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Self-rated Health and Type 2 Diabetes Risk in the EPIC-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.

Design Population-based prospective case-cohort study.

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

Participants Self-rated health was assessed by baseline questionnaire in 3,399 incident type 2 diabetic case participants and a centre-stratified subcohort of 4,619 individuals from the EPIC-InterAct study which was drawn from a total cohort of 340,234 participants in the European Prospective Investigation into Cancer and Nutrition (EPIC).

Primary outcome measure Prentice-weighted Cox regression was used to estimate centre-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for incident type 2 diabetes controlling for age, sex, centre, education, BMI, smoking, alcohol consumption, energy intake, physical activity, and hypertension. The centre-specific HRs were pooled across centres by random effects meta-analysis.

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 (pooled HR 1.29, 95% CI 1.09 to 1.53). I^2 index for heterogeneity across centres was 13.3% (p=0.33).

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.

Article Summary

Article focus

- Self-rated health has been widely used as a global health measure. Several cross-sectional studies have suggested an association between low self-rated health and type 2 diabetes mellitus.
- We aimed to prospectively investigate the association between self-rated health and risk of type 2 diabetes. A population-based case-cohort study design was used and five European centers were included in the study.

Key messages

- Results from this study provide some evidence that low self-rated health is associated with a higher risk of type 2 diabetes mellitus. 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 centres.

Strength and limitations

- The study used a thorough ascertainment and verification of type 2 diabetes mellitus cases and included populations from four different European countries.
- The assessment of self-rated health differed somewhat between centres regarding time frames for the self-rated health question.

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) worldwide has more than doubled since 1980.[1] In 2010, it was estimated that over 250 million people suffered from T2DM.[2] Several risk factors have been identified (e.g. age, BMI, family history and physical inactivity) but the aetiology of T2DM is complex and still largely 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[3]. Furthermore, SRH has been associated with bodily sensations and symptoms that can reflect disease in clinical or pre-clinical stages.[4-5] Individuals with poor self-rated health (SRH) tend to have higher mortality,[3 6] poorer physical activity[7] and higher health care utilization[8] than individuals rating their health as excellent or good. Several cross-sectional studies in different populations have reported associations between poor SRH and prevalent diabetes[9-11] or glucometabolic disturbance.[12] To our knowledge, only one previous prospective study on the association between SRH and incidence of T2DM has been published, showing that reduced SRH is associated with newly diagnosed T2DM after a five year follow-up.[13] However, this prospective study was limited by high loss to follow-up. The EPIC-InterAct Study is a large case-cohort study that provides an ideal setting to investigate the association between SRH and T2DM across several European countries.

Methods

Study population

The InterAct Project was initiated to investigate how genetic and lifestyle behavioural factors, particularly diet and physical activity, 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 European Prospective

Investigation into Cancer and Nutrition (EPIC), which in total consists of 519,978 men and women across Europe.[14] 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 United Kingdom). A detailed description of the study design and methods can be found elsewhere.[15] In the present analysis we only included centres that had baseline data available on self-rated health (Germany: Heidelberg and Potsdam; the U.K.: Cambridge; the Netherlands: Bilthoven; Sweden: Umeå). Participants were 25 to 70 years old at enrolment between 1992 and 2000. Among the participants from the five centres included in this study, 3,412 incident T2DM cases were identified and a subcohort of 4,637 individuals were randomly selected after exclusions for prevalent diabetes or unknown diabetes status. Data on self-rated health was available for 4,619 individuals in the subcohort and 3,399 incident T2DM cases. Due 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 anti-diabetic drug use), linkage to primary and secondary care registers, medication use (prescription registers), hospital admission and mortality data. Cases in Sweden were not ascertained by self-report, but identified via local and national diabetes and pharmaceutical registers and hence all ascertained cases were considered to be verified.[15] 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, including individual medical-record review.

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=305 in the lowest category) we dichotomized the SRH variable in the analysis by combining the two highest categories (high SRH) and the two lowest categories (low SRH) in conformity with previous research.[16-18]

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.[19] Body mass index (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 versus non-smoker or ex-smoker), diet, physical activity level, alcohol consumption, and previous myocardial infarction. Physical activity (PA) was assessed using the Cambridge index, a validated ordered categorical global index of activity derived from simple questions assessing recreational and occupational activity.[20]

Statistical analysis

The association between SRH and various baseline characteristics within the subcohort was tested using a chi-square 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,[21] was used to estimate centre-specific

hazard ratios (HRs) and 95% confidence intervals (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 22] 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, physical activity and hypertension were included as categorical variables, whereas BMI, alcohol consumption and energy intake were included as continuous variables. I^2 – 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 two years of follow-up. In a second sensitivity analysis we excluded all participants with history of myocardial infarction at baseline. To investigate the impact of missing data, 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.[23] All analyses were performed using Stata 11.2, except for the random effects meta-analysis which was performed using Comprehensive Meta-Analysis version 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 1. Table 2** shows the baseline characteristics of individuals in the subcohort by categories of SRH. Participants with low SRH were younger, had 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 3**). 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, physical activity, 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 1**. We found no indication of heterogeneity in the association between SRH and T2DM across centres (I^2 index 13.3%, p=0.33).

