 1.54)
Men	<i>1st tertile</i>	<26.64	42.9	2.11 (1.33 to 3.35)	2.19 (1.38 to 3.47)	2.06 (1.30 to 3.27)
	<i>2nd tertile</i>	26.64-29.90	35.8	1.55 (0.99 to 2.42)	1.39 (0.87 to 2.22)	1.25 (0.78 to 2.00)
	<i>3rd tertile</i>	>29.90	47.0	1.68 (1.08 to 2.63)	1.48 (0.94 to 2.32)	1.41 (0.90 to 2.23)
Women	<i>1st tertile</i>	<26.88	36.7	2.57 (1.19 to 5.58)	2.18 (0.97 to 4.89)	1.60 (0.70 to 3.64)
	<i>2nd tertile</i>	26.88-31.36	32.1	1.03 (0.47 to 2.27)	0.81 (0.34 to 1.90)	0.79 (0.33 to 1.87)
	<i>3rd tertile</i>	>31.36	40.0	0.92 (0.50 to 1.70)	0.85 (0.45 to 1.60)	0.82 (0.43 to 1.56)

CV= Cardiovascular

*Adjusted for age and centre.

†Adjusted for age, centre, sex, BMI, physical inactivity, insulin treatment and hypertension.

‡Adjusted for age, centre, sex, BMI, physical inactivity, insulin treatment, hypertension and history of myocardial infarction, stroke or cancer.

Footnotes

Contributors: PW, OR, and UN were involved in the study concept and planned the analyses. PW, OR, HB, DS, RK, BT, AS, BBN, and UN contributed in the acquisition of the data. PW was responsible for statistical analyses and drafted the paper. PW, OR, LJ, and UN interpreted the results. All authors participated in critical revision of the manuscript. PW is the guarantor.

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Data sharing: No additional data available.

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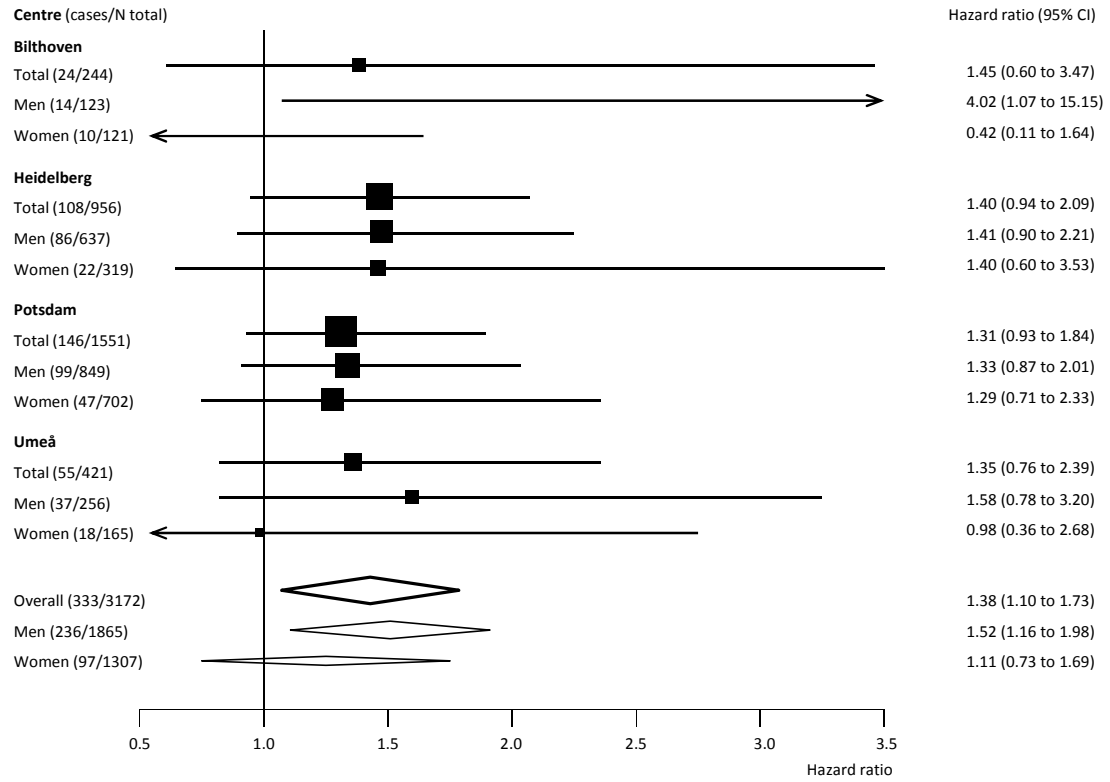
Figure legends

Figure 1 Forest plot showing adjusted hazard ratios and 95% confidence intervals for the centres included in the study investigating the association between low self-rated health and mortality in patients with diabetes.

