BMJ Open

Education achievement and type 2 diabetes—what mediates the relationship in older adults? Data from the ESTHER study: a population-based cohort study

Christopher J Steele,[1,2] Ben Schöttker,[3,4] Adele H Marshall,[1,2] Anne Kouvonen,[5,6] Mark G O'Doherty,[1] Ute Mons,[3] Kai-Uwe Saum,[3] Paolo Boffetta,[7,8] Antonia Trichopoulou,[8,9] Hermann Brenner,[3,10] Frank Kee[1]

To cite: Steele CJ, Schöttker B, Marshall AH, *et al*. Education achievement and type 2 diabetes—what mediates the relationship in older adults? Data from the ESTHER study: a population-based cohort study. *BMJ Open* 2017;**7**:e013569. doi:10.1136/bmjopen-2016-013569

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-013569).

HB and FK contributed equally. CJS and BS contributed equally.

Received 21 July 2016
Revised 28 October 2016
Accepted 6 January 2017

For numbered affiliations see end of article.

Correspondence to
Christopher J Steele;
csteele09@qub.ac.uk

ABSTRACT

Objective The study aims to identify the mediating factors of the relationship between education achievement and incident type 2 diabetes mellitus (T2DM) in older adults.

Design Population-based cohort study.

Setting Participants were recruited from the German federal state of Saarland.

Participants Participants were excluded if they had prevalent T2DM or missing data on prevalent T2DM, missing or zero follow-up time for incident T2DM or were under 50 years of age. The total sample consisted of 7462 individuals aged 50–75 years (42.8% men, mean age 61.7 years) at baseline (2000–02). The median follow-up time was 8.0 years.

Methods Cox proportional hazards regression was initially used to determine the direct association between education achievement and incident T2DM. Using the Baron and Kenny approach, we then investigated the associations between education achievement and incident T2DM with the potential mediators. The contribution of each of the putative mediating variables was then calculated.

Results A clear socioeconomic gradient was observed with regard to T2DM incidence with the lowest educated individuals at a greater risk of developing the disease during the follow-up period: HR (95% CI) high education: 0.52 (0.34 to 0.80); medium education: 0.80 (0.66 to 0.96). Seven of the variables considered explained a proportion of the education–T2DM relationship (body mass index, alcohol consumption, hypertension, fasting triglycerides, high-density lipoprotein (HDL) cholesterol, physical activity and smoking status), where the contribution of the variables ranged from 1.0% to 17.7%. Overall, the mediators explained 31.7% of the relationship.

Conclusion By identifying the possible mediating factors of the relationship between education achievement and incident T2DM in older adults, the results of this study can be used to assist with the development of public health strategies that aim to reduce socioeconomic inequalities in T2DM.

Strengths and limitations of this study

- Few studies have assessed the mediating factors of the relationship between socioeconomic position (SEP) and type 2 diabetes mellitus (T2DM) in older adults specifically.
- Education was the only available indicator of SEP.
- Alternative SEP indicators, such as income and occupation, could not be investigated.
- Using a well-established method, our mediation analysis points to possible mechanisms underlying the relationship between education achievement and T2DM in a population-based cohort study of older adults.
- The results of this study can be used to help target intervention strategies which aim to reduce the socioeconomic inequalities in T2DM incidence in older adults.

INTRODUCTION

Globally, the prevalence of type 2 diabetes mellitus (T2DM) is growing at an alarming rate. The International Diabetes Federation has predicted that the world's diabetic population will rise from 415 million in 2014 to 642 million by the year 2040[1] and states that one in two people with diabetes do not know that they have the disease.[2] The rapid ageing of the world's population coupled with the global rise in obesity rates means that the overwhelming majority of new diabetes cases will be T2DM.

Although the prevalence of T2DM is rising in all socioeconomic groups, the epidemic is increasing at a greater rate among individuals from a lower socioeconomic position (SEP).[3] An inverse association between SEP and the risk of T2DM has been found in various studies where the majority of these

use education, occupation or income to measure SEP.[4–6] Demakakos and colleagues[5] found that lower SEP was associated with an increased risk of T2DM in older adults. In 2011, Agardh *et al*[7] conducted a systematic review and meta-analysis of the association between SEP and T2DM. In the 23 studies used in the meta-analysis, low levels of all three SEP indicators were associated with an increased risk of T2DM.