In a first sensitivity analysis we excluded participants who were diagnosed with T2DM within two years of follow-up (n=398). These exclusions had only 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 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). Because of missing data on covariates, 323 T2DM cases and 405 members of the subcohort were excluded from 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 to 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. 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 [6 24]. A few studies have investigated the association between SRH and mortality in populations of diabetes patients with results similar to those of general populations [17 25-26]. SRH and prevalent diabetes have been associated in several cross-sectional studies [9-12 27]. However, cross-sectional studies are limited by their inability to study the temporal sequence of exposure and disease. Furthermore, these studies have not separated type 2 and type 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 association from low SRH to T2DM (i.e. a temporal relationship). We have only found one previous prospective study of the association between SRH and T2DM in a large general population. In the Australian Diabetes Obesity and Lifestyle study, Tapp et al. [13] 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 they did not present any sensitivity analysis with exclusion of participants, who were diagnosed with T2DM shortly after baseline, which makes a bidirectional association more likely. Furthermore, the study was limited by a low follow-up response rate.

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 self-rated health and obesity, Prosper et al. found that obese individuals had a 3-fold greater odds of reporting reduced health compared to individuals with normal weight or overweight. As obesity is also considered to be a major risk factor for diabetes [28], obesity 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.

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 [22]. One study that used in-depth interviews found that the same frame of reference is not used by all respondents in answering this question [29]. 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 (e.g. perception of health *today* in Germany and perception of health over the *last year* in Sweden). SRH has 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 [30]. Thus, the impact of different time frames on SRH assessment is likely to be small.

Compared to studies of SRH with mortality outcomes in individuals with diabetes [17 25-26] 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 mortality rates from several causes [31], including cancer [32]. It is likely that the comparatively strong association between SRH and mortality is due to a higher ability for SRH to summarize 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" (i.e. how optimistic or pessimistic people are about their health) [33] in a generally healthier population compared to subjective health ratings later on in the disease process.

Previous findings suggest that there may be sex differences in the SRH-mortality association [34] but we found no sex difference in the association between SRH and T2DM. SRH may also vary across countries [35]. In the present study, it is likely that the differences in SRH across centres to some extent can 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.

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 [36]. Several limitations of the study have already been listed, such as different time frames for the SRH question and the restriction to countries in northern Europe. We would also like to point out that it is possible that participants reporting low SRH at baseline were more likely to seek medical advice during follow-up and hence were more likely to be tested for diabetes (detection bias). If this was the case, the study may have overestimated the risk of T2DM associated with low SRH.

In our study, part of the SRH-T2DM association seemed to be explained by medical history as well as lifestyle variables. SRH may therefore be considered as a summary health measure – also for metabolic health. If there is access to several of the

established risk factors for diabetes, self-rated health is not likely to add more than marginally to risk prediction on top of the conventional risk factors. However, whether SRH adds predictive value over and above established risk factors needs to be further analysed using adequate methods [37].

In conclusion, results from this prospective case-cohort study provide some evidence that low self-rated health is associated with a higher risk of type 2 diabetes mellitus. The association could be only partly explained by other health-related variables, of which obesity was the strongest.

Footnotes

Contributors: PW had access to all data for this study, analysed the data, drafted the manuscript and is the guarantor. All authors qualify for authorship according to BMJ Open criteria. They have all contributed to conception and design, and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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

Data sharing: No additional data available.

Table 1 Self-rated health by centre in 3,399 incident cases of type 2 diabetes mellitus and 4,619 participants in the subcohort in the EPIC-InterAct study. Data shown are numbers of individuals (percentage).

Centre		Self-rated health			
		High		*Low*	
		Excellent	Good	Moderate	Poor
Bilthoven	Cases	13 (4.3)	184 (61.5)	73 (24.4)	29 (9.7)
	Subcohort	52 (9.0)	403 (70.0)	101 (17.5)	21 (3.6)
Cambridge	Cases	92 (12.3)	428 (57.1)	206 (27.5)	24 (3.2)
	Subcohort	159 (16.2)	624 (63.4)	170 (17.4)	23 (2.3)
Heidelberg	Cases	173 (23.1)	395 (52.8)	156 (20.9)	24 (3.2)
	Subcohort	286 (32.9)	448 (51.5)	125 (14.4)	11 (1.3)
Potsdam	Cases	118 (15.2)	460 (59.4)	171 (22.1)	26 (3.4)
	Subcohort	274 (23.1)	721 (60.9)	164 (13.9)	25 (2.1)
Umeå	Cases	155 (18.7)	369 (44.6)	236 (28.5)	67 (8.1)
	Subcohort	265 (26.2)	477 (47.1)	215 (21.2)	55 (5.4)

Table 2 Baseline characteristics of subcohort individuals in the EPIC-InterAct study by categories of self-rated health. Data are presented as mean and standard deviations (SD) for continuous variables and percentages and frequencies for categorical variables.