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Appendix

All questionnaires were standardized to fit the question (with four response alternatives):

How satisfied are you today with your health?

1 Excellent

2 Good

3 Moderate

4 Poor

Description of the original questions and how they were standardized:

Bilthoven 1993–94

Question: *What do you think about your health in general?*

Response alternatives	Standardized
1 Excellent	1 Excellent
2 Good	2 Good
3 Reasonable	3 Moderate
4 Mediocre	4 Poor
5 Poor	4 Poor
9 More than 1 option indicated	Missing value

Bilthoven 1995–97

Question: *What do you think about your health in general?*

Response alternatives	Standardized
1 Excellent	1 Excellent
2 Very Good	2 Good
3 Good	2 Good
4 Reasonable	3 Moderate
5 Mediocre	4 Poor
9 More than 1 option indicated	Missing value

Heidelberg

Question: *On the whole, how satisfied are you today with your health?*

Response alternatives	Standardized
1 Very satisfied	1 Excellent
2 More satisfied	2 Good
3 More dissatisfied	3 Moderate
4 Very dissatisfied	4 Poor
8 Do not know	Missing value

Potsdam

Question: *On the whole, how satisfied are you today with your health?*

Response alternatives	Standardized
1 Very satisfied	1 Excellent
2 More likely satisfied	2 Good
3 More likely dissatisfied	3 Moderate
4 Very dissatisfied	4 Poor
8 Do not know	Missing value

Umeå

Question: *How do you judge that your state of health has been in the last year?*

Response alternatives	Standardized
1 Very well	1 Excellent
2 Quiet well	2 Good
3 Fairly well	3 Moderate
4 Quiet bad	4 Poor
5 Bad	4 Poor
9 Inconsistent answer	Missing value

Research checklist

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (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 (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
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 (b) Report category boundaries when continuous variables were categorized

		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

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 <http://www.strobe-statement.org>.



Self-rated health and mortality in individuals with diabetes mellitus: prospective cohort study

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Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, PREVENTIVE MEDICINE, PRIMARY CARE

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4 **cohort study**
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47 Running title: Diabetes, self-rated health and mortality

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49 *Key words:* Diabetes, self-rated health, mortality, prevention, cohort

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Abstract

Objectives To investigate whether low self-rated health is associated with increased mortality **in individuals with diabetes**.

Design Population-based prospective cohort study

Setting Enrolment took place between 1992 and 2000 in four centers (Bilthoven, Heidelberg, Potsdam, Umeå) in a sub-cohort nested in the European Prospective Investigation into Cancer and Nutrition.

Participants 3,257 individuals (mean \pm SD age was 55.8 ± 7.6 years and 42% women) with confirmed diagnosis of diabetes mellitus.

Primary outcome measure We used Cox proportional hazards modeling to estimate hazard ratios (HRs) for total mortality controlling for age, center, sex, educational level, BMI, physical inactivity, smoking, insulin treatment, hypertension, hyperlipidaemia, history of myocardial infarction, stroke or cancer.

Results During follow-up (mean follow-up \pm SD was 8.6 ± 2.3 years) 344 deaths (241 men/103 women) occurred. In a multivariate model, individuals with low self-rated health were at higher risk of mortality (hazard ratio 1.38, 95% confidence interval 1.10 to 1.73) than individuals with high self-rated health. The association was mainly driven by increased five-year mortality **and was stronger among individuals with BMI <25 than in obese individuals. In sex-specific analyses the association was statistically significant in men only.** There was no indication of heterogeneity across centres.

Conclusions Low self-rated health was associated with increased mortality in **individuals with diabetes** after controlling for established risk factors. In diabetes patients with low self-rated health, the physician should consider a more detailed consultation and intensified support.

Article summary

Article focus

- Is low self-rated health associated with increased mortality in individuals with diabetes?
- If so, is the association between self-rated health and mortality in individuals with diabetes moderated by socio-demographic and health-related variables?

Key messages

- Low self-rated health was associated with increased mortality in individuals with diabetes after controlling for established risk factors. The association was homogeneous across the four EPIC centres situated in three different European countries.
- The association between low self-rated health and mortality was mainly driven by increased five-year mortality in men and was stronger among individuals with BMI <25 than in obese individuals.

Strength and limitations of this study

- To our knowledge, this is the first study that evaluates this research question in a population-based cohort of individuals with diabetes with long-term follow-up (up to a maximum of 14 years) in different European countries.
- The association between self-rated health and mortality remained robust after controlling for potential confounders including previous myocardial infarction, stroke or cancer, but we cannot rule out residual confounding from other comorbidity that was not assessed at baseline.