Given the social gradient, uncovering mechanisms that underlie the relationship between SEP and T2DM remains a key research agenda. Williams *et al*[8] investigated the mediating role of health behaviours using data from the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). In their analysis, mediation was tested and used to identify the influence of health behaviours on the relationship between SEP and impaired glucose metabolism. In particular, it was found that smoking and physical activity partly mediated the association between education and T2DM. Hence, by identifying these modifiable risk factors of T2DM, the study highlights how public health interventions could target those at high risk of developing T2DM. On the other hand, Lee *et al*[9] examined potential mediating factors of the relationship between SEP and T2DM using data from the Women's Health Study, but this and several other earlier studies used less robust methods to demonstrate mediation.[10 11] These studies simply compared regression models with and without the risk factor of interest and conclusions were drawn regarding mediation based on this comparison, without ascertaining whether statistically significant associations between T2DM and SEP were present.

It has been recognised that knowledge relating to how SEP is associated with T2DM in older adults is limited. Few previous studies have focused on older people[5] and thus, even though some have identified risk factors that significantly affect the SEP gradient in T2DM incidence in adults,[8 10 11] no specific conclusions concerning older adults can be made from these studies. The aim of this current study was to investigate the potential mediating factors of the SEP–T2DM relationship in a large cohort of older adults.

METHODS

Study population

This analysis is based on the ESTHER study, an ongoing population-based cohort study set up with the aim of improving the prevention, early detection and treatment of chronic diseases in older adults. In total, 9949 men and women aged between 50 and 75 years were recruited during a routine health check-up by their general practitioner (GP) between June 2000 and December 2002 in the federal state of Saarland, Germany. Each participant of the ESTHER study completed a comprehensive health questionnaire and was invited to undertake a personal interview and medical assessment carried out by a trained study physician. Through the completion of the standardised study questionnaire and medical assessment, comprehensive information was collected on sociodemographic, medical and lifestyle factors. Further details of the ESTHER study have been reported elsewhere.[12–14] Participants were excluded if they had prevalent T2DM or missing data on prevalent T2DM (prevalent, n=1444; missing, n=119), missing or zero follow-up time for incident T2DM (zero follow-up, n=412; missing, n=10) or were under 50 years of age (n=17). Additionally, individuals with glycated hemoglobin (HbA_{1c}) >6.4% or fasting glucose >125 mg/dL were excluded to deal with the issue of potential undiagnosed T2DM (n=485). Hence, the final sample size consisted of 7462 individuals.

Education

During this study, education is used as the main indicator of SEP. Unfortunately, other traditional indicators of SEP, such as income or occupation, were not available in sufficient detail for meaningful analyses. However, using education as an indicator of SEP has various advantages. Information regarding an individual's level of education is generally available for both men and women and excludes few individuals in the population. There is also a strong association between education and the prospect of future success. Higher levels of education generally lead to better jobs, higher income and better housing, neighbourhood and working conditions.[15] Moreover, education is easy to measure in self-administered questionnaires and gives a high response rate, which is not the case with many other indicators of SEP.[16] Participants were asked in the baseline questionnaire to state the highest level of education that they had ever completed. Education was categorised into three groups: low (0–9 years), medium (10–12 years) and high education (≥13 years).

Type 2 diabetes mellitus

Diagnosis of T2DM at baseline was confirmed by a documented diagnosis by the GP at the health check-up or prescribed use of antidiabetic drugs. Information was also collected at baseline on whether or not a first-degree relative had a diagnosis of diabetes. Diabetes incidence was ascertained by four different sources as described previously.[17] Study participants were asked in mailed standardised questionnaires at 2-year, 5-year and 8-year follow-up to document currently prescribed drugs (source 1: drugs of Anatomical Therapeutic Chemical (ATC) code A10 'Drugs used in diabetes') and to answer the question whether diabetes had been diagnosed after the baseline examination (source 2). The questionnaire response rates at 2-year, 5-year and 8-year follow-up were 95.6%, 87.3% and 78.3%, respectively. All self-reported diabetes diagnoses were validated by standardised questionnaires sent to the study participants' GPs and the validated self-reports were confirmed in 90% of cases. In addition, to minimise under-reporting by study participants, all study participants' GPs were asked at 8-year follow-up for new diabetes diagnoses made during the last 3 years (source 3). To identify undiagnosed incident diabetes cases, HbA_{1c} was measured at 8-year follow-up

(source 4: HbA_{1c} ≥6.5%). The response rate for blood sample donation at the 8-year follow-up was 53.3%. HbA_{1c} was measured from baseline EDTA blood by high-performance liquid chromatography (HPLC) and measured at the 8-year recontact by immunoturbidimetry.[17] Self-report was the only source of information for 16% of the incident cases and most diagnoses were identified by more than one source.