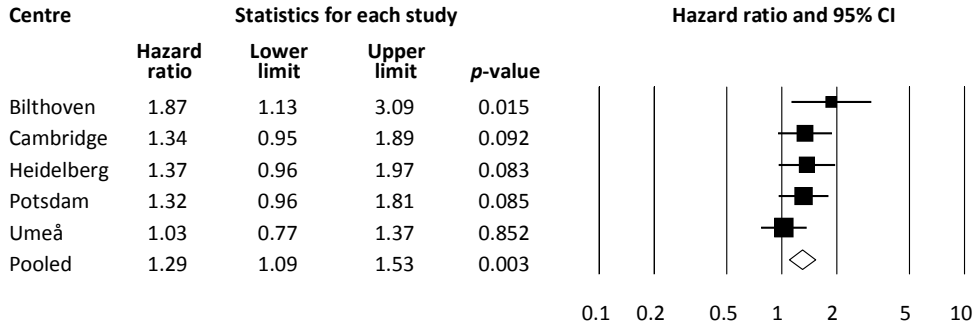
	Self-rated health								
	High				*Low*				
	Excellent		Good		Moderate		Poor		*p*-value for overall difference*
	Mean/%	SD/N	Mean/%	SD/N	Mean/%	SD/N	Mean/%	SD/N	
Age (years)	48.8	10.3	50.5	11.1	51.7	10.9	50.3	10.2	<0.001
Sex (% men)	42.8	443	45.2	1208	44.8	347	37.8	51	0.24
Educational level (%)									<0.001
Primary school or none	19.2	194	24.4	635	37.9	287	30.8	40	
Technical/ professional school	34.6	351	35.0	910	29.6	224	32.3	42	
Secondary school	14.9	151	14.2	369	14.4	109	18.5	24	
Higher (incl. university degree)	31.3	317	26.4	688	18.1	137	18.5	24	
BMI (kg/m^2)	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	
Former	27.5	285	30.1	804	30.1	233	23.7	32	
Current	18.8	195	21.0	561	26.1	202	32.6	44	
Unknown	1.5	16	2.3	62	2.2	17	3.0	4	
Physical activity (%)									<0.001
Inactive	15.9	160	21.3	548	31.1	231	43.3	52	
Moderately inactive	33.2	335	31.7	818	28.8	214	29.2	35	
Moderately active	25.5	257	26.8	689	21.8	162	15.0	18	
Active	25.5	257	20.2	521	18.2	135	12.5	15	
Alcohol consumption (g/d)	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

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

Table 3 Pooled hazard ratios of incident T2DM comparing low (moderate or poor) versus high (excellent or good) self-related health.

	High self-rated health	Low self-rated health
	Pooled HR (95% CI)	Pooled HR (95% CI)*
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)	1.59 (1.41 to 1.80)
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 1.88)
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 hazard ratios calculated using a centre-stratified approach in combination with a random effects meta-analysis.



p-value for heterogeneity 0.33, I^2 index 13.3%

Figure 1 Centre-specific and pooled hazard ratios of incident T2DM adjusted for the variables in the final model (age, sex, education, BMI, smoking, physical activity, alcohol consumption, energy intake and hypertension).

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CONTRIBUTORSHIP

PW had access to all data for this study, analysed the data, drafted the manuscript and is the guarantor. All authors qualify for authorship according to BMJ Open criteria. They have all contributed to conception and design, and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

COMPETING INTERESTS

None

DATA SHARING

No additional data available.

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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

Cambridge

Question: *How would you rate your general health?*

Response alternatives	Standardized
1 Excellent	1 Excellent
2 Good	2 Good
3 Moderate	3 Moderate

4 Poor	4 Poor

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

STROBE Statement—checklist of items that should be included in reports of observational 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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

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) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*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 cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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

Self-rated Health and Type 2 Diabetes Risk in the EPIC-InterAct Study: a case-cohort study

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Self-rated Health and Type 2 Diabetes Risk in the EPIC-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, Umeå).

Participants Self-rated health was assessed by baseline questionnaire in 3,399 incident type 2 diabetic case participants and a centre-stratified subcohort of 4,619 individuals from the EPIC-InterAct study which was drawn from a total cohort of 340,234 participants in the European Prospective Investigation into Cancer and Nutrition (EPIC).

Primary outcome measure Prentice-weighted Cox regression was used to estimate centre-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for incident type 2 diabetes controlling for age, sex, centre, education, BMI, smoking, alcohol consumption, energy intake, physical activity, and hypertension. The centre-specific HRs were pooled across centres by random effects meta-analysis.

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 (pooled HR 1.29, 95% CI 1.09 to 1.53). I^2 index for heterogeneity across centres was 13.3% (p=0.33).

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.

Article Summary

Article focus

- Self-rated health has been widely used as a global health measure. Several cross-sectional studies have suggested an association between low self-rated health and type 2 diabetes mellitus.
- We aimed to prospectively 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. A population-based case-cohort study design was used in the study.

Key messages

- Results from this study provide some evidence that low self-rated health is associated with a higher risk of type 2 diabetes mellitus. 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 centres.

Strength and limitations

- The study used a thorough ascertainment and verification of type 2 diabetes mellitus cases and included populations from four different European countries.
- The assessment of self-rated health differed somewhat between centres regarding the construct (formulation, response alternatives and time frames) of the self-rated health question.

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) worldwide has more than doubled since 1980.[1] In 2010, it was estimated that over 250 million people suffered from T2DM.[2] Several risk factors have been identified (e.g. age, BMI, family history and physical inactivity) but the aetiology of T2DM is complex and still largely 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[3]. Furthermore, SRH has been associated with "bodily sensations and symptoms that can reflect disease in clinical or pre-clinical stages".[4-5] Individuals with poor SRH tend to have higher mortality,[3 6] poorer physical activity[7] and higher health care utilization[8] than individuals rating their health as excellent or good. It is likely that individuals with poor SRH face larger or different barriers to adopt a healthy lifestyle, which may be of relevance to how prevention efforts should be targeted. Several cross-sectional studies in different populations have reported associations between poor SRH and prevalent diabetes[9-11] or glucometabolic disturbance.[12] The primary aim of this study was to investigate the association between SRH and risk of T2DM. As a secondary aim, we investigated whether the strength of this association was consistent across five European centres. A few previous prospective studies have evaluated the association between SRH and incidence of T2DM. A study by Tapp et al.[13] showed that poorer SRH is associated with newly diagnosed T2DM after a five year follow-up[13], but the study was limited by high loss to follow-up. In a recent study, Latham and Peek found that SRH was a significant predictor for six major chronic diseases, including diabetes, among late midlife U.S. adults.[14] However, the outcome assessment in the study was based on self-reports, which makes the measurement susceptible for misclassification. The EPIC-InterAct Study is a large case-cohort study with thorough ascertainment and verification of T2DM that provides an ideal setting to investigate the association between SRH and T2DM across several European countries.