Introduction

Patients with diabetes have a 1.5–2.5-fold higher risk of death compared to a non-diabetic population.[1-4] The excess mortality in diabetes patients is mainly caused by a higher risk of cardiovascular (CVD) mortality,[3-4] but mortality due to cancer is also increased.[5] It is of great importance to identify diabetes patients with high risk of CVD morbidity and mortality early on in the disease process in order to intervene with medication and lifestyle changes.[6] Hence, risk engines[7] or risk scores[8] have been developed to identify the subjects at highest risk of developing CVD. None of these tools have utilized subjective measures of health.

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 has been associated with future health outcomes such as cardiovascular events[9] and mortality both in representative community samples[10] and in defined patient cohorts.[11-13] Although there is no consensus on what SRH really represents, SRH is drawing increasingly attention as a key parameter in health care, including health policy evaluation, population surveys and research.[14] Previous research in different populations has suggested that the predictive strength of SRH for subsequent mortality may differ by sex,[15] age,[16] race,[17] education level,[18] and experience of chronic disease.[19] Studies evaluating SRH among **individuals with diabetes** are scarce. One previous study showed that SRH predicted vascular events and major complications in diabetes patients.[20]

The primary aim of this study was to investigate whether low self-rated health is associated with increased mortality in individuals with diabetes. Prospective studies investigating this research question have been restricted to short-term mortality (up to four years),[21-22] whereas we can present data from a study with a mean follow-up of 8.6 years. As a secondary aim we investigated whether socio-demographic and health-

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3 related variables moderate the association between SRH and mortality in this cohort of
4 individuals with diabetes.
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8 **Methods**

9 *Study population*

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14 The study was nested in the European Prospective Investigation into Cancer and Nutrition
15 (EPIC). EPIC is an ongoing cohort study, which consists of 519,978 men and women from
16 ten European countries. A detailed description of the study design and methods can be
17 found elsewhere.[23-24] Participants were 35 to 70 years at enrolment between 1992
18 and 2000 and were recruited predominantly from the general population residing in a
19 given geographic area. Participants gave their written consent and the study was
20 approved by the ethical review boards of the International Agency for Research on
21 Cancer and by the review boards at the local centres where participants had been
22 recruited for the EPIC study. Originally, the EPIC centres in Denmark, Germany, Italy,
23 Spain, Sweden and the Netherlands contributed 7,048 cases of self-reported diabetes at
24 baseline. Self-reports of diabetes obtained at baseline were confirmed by additional
25 information sources, which include the following depending on the available options in
26 the different countries: contact with a medical practitioner, use of diabetes-related
27 medication (e.g. insulin and blood glucose lowering drugs), repeated self-report during
28 follow-up, linkage to diabetes registries, or a measure of glycated haemoglobin (HbA1c)
29 above 6%.[25] A total of 5,542 cases of diabetes mellitus could be confirmed. We also
30 included 870 participants whose diabetes diagnosis was confirmed within another project
31 in EPIC, leading to a sub-cohort of 6,412 individuals with confirmed diabetes at
32 baseline.[26] For the current study, only EPIC study centres which could provide data on
33 SRH were included (Germany: Heidelberg and Potsdam; the Netherlands: Bilthoven;
34 Sweden: Umeå). For this reason, 3,155 participants (from the centres in Denmark, Italy
35 and Spain) were excluded. The final dataset therefore comprised 3,257 participants from
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3 four EPIC study centres with a confirmed diagnosis of diabetes mellitus at baseline. No
4 clear separation between type 1 and type 2 diabetes could be made.
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7 *Assessment of self-rated health*

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10 SRH was assessed at baseline using self-administered questionnaires in the native
11 language. The questionnaires were somewhat differently formulated at each centre and
12 were therefore standardized (described in **Appendix**). Given the low frequency of
13 responses in the extreme categories (n=316 in the highest and n=241 in the lowest), we
14 dichotomized the SRH variable by combining the two highest categories (high SRH) and
15 the two lowest categories (low SRH) **in conformity with previous studies.[12 17 21]**
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23 *Covariates and outcome*

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25 Weight and height were measured with participants not wearing shoes. Each participant's
26 body weight was corrected for clothing worn during measurement in order to reduce
27 heterogeneity due to protocol differences among centres.[27] Body mass index (BMI)
28 was calculated after measurement of body weight and height, as weight (kilograms)
29 divided by height (metres squared). **Overweight was defined as a BMI of 25-29.9 and**
30 **obesity as greater than or equal to 30 according to WHO guidelines. Underweight was**
31 **defined as a BMI value <20. Since there were only 43 persons with underweight, we**
32 **merged underweight with the normal BMI category.** For the blood pressure
33 measurements, uniform procedures were recommended. Hypertension was defined by a
34 hypertension diagnosis or use of hypertensive medication or blood pressure $\geq 140/90$
35 mmHg. Further health-related variables were collected using questionnaires including
36 questions on educational level, smoking status (current smoker versus non-smoker or
37 ex-smoker), physical activity level, and medical history including history of myocardial
38 infarction, stroke and cancer. Physical inactivity was defined using the Cambridge Index.
39 [28] Hyperlipidaemia was defined by use of medication for hyperlipidaemia.
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56 Participants were followed from study entry until death, emigration, withdrawal, or end of
57 follow-up period. Causes and dates of deaths were ascertained using record linkages with
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3 central cancer registries, death indexes or by follow-up mailings and subsequent inquiries
4 to municipality registries, regional health departments, physicians or hospitals. Mortality
5 data were coded following the 10th revision of the International Classification of
6 Diseases, Injuries and Causes of Death (ICD-10). ICD-10 codes I00–I99 were used to
7 calculate proportions of cardiovascular mortality. Hazard ratios were calculated for all-
8 cause mortality only, since we did not have statistical power for analyses of specified
9 mortality.