Potential mediators

Height and weight were measured and documented during the health check-up with a few missing values filled in using self-reported information. Body mass index (BMI) was categorised as underweight (<18.5 kg/m2), normal (≥18.5 kg/m^2–<25 kg/m^2), overweight (≥25 kg/m^2–<30 kg/m^2) and obese (≥30 kg/m^2).[18] Serum blood samples were collected and stored at −80°C. C reactive protein (CRP) and total/HDL-cholesterol levels were measured using turbidimetry and routine HPLC, respectively. Fasting triglycerides were measured using routine HPLC methods. Blood pressure was measured during the health check-up. Physical activity was defined as performing vigorous exercise at least once per week (yes/no) and smoking status was grouped into three categories (never smoker/former smoker/current smoker). Fruit, vegetable and multivitamin supplement use were categorised as daily consumption (yes/no) and meat consumption was categorised as consumption at least once per week (yes/no). Alcohol consumption was categorised using intake in grams/day (men: 0, >0–<40, ≥40–<60, ≥60, women: 0, >0–<20, ≥20–<40, ≥40) and hypertension was based on measured blood pressure and/or hypertensive drug use (yes=hypertensive drug treatment or systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg; no=no/missing hypertensive drug treatment and systolic blood pressure ≤140 mm Hg and diastolic blood pressure ≤90 mm Hg). The percentage of data missing, after exclusion criteria were applied, was as follows: alcohol consumption (9.0%), age (0%), BMI (0.1%), CRP (1.7%), education (2.1%), family history of diabetes (1.6%), fasting glucose (13.8%), fasting triglycerides (10.8%), fruit consumption (2.8%), gender (0%), HbA_{1c} (0.7%), HDL-cholesterol (37.6%), hypertension (1.7%), meat consumption (5.3%), multivitamin supplement consumption (4.7%), smoking status (2.6%), total cholesterol (0.4%), vegetable consumption (2.1%) and vigorous physical activity (0.2%).

Statistical analysis

Following the model of Baron and Kenny,[19] we first determined the direct association between education and incident T2DM (step 1; using Cox proportional hazards regression). We then investigated the association between education and the baseline potential mediators (step 2; using linear regression for continuous variables and logistic regression for categorical variables) before examining the association between the potential baseline mediators and incident T2DM (step 3; using Cox proportional hazards regression). Finally, we investigated the contribution of each individual mediating factor on the relationship between education and incident T2DM (step 4; using Cox proportional hazards regression). The following formula was used to calculate the magnitude of change in the HR for incident diabetes explained by the individual mediating factor:

$$(HR_{\text{base model}}-HR_{\text{adjusted model}})/(HR_{\text{base model}}-1)\times 100\%,$$

where the base model was adjusted for age, gender and family history of diabetes. Specifically, the mediated percentage was evaluated using the magnitude of change in HR for individuals in the highest educational category compared with individuals in the lowest educational category. The individual risk factors that met all the steps of the Baron and Kenny model were identified as mediators of the relationship between education achievement and T2DM. Analyses were conducted using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA).

Multiple imputation by chained equations[20] was used to deal with missing data in the original data sets using all available information in the imputation model.[13] Five imputed data sets were derived and the results were combined in the analysis where the multiple imputation procedure was carried out using STATA IC V.11.0 (StataCorp, Texas, USA). The results of the analysis using the original ESTHER data are given in the online supplementary material. In the tables presented, individuals with missing information on any of the variables involved in the given statistical model were excluded. In other words, only complete cases were considered where the number of missing observations in each statistical model is also provided in the online supplementary material.

RESULTS

Baseline characteristics

Using the original baseline data before performing the multiple imputation procedure, table 1 and table 2 display the distribution of baseline variables considered for mediation across individuals with and without incident T2DM and across levels of education, respectively. Note that table 1 reports 7462 eligible participants since all individuals had available information on incident T2DM after the exclusion criteria were applied. However, after these exclusions were made, 156 participants had missing information regarding education, resulting in 7306 eligible participants for investigation during table 2. In total, the study period consisted of 53 101 person-years of follow-up (the median follow-up, 8.0 years) during which 718 of the 7462 included individuals developed T2DM. Expected differences in T2DM incidence were observed across educational level, BMI categories, hypertension and family history of diabetes. Furthermore, individuals with incident T2DM had significantly lower HDL-cholesterol levels and had a significantly higher total/HDL-cholesterol ratio. Differences in T2DM incidence were observed across alcohol consumption and