Methods

Study population

The InterAct Project was initiated to investigate how genetic and lifestyle behavioural factors, particularly diet and physical activity, 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 European Prospective Investigation into Cancer and Nutrition (EPIC), which in total consists of 519,978 men and women across Europe.[15] 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 United Kingdom). A detailed description of the study design and methods can be found elsewhere.[16] In the present analysis we only included centres that had baseline data available on self-rated health (Germany: Heidelberg and Potsdam; the U.K.: 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 remainedafter exclusions (**Figure 1**). Due 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 anti-diabetic 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 identified via local and national diabetes and pharmaceutical registers and hence all ascertained cases were considered to be verified.[16]

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=305 in the lowest category) we dichotomized 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] Body mass index (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 versus non-smoker or ex-smoker), diet, physical activity level, alcohol consumption, and previous myocardial infarction. Physical activity (PA) was assessed

using the Cambridge index, a validated ordered 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 chi-square 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 hazard ratios (HRs) and 95% confidence intervals (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, physical activity and hypertension were included as categorical variables, whereas BMI, alcohol consumption and energy intake were included as continuous variables. I^2 – 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 two years of follow-up. In a second sensitivity analysis we excluded all participants with 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.[24] All analyses were performed using Stata 11.2, except for the random effects meta-analysis which was performed using Comprehensive Meta-Analysis version 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 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, physical activity, 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 (I^2 index 13.3%, p=0.33).

In a first sensitivity analysis we excluded participants who were diagnosed with T2DM within two years of follow-up (n=398). These exclusions had only 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 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). Because of missing data on covariates, 323 T2DM cases and 405 members of the subcohort were excluded from 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 to 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 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 [6 25]. 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 type 2 and type 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 association from low SRH to T2DM (i.e. a temporal relationship). We have only found two previous prospective studies of the association between SRH and T2DM in large general populations. In the Australian Diabetes Obesity and Lifestyle study, Tapp et al. [13] 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 they did not present any sensitivity analysis with exclusion of 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 two years of follow-up. Recently, Latham and Peek published a report from the Health and Retirement Study, a longitudinal survey of a U.S. midlife cohort.[14] 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 showing an association between SRH and T2DM also 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 self-rated health and obesity, Prosper et al. found that obese individuals had a 3-fold greater odds of reporting reduced health compared to individuals with normal weight or overweight. As obesity is also considered to be a major risk factor for diabetes [29], obesity 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 [23]. One study that used in-depth interviews found that the same frame of reference is not used by all respondents in answering this question [30]. 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 (e.g. satisfaction with health *today* in Germany and perception of health over the *last year* in Sweden). SRH has 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 [31]. Thus, the impact of different time frames on SRH assessment is likely to be small.

Compared to studies of SRH with mortality outcomes in individuals with diabetes [18 26-27] 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 mortality rates from several causes [32], including cancer [33]. It is likely that the comparatively strong association between SRH and mortality is due to a higher ability for SRH to summarize 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" (i.e. how optimistic or pessimistic people are about their health) [34] in a generally healthier population compared to subjective health ratings later on in the disease process.

Previous findings suggest that there may be sex differences in the SRH-mortality association [35] but we found no sex difference in the association between SRH and T2DM. SRH may also vary across countries [36]. In the present study, it is likely that the differences in SRH across centres to some extent can 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 standardization but the differences in the construct of the SRH question between centres are limitations to this study, particularly to the analysis of heterogeneity.

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 [37]. Several limitations of the study have already been listed, such as different construct of the SRH question and the restriction to countries in northern Europe. We would also like to point out that it is possible that participants reporting low SRH at baseline were more likely to seek medical advice during follow-up and hence were more likely to be tested for diabetes (detection bias). If this was the case, the study may have overestimated the risk of T2DM associated with low SRH.

In our study, part of the SRH-T2DM association seemed to be explained by medical history as well as lifestyle variables. SRH may therefore be considered as a summary health measure – also for metabolic health. If there is access to several of the established risk factors for diabetes, SRH is not likely to add more than marginally to risk prediction on top of the conventional risk factors. However, whether SRH adds

predictive value over and above established risk factors needs to be further analysed using adequate methods [38].

In conclusion, results from this prospective case-cohort study provide some evidence that low self-rated health is associated with a higher risk of type 2 diabetes mellitus. The association could be only partly explained by other health-related variables, of which obesity was the strongest.

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Footnotes

Contributors: PW had access to all data for this study, analysed the data, drafted the manuscript and is the guarantor. All authors qualify for authorship according to BMJ Open criteria. They have all contributed to conception and design, and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

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Table 1 Overview of the five centres included in the study from the EPIC-InterAct study.

Centre	Description of source population	Baseline collection		
		n	Women (%)	5th and 95th age percentiles
Bilthoven	Participants were invited as age- and sex-stratified random sample of the general population	22,715	55	23–58
Cambridge	Volunteers were invited as a random sample of the population listed at general practitioners	30,441	55	45–74
Heidelberg	Volunteers were invited from the general population	25,540	53	37–63
Potsdam	Volunteers were invited from the general population	27,548	60	36–64
Umeå	Participants were invited as a random sample of the population	25,728	52	30–60

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Ethical approval: The study was approved by the IARC Institutional Review Board and by the local review boards of the participating centers.

Data sharing: No additional data available.