17 *Statistical analyses*

20 Chi-square test was used for testing proportions in categorical variables. Kruskal-Wallis
21 test was used for significance testing in continuous variables. Hazard ratios (HRs) and
22 95% confidence intervals (CI) were estimated using Cox proportional hazards models.
23 Age was used as the primary time variable, with entry time defined as the subject's age
24 in years at recruitment and exit time defined as the subject's age in years at death or
25 censoring. Multivariate models were constructed to determine HRs adjusted for
26 covariates. Age, centre, sex, BMI, physical inactivity, insulin treatment, hypertension and
27 history of myocardial infarction, stroke or cancer were tested as covariates and included
28 in the multivariate model since they met the criteria of being significantly associated with
29 both SRH and mortality during follow-up in men or in women. Given the low frequencies
30 of previous myocardial infarction, stroke and cancer, these covariates were combined in
31 one variable in the multivariate analysis to ensure a good model fit. Interaction was
32 tested by including interaction terms in the Cox proportional hazards analysis. The
33 hazard ratios were combined across centres using random effects meta-analysis, and I^2 –
34 the percentage of variation between centres due to real heterogeneity – was calculated.
35 The first sensitivity analysis was performed to see if the strength of the association
36 between SRH and mortality differed for short-term mortality and long-term mortality.
37 **Short-term mortality was defined as death within 5 years and long-term mortality as**
38 **death after 5 years or more. This cut-off point was close to the median follow-up time of**
39 **the decedents (5.4 years).** The second sensitivity analysis was performed by excluding

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3 participants with **underweight** (BMI<20). A *P*-value under 0.05 was considered
4 significant. All analyses were performed using SPSS Statistics 19.0 except for the *I*² index
5 test which was performed using Comprehensive Meta-Analysis version 2.
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8 9 *Missing values*

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12 There was no information on history of stroke and cancer from the centre in Umeå
13 (n=427) and these missing values were assigned to a separate category in multivariate
14 analysis. The proportions of missing values for other variables were all less than 2.5%
15 and coded as missing in multivariate analysis. Consequently, 85 persons including eight
16 decedents were lost in the multivariate analysis.
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22 23 24 25 **Results**

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27 The mean follow-up time was 8.6 years (\pm 2.3). Baseline characteristics for the 1,903
28 men and 1,354 women are presented in **Table 1**. Mean age at baseline was 56.2 years
29 (\pm 7.1) for men and 55.4 years (\pm 8.2) for women. Among the 3,257 persons included
30 in the study there were 241 deaths (13%) in men and 103 deaths (8%) in women. Of
31 the 344 persons who died, 40% were cardiovascular deaths, 52% were non-
32 cardiovascular deaths and in 8% the cause of death was unknown.
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41 **Table 2** shows the baseline characteristics in relation to categories of SRH. Persons with
42 low SRH were younger, more frequently women, had higher BMI and had more
43 frequently a history of myocardial infarction or stroke compared to persons with high
44 SRH. Moreover, in men with low SRH, insulin treatment was more common and in
45 women with low SRH, hypertension and a history of cancer were more common.
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52 In a model adjusted for age and centre, low SRH was associated with increased
53 mortality (**Table 3**). In sex-specific analyses, this association was significant in men but
54 not in women. After further adjustments for potential confounders, the association
55 between low SRH and mortality was attenuated but remained significant in men and in
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3 both sexes combined. The fully adjusted HR for both sexes was 1.38 (95% confidence
4 interval 1.10 to 1.73). In a sensitivity analyses we calculated HRs for low SRH for short-
5 term mortality (participants who died within 5 years of follow-up, n=158) and long-term
6 mortality (participants who died after 5 years or more, n=186). HR of low SRH for short-
7 term mortality was 1.91 (1.30 to 2.80) for men and 1.38 (0.75 to 2.55) for women in
8 the fully adjusted model. HR of low SRH for long-term mortality was 1.24 (0.85 to 1.79)
9 for men and 0.94 (0.53 to 1.67) for women in the same multivariate model.
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18 Interaction analyses were performed between SRH and covariates in relation to
19 mortality. We found a significant interaction between SRH and BMI with $P_{\text{interaction}}$ value
20 0.03. When analysing HRs for SRH in different categories of BMI we found stronger
21 associations between SRH and mortality at lower levels of BMI, indicating an
22 antagonistic interaction (Table 4). For example, in the category normal or underweight
23 the fully adjusted HR for both sexes combined was 2.95 (1.71 to 5.10), compared to
24 1.14 (0.79 to 1.65) in obese individuals. Consequently, we performed a second
25 sensitivity analysis by excluding persons with underweight (BMI <20, 43 persons) from
26 the main analysis of SRH and mortality, which attenuated the fully adjusted HR from
27 1.38 to 1.36 (1.08 to 1.70) in both sexes combined. We found no statistical interaction
28 between SRH and sex ($P_{\text{interaction}}$ value 0.30), age ($P_{\text{interaction}}$ value 0.22), education level
29 ($P_{\text{interaction}}$ value 0.14), smoking ($P_{\text{interaction}}$ value 0.13), physical inactivity ($P_{\text{interaction}}$ value
30 0.24), insulin treatment ($P_{\text{interaction}}$ value 0.18), hypertension ($P_{\text{interaction}}$ value 0.23),
31 hyperlipidaemia ($P_{\text{interaction}}$ value 0.16) and history of myocardial infarction, stroke or
32 cancer ($P_{\text{interaction}}$ value 0.29).
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50 **Figure 1** shows a forest plot with adjusted HRs for low SRH by sex and in both sexes
51 combined for each centre. We found no clear indication of heterogeneity in the
52 association between SRH and mortality across centres (I^2 index=0).
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58 Discussion