Table 1 Distribution of baseline variables in participants with and without incident type 2 diabetes mellitus (T2DM)

Characteristic*	Eligible participants, n=7462		
	No incident T2DM	Incident T2DM	p Value
% in each category	90.4	9.6	–
Age, mean (SD)	61.7 (6.6)	61.9 (6.5)	0.3521
Alcohol consumption (%)			<0.0001
Abstainer	28.8	37.1	
Light	68.9	61.8	
Moderate	2.1	0.9	
Heavy	0.3	0.2	
Body mass index (BMI) (%)			<0.0001
Underweight	0.4	0.6	
Normal	31.9	13.5	
Overweight	47.8	47.3	
Obese	20.0	38.6	
C reactive protein (CRP) (mg/L), median (IQR)	1.9 (0.9–4.0)	2.6 (1.3–5.1)	<0.0001
Daily consumption of fruit (%)	63.1	58.3	0.0130
Daily consumption of multivitamin supplements (%)	15.8	16.8	0.5100
Daily consumption of vegetables (%)	35.5	35.7	0.9312
Education (%)			0.0021
Low	72.5	78.0	
Medium	22.0	19.0	
High	5.4	3.0	
Family history of diabetes (%)	34.3	43.8	<0.0001
Fasting triglycerides (mmol/L), median (IQR)	1.2 (0.8–1.7)	1.5 (1.0–2.1)	<0.0001
HDL-cholesterol (mmol/L), mean (SD)	1.4 (0.4)	1.3 (0.4)	<0.0001
Hypertension (%)	55.5	68.9	<0.0001
Sex, men (%)	42.6	45.4	0.1448
Smoking status (%)			0.0077
Never smoker	52.4	46.2	
Former smoker	31.4	35.7	
Current smoker	16.3	18.1	
Total/HDL-cholesterol ratio, mean (SD)	4.3 (1.5)	4.7 (1.7)	<0.0001
Total cholesterol (mmol/L), mean (SD)	5.7 (1.3)	5.7 (1.4)	0.3726
Vigorous physical activity (%)	44.6	40.8	0.0543
Weekly consumption of meat (%)	88.7	90.8	0.0929

*Missing values: alcohol consumption 669, BMI 7, CRP 130, daily consumption of fruit 206, daily consumption of multivitamin supplements 349, daily consumption of vegetables 158, education 156, family history of diabetes 122, fasting triglycerides 804, HDL-cholesterol 2805, hypertension 128, smoking status 197, total/HDL-cholesterol ratio 2828, total cholesterol 30, vigorous physical activity 17 and weekly consumption of meat 393.

smoking categories where participants with incident T2DM were more often former or current smokers and alcohol abstainers. However, the majority of individuals with incident T2DM were alcohol drinkers (mild, moderate or heavy). Participants with incident T2DM also consumed fruit less often. Moreover, higher median levels of CRP and fasting triglycerides were observed among individuals with incident T2DM. A clear educational gradient was observed with regard to T2DM incidence where 5.5% of highly educated individuals developed the disease in comparison with 8.4% and 10.2% of participants in the medium and low educational categories, respectively.

Education achievement, incident T2DM and mediating factors

Using the imputed data, the association between education and the incidence of T2DM was determined using Cox proportional hazards regression (step 1). It was found