Table 2 Self-rated health by centre in 3,399 incident cases of type 2 diabetes mellitus and 4,619 participants in the subcohort in the EPIC-InterAct study. Data shown are numbers of individuals (percentage).

Centre		Self-rated health			
		High		*Low*	
		Excellent	Good	Moderate	Poor
Bilthoven	Cases	13 (4.3)	184 (61.5)	73 (24.4)	29 (9.7)
	Subcohort	52 (9.0)	403 (70.0)	101 (17.5)	21 (3.6)
Cambridge	Cases	92 (12.3)	428 (57.1)	206 (27.5)	24 (3.2)
	Subcohort	159 (16.2)	624 (63.4)	170 (17.4)	23 (2.3)
Heidelberg	Cases	173 (23.1)	395 (52.8)	156 (20.9)	24 (3.2)
	Subcohort	286 (32.9)	448 (51.5)	125 (14.4)	11 (1.3)
Potsdam	Cases	118 (15.2)	460 (59.4)	171 (22.1)	26 (3.4)
	Subcohort	274 (23.1)	721 (60.9)	164 (13.9)	25 (2.1)
Umeå	Cases	155 (18.7)	369 (44.6)	236 (28.5)	67 (8.1)
	Subcohort	265 (26.2)	477 (47.1)	215 (21.2)	55 (5.4)

Table 3 Baseline characteristics of subcohort individuals in the EPIC-InterAct study by categories of self-rated health. Data are presented as mean and standard deviations (SD) for continuous variables and percentages and frequencies for categorical variables.

	Self-rated health								
	High				*Low*				
	Excellent		Good		Moderate		Poor		*p*-value for overall difference*
	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	
Technical/ professional school	34.6	351	35.0	910	29.6	224	32.3	42	
Secondary school	14.9	151	14.2	369	14.4	109	18.5	24	
Higher (incl. university degree)	31.3	317	26.4	688	18.1	137	18.5	24	
BMI (kg/m^2)	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	
Former	27.5	285	30.1	804	30.1	233	23.7	32	
Current	18.8	195	21.0	561	26.1	202	32.6	44	
Unknown	1.5	16	2.3	62	2.2	17	3.0	4	
Physical activity (%)									<0.001
Inactive	15.9	160	21.3	548	31.1	231	43.3	52	
Moderately inactive	33.2	335	31.7	818	28.8	214	29.2	35	
Moderately active	25.5	257	26.8	689	21.8	162	15.0	18	
Active	25.5	257	20.2	521	18.2	135	12.5	15	
Alcohol consumption (g/d)	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

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

Table 4 Pooled hazard ratios of incident T2DM comparing low (moderate or poor) versus high (excellent or good) self-related health.

	High self-rated health	Low self-rated health
	Pooled HR (95% CI)	Pooled HR (95% CI)*
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)	1.59 (1.41 to 1.80)
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 1.88)
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 hazard ratios calculated using a centre-stratified approach in combination with a random effects meta-analysis.

FIGURE LEGENDS

Figure 1 Overview of the five centres included in the study from the EPIC-InterAct study.

Figure 2 Centre-specific and pooled hazard ratios of incident T2DM adjusted for the variables in the final model (age, sex, education, BMI, smoking, physical activity, alcohol consumption, energy intake and hypertension).

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Self-rated Health and Type 2 Diabetes Risk in the EPIC-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, Umeå).

Participants Self-rated health was assessed by baseline questionnaire in 3,399 incident type 2 diabetic case participants and a centre-stratified subcohort of 4,619 individuals from the EPIC-InterAct study which was drawn from a total cohort of 340,234 participants in the European Prospective Investigation into Cancer and Nutrition (EPIC).

Primary outcome measure Prentice-weighted Cox regression was used to estimate centre-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for incident type 2 diabetes controlling for age, sex, centre, education, BMI, smoking, alcohol consumption, energy intake, physical activity, and hypertension. The centre-specific HRs were pooled across centres by random effects meta-analysis.

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 (pooled HR 1.29, 95% CI 1.09 to 1.53). I^2 index for heterogeneity across centres was 13.3% (p=0.33).

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.

Article Summary

Article focus

- Self-rated health has been widely used as a global health measure. Several cross-sectional studies have suggested an association between low self-rated health and type 2 diabetes mellitus.
- We aimed to prospectively 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. A population-based case-cohort study design was used ~~and five European centers were included~~ in the study.

Key messages

- Results from this study provide some evidence that low self-rated health is associated with a higher risk of type 2 diabetes mellitus. 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 centres.

Strength and limitations

- The study used a thorough ascertainment and verification of type 2 diabetes mellitus cases and included populations from four different European countries.
- The assessment of self-rated health differed somewhat between centres regarding the construct (formulation, response alternatives and time frames) off~~or~~ the self-rated health question.

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) worldwide has more than doubled since 1980.[1] In 2010, it was estimated that over 250 million people suffered from T2DM.[2] Several risk factors have been identified (e.g. age, BMI, family history and physical inactivity) but the aetiology of T2DM is complex and still largely 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[3]. Furthermore, SRH has been associated with "bodily sensations and symptoms that can reflect disease in clinical or pre-clinical stages".[4-5] Individuals with poor ~~self-rated health (~~SRH~~)~~ tend to have higher mortality,[3 6] poorer physical activity[7] and higher health care utilization[8] than individuals rating their health as excellent or good. It is likely that individuals with poor SRH face larger or different barriers to adopt a healthy lifestyle, which may be of relevance to how prevention efforts should be targeted. Several cross-sectional studies in different populations have reported associations between poor SRH and prevalent diabetes[9-11] or glucometabolic disturbance.[12] The primary aim of this study was to investigate the association between SRH and risk of T2DM. As a secondary aim, we investigated whether the strength of this association was consistent across five European centres. A few ~~To our knowledge, only one~~ previous prospective studies have evaluated~~y on~~ the association between SRH and incidence of T2DM~~ has been published.~~; A study by Tapp et al.[13] showed~~ing~~ that poorer~~reduced~~ SRH is associated with newly diagnosed T2DM after a five year follow-up.~~[13]~~, but the ~~However, this prospective~~ study was limited by high loss to follow-up. In a recent study, Latham and Peek found that SRH was a significant predictor for six major chronic diseases, including diabetes, among late midlife U.S. adults.[14] However, the outcome assessment in the study was based on self-reports, which makes the measurement susceptible for misclassification. The EPIC-InterAct Study is a large case-cohort study with thorough ascertainment and verification of T2DM that provides an ideal