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3 We found that low SRH was associated with an increased risk of mortality in **individuals**
4 **with diabetes** after adjusting for major established risk factors. This association was
5 homogeneous across the four EPIC centres situated in three different European countries.
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7 The strength of the association between SRH and mortality in this study was similar to
8 results in general populations.[29] In sex-specific analyses we found that the association
9 between SRH and mortality was significant in men but not in women. However, the HR in
10 women pointed in the same direction as in men, and we cannot rule out that the lack of
11 significance was due to the lower statistical power to detect an association in women.
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13 Interestingly, the association between SRH and mortality was stronger among **individuals**
14 **with BMI <25** than among obese individuals in both men and women. This finding could
15 possibly be explained by the presence of other chronic diseases leading to low body
16 weight, low SRH and higher risk of premature death. However, the association between
17 low SRH and mortality remained significant even after the exclusion of persons with BMI
18 <20. Therefore, there are likely other factors contributing to the weaker association
19 between SRH and overall mortality in obese **individuals with diabetes**. First, we found
20 that the proportion of cardiovascular mortality was highest **among obese individuals** in
21 both men and women, suggesting that the mortality pattern may be different at
22 different levels of BMI. Previous research has shown that the link between SRH and
23 mortality may be weaker for cardiovascular mortality than for cancer mortality or
24 mortality from other causes.[30] Second, we found that the obese individuals rated their
25 health lower than **individuals** with normal weight, which is in line with studies on general
26 populations.[31] Previous studies have shown that obese **persons** may experience
27 discrimination, stigmatization and major limitations in daily life linked to their
28 obesity.[32-33] These factors will likely have a considerable impact on their health
29 perception. We hypothesize that these factors related to obesity may overshadow other
30 important health problems or health behaviours in the perception of health and possibly
31 weaken the association between SRH and mortality in obese **individuals**.
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3 The association between SRH and mortality has been of interest in medical research for
4 several decades. Already in 1973, Maddox, one of the pioneers in this research field
5 stated that SRH “clearly measure something more—and something less—than objective
6 medical ratings”.^[34] It is still debated what information individuals rely on when rating
7 their health. Qualitative research has suggested that SRH reflects a combination of
8 specific health problems, general physical functioning and health behaviours.^[35] Cultural
9 differences may also have an impact on SRH, even within Europe.^[36] A previous
10 quantitative study from NHANES found that low SRH is particularly predictive for
11 respondents with self-reported history of circulatory system diagnoses and perception of
12 symptoms, but not for respondents without symptoms or diagnoses.^[19]
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24 Only a few studies have evaluated the association between SRH and mortality in well-
25 defined cohorts of diabetes patients.^[21-22 37] In 1994, Dasbach and colleagues found
26 increased mortality in 987 patients with older onset of diabetes who rated their health
27 as worse than other people of similar age. The average age in their study was 64.7
28 years (± 11.0) compared to 55.8 years (± 7.6) in our study. More recently, McEwen and
29 co-workers found that SRH predicted mortality in an American multi-ethnic cohort of
30 over 7,000 diabetes patients.^[21] However, their study was restricted to patients with
31 longer duration of diabetes (diagnosed at least 18 months before survey) in managed
32 care and a relatively short follow-up (the average length was 3.7 years). In the FIELD
33 study, a controlled trial of fenofibrate performed in Australia, New Zealand and Finland,
34 the mean duration of follow-up was even shorter, only 2.4 years. In this study involving
35 7348 diabetes patients, Clarke and colleagues found that low SRH was associated with
36 vascular events, diabetes complications and all-cause mortality.^[22] In our study, which
37 was population-based, the participants were younger and followed for an average of 8.6
38 years. We found that the association between SRH and mortality was weaker and no
39 longer statistically significant when we restricted the analysis to long-term mortality.
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3 of health and we therefore suggest that future research in **individuals with diabetes**
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5 should include repeated self-ratings and follow-up for long-term mortality.
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9 There are some limitations to our study. Even if the association between SRH and
10 mortality was robust when individuals with **underweight** were excluded, we cannot rule
11 out other potential residual confounding from co-morbidity other than MI, stroke or
12 cancer that was not assessed at baseline health examinations. Moreover, the sample size
13 in the present study did not allow any clear conclusions in relation to sex-specific
14 analyses and **we could not make a separation between type 1 and type 2 diabetes**. The
15 questions and the response alternatives on SRH were formulated somewhat differently
16 and in the native language at each centre. The questions and answers were translated
17 and standardized in four response alternatives, which may have led to some degree of
18 misclassification, particularly for the centres in Bilthoven and Umeå (which had five
19 response alternatives). However, the forest plot gave no indication that the
20 standardization in four response alternatives had a major impact on the risk estimates.
21 The multivariate models used in this study were similar but not identical with equations
22 used in risk engines[7] and risk scores.[8] Whether SRH adds predictive value over and
23 above these models needs to be further analysed in future studies using adequate
24 methods.[38]
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42 Although more research is needed to gain a more complete understanding of the
43 relationship between SRH and mortality in **individuals with diabetes**, we find that self-
44 ratings of health are an inexpensive and time-efficient way to obtain subjective
45 prognostic information that may be difficult to assess by objective health measurements.
46 In diabetes patients with low SRH the physician should consider a more detailed
47 consultation and intensified support.
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56 *Conclusions*
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3 This is the first study investigating the association between self-rated health and
4 mortality in individuals with diabetes with a long-term follow-up in different European
5 countries. We found that low self-rated health was associated with increased mortality in
6 individuals with diabetes after controlling for established risk factors. The association
7 was mainly driven by increased five-year mortality in men and was stronger among
8 individuals with BMI <25 than in obese individuals.
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Table 1 Baseline characteristics of 3257 individuals with diabetes participating in the European Prospective Investigation into Cancer and Nutrition. Data are presented as percent or mean (standard deviation).

	Men N=1903	Women N=1354
Age (years)	56.2 (7.1)	55.4 (8.2)
Self-rated health (%)		
High		
<i>Excellent</i>	10.5	8.6
<i>Good</i>	54.1	49.9
Low		
<i>Moderate</i>	28.4	33.5
<i>Poor</i>	7.0	8.0
Education (%)		
<i>None</i>	0.6	1.8
<i>Primary school</i>	35.0	43.9
<i>Technical/professional school</i>	29.1	33.7
<i>Secondary school</i>	6.8	7.6
<i>Longer (incl. university degree)</i>	28.6	13.1
BMI (kg/m ²)	28.6 (4.3)	29.5 (5.6)
Current smoking (%)	24.0	16.2
Physical inactivity (%)	26.8	33.0
Insulin treatment (%)	22.8	24.3
Hypertension (%)	70.0	71.3
Hyperlipidaemia (%)	21.8	18.5
History of myocardial infarction (%)	9.2	3.8
History of stroke (%)	3.5	3.0
History of cancer (%)	4.1	6.4

Table 2 Baseline characteristics in relation to categories of self-rated health. Data are presented as percent or mean.

	Men					Women				
	Self-rated health				P	Self-rated health				P
	High		Low			High		Low		
	Excellent	Good	Moderate	Poor		Excellent	Good	Moderate	Poor	
Age (years)	57.1	56.6	55.2	55.4	<0.001	53.8	55.8	55.4	54.1	0.001
Education (%)										
None	0.5	0.5	0.7	0.8	0.42	1.7	1.5	2.0	2.9	0.40
Primary school	35.9	33.1	36.8	42.4		35.3	44.6	44.5	44.8	
Technical/ professional school	31.8	28.4	29.3	28.8		41.4	33.2	32.3	34.3	
Secondary school	6.6	6.7	7.5	4.5		8.6	6.3	9.8	5.7	
Longer (incl. university degree)	25.3	31.3	25.7	23.5		12.9	14.5	11.4	12.4	
BMI (kg/m ²)	28.6	28.4	28.9	29.0	0.05	28.1	29.2	30.0	31.1	<0.001
Current smoking (%)	25.5	23.4	24.8	23.7	0.89	16.4	15.6	15.4	21.3	0.49
Physical inactivity (%)	20.6	26.3	26.6	41.1	0.001	18.3	32.8	35.8	39.8	0.002
Insulin treatment (%)	15.2	20.8	27.4	29.2	0.002	18.1	23.0	28.0	24.1	0.15
Hypertension (%)	67.5	68.5	74.0	70.7	0.11	56.9	72.4	72.3	75.0	0.004
Hyperlipidaemia (%)	22.0	20.4	24.1	21.8	0.42	14.7	18.6	19.0	20.4	0.69
History of myocardial infarction (%)	9.0	6.9	11.5	17.3	<0.001	1.7	2.4	6.0	4.6	0.009
History of stroke (%)	2.8	2.4	4.5	9.5	0.001	1.0	2.1	4.7	3.3	0.07
History of cancer (%)	5.1	5.1	3.6	5.7	0.61	4.9	5.8	6.1	14.3	0.02

Table 3 Hazard ratios (HRs) of low (moderate or poor) versus high (excellent or good) self-rated health for all-cause mortality during follow-up.

	Model 1*	Model 2†	Model 3‡
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Both sexes	1.56 (1.25 to 1.94)	1.49 (1.19 to 1.86)	1.38 (1.10 to 1.73)
Men	1.75 (1.35 to 2.27)	1.63 (1.25 to 2.12)	1.52 (1.16 to 1.98)