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setting to investigate the association between SRH and T2DM across several European countries.

Methods

Study population

The InterAct Project was initiated to investigate how genetic and lifestyle behavioural factors, particularly diet and physical activity, 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 European Prospective Investigation into Cancer and Nutrition (EPIC), which in total consists of 519,978 men and women across Europe.[15~~14~~] 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 United Kingdom). A detailed description of the study design and methods can be found elsewhere.[16~~15~~] In the present analysis we only included centres that had baseline data available on self-rated health (Germany: Heidelberg and Potsdam; the U.K.: Cambridge; the Netherlands: Bilthoven; Sweden: Umeå). Participants were ~~25 to 70 years old at~~ enrolled~~ment~~ 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 ~~3,412 incident T2DM cases were identified~~ and a subcohort of 4,619~~4,637~~ individuals remained~~were randomly selected~~ after exclusions ~~for prevalent diabetes or unknown diabetes status. Data on self rated health was available for 4,619 individuals in the subcohort and 3,399 incident T2DM cases~~(**Figure 1**). Due 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.

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Ascertainment of T2DM cases

Incident cases of T2DM until 31 December 2007 were ascertained and verified at each EPIC centre participating in the Epic-InterAact project using follow-up questionnaires (T2DM diagnosed by a medical doctor or anti-diabetic 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 UmeåSweden were not ascertained by self-report, but identified via local and national diabetes and pharmaceutical registers and hence all ascertained cases were considered to be verified.[16][15] 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, including individual medical record review.

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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=305 in the lowest category) we dichotomized 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][16 18]

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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 19] Body mass index (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 versus non-smoker or ex-smoker), diet, physical activity level, alcohol consumption, and previous myocardial infarction. Physical activity (PA) was assessed using the Cambridge index, a validated ordered categorical global index of activity derived from simple questions assessing recreational and occupational activity.[21 20]

Statistical analysis

The association between SRH and various baseline characteristics within the subcohort was tested using a chi-square 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 21] was used to estimate centre-specific hazard ratios (HRs) and 95% confidence intervals (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 22] 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,

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smoking status, physical activity and hypertension were included as categorical variables, whereas BMI, alcohol consumption and energy intake were included as continuous variables. I^2 – 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 two years of follow-up. In a second sensitivity analysis we excluded all participants with history of myocardial infarction at baseline. To investigate the impact of excluding 323 T2DM cases and 405 members of the subcohort with~~of~~ 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.[24~~23~~] All analyses were performed using Stata 11.2, except for the random effects meta-analysis which was performed using Comprehensive Meta-Analysis version 2.

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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~~1~~. Table 3~~2~~** shows the baseline characteristics of individuals in the subcohort by categories of SRH. Participants with low SRH were younger, had 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~~3~~**). 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, physical activity, 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 21**. We found no indication of heterogeneity in the association between SRH and T2DM across centres (I^2 index 13.3%, p=0.33).

In a first sensitivity analysis we excluded participants who were diagnosed with T2DM within two years of follow-up (n=398). These exclusions had only 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 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). Because of missing data on covariates, 323 T2DM cases and 405 members of the subcohort were excluded from 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 to 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 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 [6 25~~6 24~~]. 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~~17 25 26~~]. SRH and prevalent diabetes have been associated in several cross-sectional studies [9-12 28~~9-12 27~~]. However, cross-sectional studies are limited by their inability to study the temporal sequence of exposure and disease. Furthermore, these studies have not separated type 2 and type 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 association from low SRH to T2DM (i.e. a temporal relationship). We have only found two~~one~~ previous prospective studies~~y~~ of the association between SRH and T2DM in ~~a~~ large general populations. In the Australian Diabetes Obesity and Lifestyle study, Tapp et al. [13] 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 they did not present any sensitivity analysis with exclusion of participants, who were diagnosed with T2DM shortly after baseline, which makes a bidirectional association more likely. ~~Furthermore, the study was limited by a low follow-up response rate.~~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 two years of follow-up. Recently, Latham and Peek published a report from the Health and Retirement Study, a longitudinal survey of a U.S. midlife cohort.[14] They found that SRH predicted diabetes as well as coronary heart disease, stroke, lung disease, and arthritis

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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 showing an association between SRH and T2DM also when a strict verification procedure for outcome measurement is applied.

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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 self-rated health and obesity, Prosper et al. found that obese individuals had a 3-fold greater odds of reporting reduced health compared to individuals with normal weight or overweight. As obesity is also considered to be a major risk factor for diabetes [29~~28~~], obesity 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 [23~~22~~]. One study that used in-depth interviews found that the same frame of reference is not used by all respondents in answering this question [30~~29~~]. 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 (e.g. satisfaction with~~perception of~~ health *today* in Germany and perception of health over the *last year* in Sweden). SRH has 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 [31,30]. Thus, the impact of different time frames on SRH assessment is likely to be small.

Compared to studies of SRH with mortality outcomes in individuals with diabetes [18,26-27,17,25,26] 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 mortality rates from several causes [32,31], including cancer [33,32]. It is likely that the comparatively strong association between SRH and mortality is due to a higher ability for SRH to summarize 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" (i.e. how optimistic or pessimistic people are about their health) [34,33] in a generally healthier population compared to subjective health ratings later on in the disease process.

Previous findings suggest that there may be sex differences in the SRH-mortality association [35,34] but we found no sex difference in the association between SRH and T2DM. SRH may also vary across countries [36,35]. In the present study, it is likely that the differences in SRH across centres to some extent can 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 standardization but the differences in the construct of the SRH question between centres are limitations to this study, particularly to the analysis of heterogeneity.

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

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Europe and we included populations from four different European countries [37,36]. Several limitations of the study have already been listed, such as different construct of ~~time frames for~~ the SRH question and the restriction to countries in northern Europe. We would also like to point out that it is possible that participants reporting low SRH at baseline were more likely to seek medical advice during follow-up and hence were more likely to be tested for diabetes (detection bias). If this was the case, the study may have overestimated the risk of T2DM associated with low SRH.

In our study, part of the SRH-T2DM association seemed to be explained by medical history as well as lifestyle variables. SRH may therefore be considered as a summary health measure – also for metabolic health. If there is access to several of the established risk factors for diabetes, SRH~~self-rated health~~ is not likely to add more than marginally to risk prediction on top of the conventional risk factors. However, whether SRH adds predictive value over and above established risk factors needs to be further analysed using adequate methods [38,37].

In conclusion, results from this prospective case-cohort study provide some evidence that low self-rated health is associated with a higher risk of type 2 diabetes mellitus. The association could be only partly explained by other health-related variables, of which obesity was the strongest.

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Footnotes

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Contributors: PW had access to all data for this study, analysed the data, drafted the manuscript and is the guarantor. All authors qualify for authorship according to BMJ Open criteria. They have all contributed to conception and design, and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Ethical approval: The study was approved by the IARC Institutional Review Board and by the local review boards of the participating ~~centres~~centers.

Data sharing: No additional data available.

Table 1 Overview of the five centres included in the study from the EPIC-InterAct study.

Centre	Description of source population	Baseline collection		
		n	Women (%)	5th and 95th age percentiles
Bilthoven	Participants were invited as age- and sex-stratified random sample of the general population	22,715	55	23–58
Cambridge	Volunteers were invited as a random sample of the population listed at general practitioners	30,441	55	45–74
Heidelberg	Volunteers were invited from the general population	25,540	53	37–63
Potsdam	Volunteers were invited from the general population	27,548	60	36–64
Umeå	Participants were invited as a random sample of the population	25,728	52	30–60

Table 21 Self-rated health by centre in 3,399 incident cases of type 2 diabetes mellitus and 4,619 participants in the subcohort in the EPIC-InterAct study. Data shown are numbers of individuals (percentage).

Centre		Self-rated health			
		High		*Low*	
		Excellent	Good	Moderate	Poor
Bilthoven	Cases	13 (4.3)	184 (61.5)	73 (24.4)	29 (9.7)
	Subcohort	52 (9.0)	403 (70.0)	101 (17.5)	21 (3.6)
Cambridge	Cases	92 (12.3)	428 (57.1)	206 (27.5)	24 (3.2)
	Subcohort	159 (16.2)	624 (63.4)	170 (17.4)	23 (2.3)
Heidelberg	Cases	173 (23.1)	395 (52.8)	156 (20.9)	24 (3.2)
	Subcohort	286 (32.9)	448 (51.5)	125 (14.4)	11 (1.3)
Potsdam	Cases	118 (15.2)	460 (59.4)	171 (22.1)	26 (3.4)
	Subcohort	274 (23.1)	721 (60.9)	164 (13.9)	25 (2.1)
Umeå	Cases	155 (18.7)	369 (44.6)	236 (28.5)	67 (8.1)
	Subcohort	265 (26.2)	477 (47.1)	215 (21.2)	55 (5.4)

Table 32 Baseline characteristics of subcohort individuals in the EPIC-InterAct study by categories of self-rated health. Data are presented as mean and standard deviations (SD) for continuous variables and percentages and frequencies for categorical variables.

	Self-rated health								
	High				*Low*				
	Excellent		Good		Moderate		Poor		*p*-value for overall difference*
	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	
Technical/ professional school	34.6	351	35.0	910	29.6	224	32.3	42	
Secondary school	14.9	151	14.2	369	14.4	109	18.5	24	
Higher (incl. university degree)	31.3	317	26.4	688	18.1	137	18.5	24	
BMI (kg/m^2)	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	
Former	27.5	285	30.1	804	30.1	233	23.7	32	
Current	18.8	195	21.0	561	26.1	202	32.6	44	
Unknown	1.5	16	2.3	62	2.2	17	3.0	4	
Physical activity (%)									<0.001
Inactive	15.9	160	21.3	548	31.1	231	43.3	52	
Moderately inactive	33.2	335	31.7	818	28.8	214	29.2	35	
Moderately active	25.5	257	26.8	689	21.8	162	15.0	18	
Active	25.5	257	20.2	521	18.2	135	12.5	15	
Alcohol consumption (g/d)	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

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

Table ~~43~~ Pooled hazard ratios of incident T2DM comparing low (moderate or poor) versus high (excellent or good) self-related health.