Women	1.35 (0.90 to 2.03)	1.21 (0.80 to 1.83)	1.11 (0.73 to 1.69)

*Adjusted for age and centre.

†Adjusted for age, centre, sex, BMI, physical inactivity, insulin treatment and hypertension.

‡Adjusted for age, centre, sex, BMI, physical inactivity, insulin treatment, hypertension and history of myocardial infarction, stroke or cancer.

Table 4 Hazard ratios (HRs) of low versus high self-rated health for all-cause mortality by categories of body mass index.

	BMI classification	BMI (kg/m ²)	CV mortality (%)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Both sexes	Normal or underweight (n=646)	<25	38.3	2.81 (1.65 to 4.79)	3.12 (1.81 to 5.37)	2.95 (1.71 to 5.10)
	Overweight (n=1408)	25-29.9	37.3	1.46 (1.05 to 2.03)	1.34 (0.96 to 1.89)	1.22 (0.87 to 1.71)
	Obesity (n=1203)	≥30	45.0	1.29 (0.90 to 1.85)	1.20 (0.83 to 1.72)	1.14 (0.79 to 1.65)
Men	Normal or underweight (n=359)	<25	39.5	2.77 (1.49 to 5.15)	3.61 (1.90 to 6.85)	3.57 (1.88 to 6.78)
	Overweight (n=921)	25-29.9	39.0	1.62 (1.12 to 2.36)	1.45 (0.99 to 2.14)	1.33 (0.90 to 1.95)
	Obesity (n=623)	≥30	47.5	1.57 (1.00 to 2.47)	1.38 (0.87 to 2.18)	1.31 (0.83 to 2.08)
Women	Normal or underweight (n=287)	<25	35.3	3.14 (1.10 to 8.94)	2.47 (0.79 to 7.66)	1.87 (0.59 to 6.00)
	Overweight (n=487)	25-29.9	31.4	1.20 (0.61 to 2.38)	1.04 (0.51 to 2.11)	0.93 (0.45 to 1.91)
	Obesity (n=580)	≥30	41.2	1.05 (0.56 to 3.85)	0.95 (0.52 to 1.74)	0.92 (0.50 to 1.69)

CV= Cardiovascular

*Adjusted for age and centre.

†Adjusted for age, centre, sex, BMI, physical inactivity, insulin treatment and hypertension.

‡Adjusted for age, centre, sex, BMI, physical inactivity, insulin treatment, hypertension and history of myocardial infarction, stroke or cancer.

Footnotes

Contributors: PW, OR, and UN were involved in the study concept and planned the analyses. PW, OR, HB, DS, RK, BT, AS, BBN, and UN contributed in the acquisition of the data. PW was responsible for statistical analyses and drafted the paper. PW, OR, LJ, and UN interpreted the results. All authors participated in critical revision of the manuscript and approved the final version. PW is the guarantor.

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Ethical approval: The study was approved by the IARC Institutional Review Board.

Data sharing: No additional data available.