	High self-rated health	**Low self-rated health**
	Pooled HR (95% CI)	Pooled HR (95% CI)*
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)	1.59 (1.41 to 1.80)
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 1.88)
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 hazard ratios calculated using a centre-stratified approach in combination with a random effects meta-analysis.

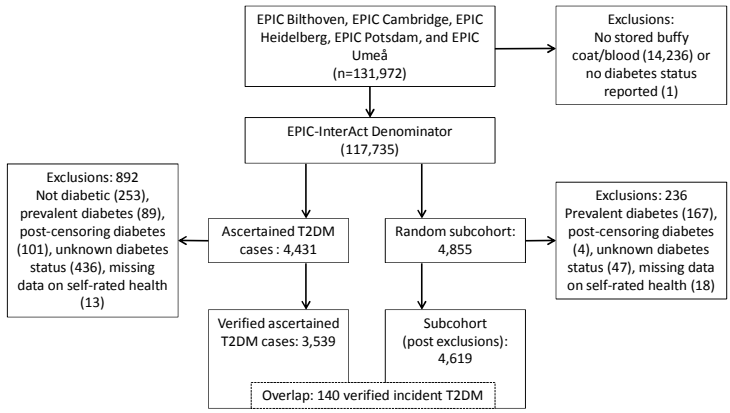

Figure 1 Overview of the five centres included in the study from the EPIC-InterAct study.

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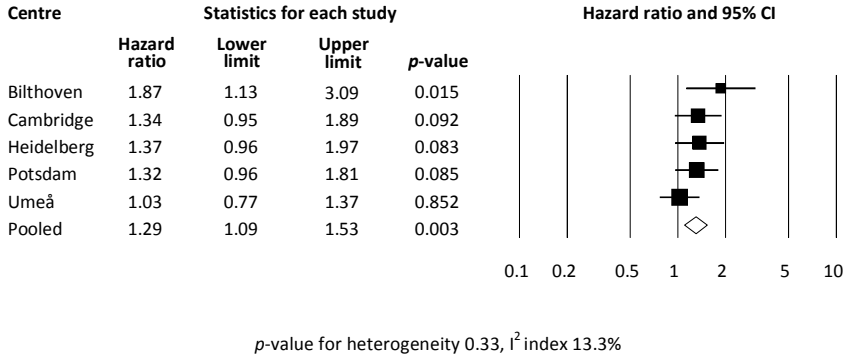

Figure 2~~1~~ Centre-specific and pooled hazard ratios of incident T2DM adjusted for the variables in the final model (age, sex, education, BMI, smoking, physical activity, alcohol consumption, energy intake and hypertension).

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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

Cambridge

Question: *How would you rate your general health?*

Response alternatives	Standardized
1 Excellent	1 Excellent
2 Good	2 Good
3 Moderate	3 Moderate
4 Poor	4 Poor

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

STROBE Statement—checklist of items that should be included in reports of observational 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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

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) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*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 cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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

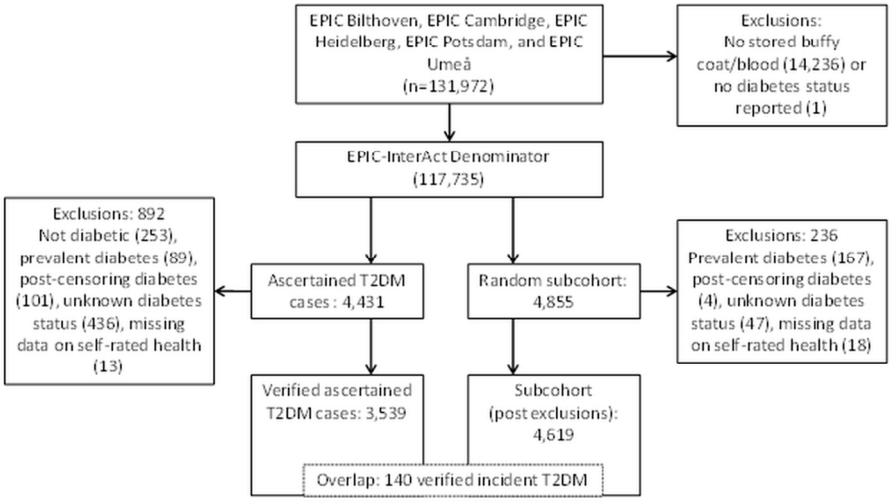

Figure 1 Overview of the five centres included in the study from the EPIC-InterAct study.

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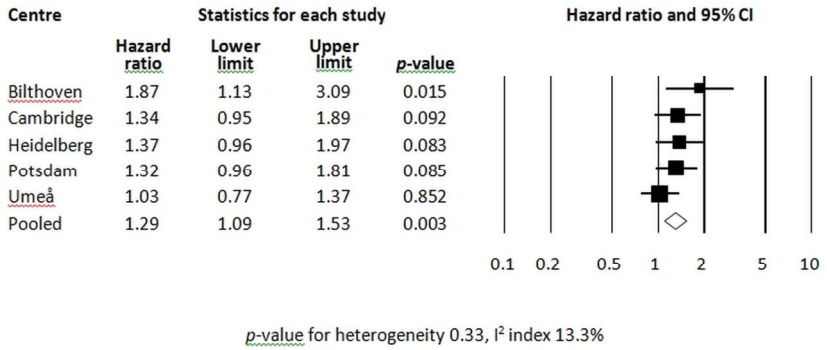

Figure 2 Centre-specific and pooled hazard ratios of incident T2DM adjusted for the variables in the final model (age, sex, education, BMI, smoking, physical activity, alcohol consumption, energy intake and hypertension).

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Appendix

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