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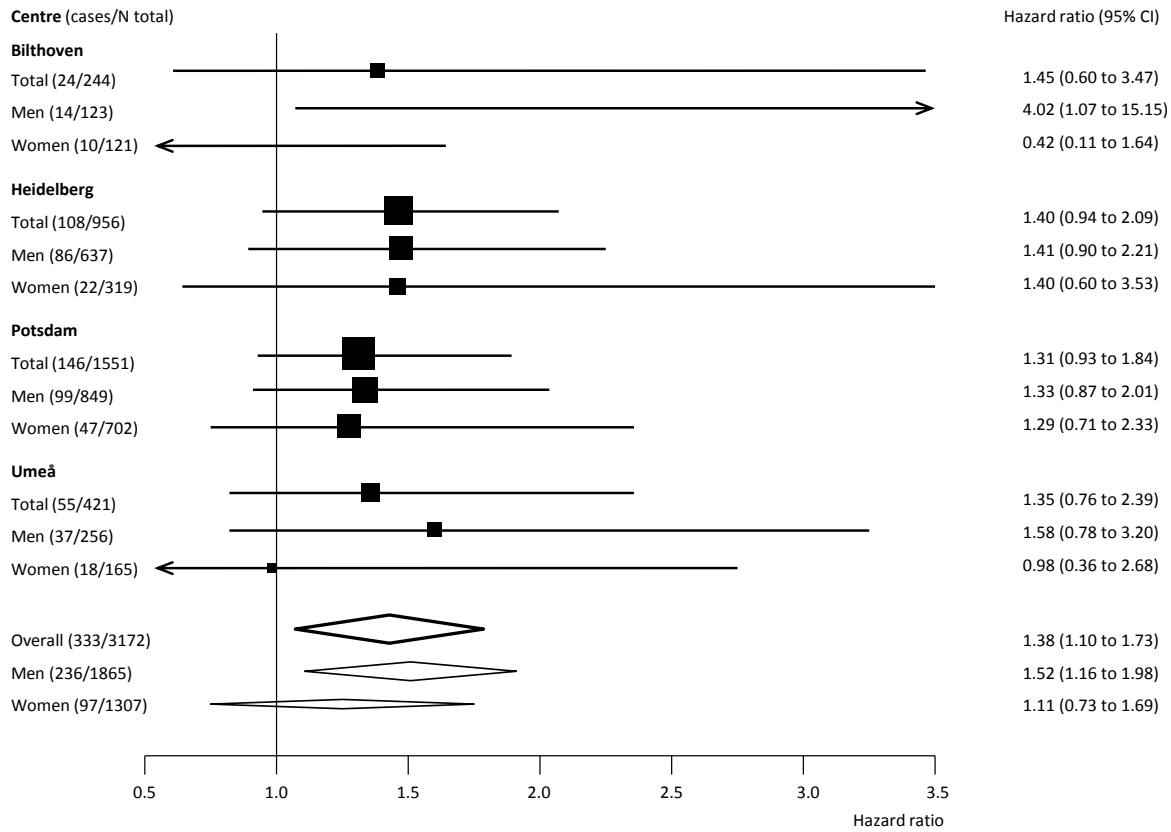
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Figure legends

Figure 1 Forest plot showing adjusted hazard ratios and 95% confidence intervals for the centres included in the study investigating the association between low self-rated health and mortality in individuals with diabetes.

For peer review only



Review only

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Appendix

All questionnaires were standardized to fit the question (with four response alternatives):

How satisfied are you today with your health?

1 Excellent

2 Good

3 Moderate

4 Poor

Description of the original questions and how they were standardized:

Bilthoven 1993–94

Question: *What do you think about your health in general?*

Response alternatives	Standardized
1 Excellent	1 Excellent
2 Good	2 Good
3 Reasonable	3 Moderate
4 Mediocre	4 Poor
5 Poor	4 Poor
9 More than 1 option indicated	Missing value

Bilthoven 1995–97

Question: *What do you think about your health in general?*

Response alternatives	Standardized
1 Excellent	1 Excellent
2 Very Good	2 Good
3 Good	2 Good
4 Reasonable	3 Moderate
5 Mediocre	4 Poor
9 More than 1 option indicated	Missing value

Heidelberg

Question: *On the whole, how satisfied are you today with your health?*

Response alternatives	Standardized
1 Very satisfied	1 Excellent
2 More satisfied	2 Good
3 More dissatisfied	3 Moderate
4 Very dissatisfied	4 Poor
8 Do not know	Missing value

Potsdam

Question: *On the whole, how satisfied are you today with your health?*

Response alternatives	Standardized
1 Very satisfied	1 Excellent
2 More likely satisfied	2 Good
3 More likely dissatisfied	3 Moderate
4 Very dissatisfied	4 Poor
8 Do not know	Missing value

Umeå

Question: *How do you judge that your state of health has been in the last year?*

Response alternatives	Standardized
1 Very well	1 Excellent
2 Quiet well	2 Good
3 Fairly well	3 Moderate
4 Quiet bad	4 Poor
5 Bad	4 Poor
9 Inconsistent answer	Missing value

Research checklist

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (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 (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
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 (b) Report category boundaries when continuous variables were categorized

		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

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 <http://www.strobe-statement.org>.