Table 2 Baseline characteristics by education level

Characteristic*	Eligible participants, n=7306			p Value
	Low education	Medium education	High education	
% in each category	73.1	21.7	5.2	
Age, mean (SD)	62.0 (6.4)	60.8 (6.9)	60.6 (7.0)	<0.0001
Alcohol consumption (%)				<0.0001
Abstainer	32.7	22.0	17.5	
Light	65.3	75.1	78.1	
Moderate	1.7	2.6	3.8	
Heavy	0.2	0.4	0.6	
Body mass index (BMI) (%)				<0.0001
Underweight	0.5	0.3	0.8	
Normal	27.5	36.1	43.7	
Overweight	48.5	46.9	40.1	
Obese	23.6	16.7	14.5	
C reactive protein (CRP) (mg/L), median (IQR)	2.0 (1.0–4.4)	1.7 (0.8–3.5)	1.3 (0.7–2.8)	0.0004
Daily consumption of fruit (%)	62.3	64.0	64.5	0.3520
Daily consumption of multivitamin supplements (%)	14.1	20.3	21.7	<0.0001
Daily consumption of vegetables (%)	33.7	39.5	44.7	<0.0001
Family history of diabetes (%)	36.8	31.9	28.7	<0.0001
Fasting triglycerides (mmol/L), median (IQR)	1.2 (0.9–1.8)	1.2 (0.8–1.6)	1.2 (0.8–1.7)	0.0175
HDL-cholesterol (mmol/L), mean (SD)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	0.4614
Hypertension (%)	58.6	52.8	47.0	<0.0001
Incident type 2 diabetes mellitus (T2DM) (%)	10.2	8.4	5.5	0.0021
Sex, men (%)	40.6	46.5	59.5	<0.0001
Smoking status (%)				0.0004
Never smoker	53.0	48.8	47.5	
Former smoker	30.3	36.0	35.0	
Current smoker	16.8	15.3	17.5	
Total/HDL-cholesterol ratio, mean (SD)	4.3 (1.5)	4.3 (1.6)	4.4 (1.5)	0.9251
Total cholesterol (mmol/L), mean (SD)	5.7 (1.3)	5.7 (1.3)	5.7 (1.3)	0.5097
Vigorous physical activity (%)	40.9	52.8	60.0	<0.0001
Weekly consumption of meat (%)	89.2	88.2	87.5	0.3571

*Missing values: age 156, alcohol consumption 762, BMI 163, CRP 285, daily consumption of fruit 368, daily consumption of multivitamin supplements 469, daily consumption of vegetables 281, education 156, family history of diabetes 255, fasting triglycerides 948, HDL-cholesterol 2889, hypertension 282, incident T2DM 156, sex 156, smoking status 328, total/HDL-cholesterol ratio 2912, total cholesterol 186, vigorous physical activity 156 and weekly consumption of meat 504.

that the hazard of incident T2DM decreased as the level of education increased even after adjustment for age, gender and family history of diabetes (base model variables): HR (95% CI) high education 0.52 (0.34 to 0.80); medium education 0.80 (0.66 to 0.96) (see online supplementary table 2). The results of performing step 1 using the original data are presented in online supplementary table 1.

The associations between education and the potential mediating factors were tested in step 2 and are displayed in table 3. It was found that there was a significant association between education and the majority of the factors considered for mediation. Significant trends were observed across educational categories for BMI, physical activity, fruit and vegetable consumption, multivitamin supplement use and hypertension after adjustment for the base model variables. Individuals in the lowest education category were significantly more likely to be obese and have hypertension. Conversely, participants from the highest education level were significantly more likely to partake in vigorous physical activity at least once a week and consume fruit, vegetables and multivitamin supplements daily. Those in the lowest education category were more likely to have higher BMI, CRP and fasting triglycerides. Conversely, those with highest education had higher alcohol consumption and HDL-cholesterol. Furthermore, no significant relationship between education groups was

Table 3 Mediation step 2 showing the relationships between education and potential categorical mediators

Characteristic	OR (95% CI)	p Value*
Body mass index		
Overweight (yes†/no)		
Low education†	1.00	
Medium education	0.67 (0.59 to 0.75)	<0.0001
High education	0.44 (0.36 to 0.55)	<0.0001
p trend	<0.0001	
Obesity (yes†/no)		
Low education†	1.00	
Medium education	0.65 (0.56 to 0.75)	<0.0001
High education	0.56 (0.41 to 0.75)	0.0001
p trend	<0.0001	
Current smoker (yes†/no)		
Low education†	1.00	
Medium education	0.91 (0.83 to 1.45)	0.5345
High education	0.89 (0.65 to 1.20)	0.4417
p trend	0.0402	
Fruit consumption (yes†/no)		
Low education†	1.00	
Medium education	1.18 (1.05 to 1.33)	0.0072
High education	1.34 (1.07 to 1.67)	0.0097
p trend	0.0005	
Hypertension (yes†/no)		
Low education†	1.00	
Medium education	0.85 (0.75 to 0.95)	0.0050
High education	0.66 (0.53 to 0.82)	0.0002
p trend	<0.0001	
Meat consumption (yes†/no)		
Low education†	1.00	
Medium education	0.88 (0.73 to 1.07)	0.2100
High education	0.75 (0.54 to 1.05)	0.0892
p trend	0.0607	
Multivitamin consumption (yes†/no)		
Low education†	1.00	
Medium education	1.63 (1.41 to 1.89)	<0.0001
High education	1.88 (1.45 to 2.44)	<0.0001
p trend	<0.0001	
Physical activity (yes†/no)		
Low education†	1.00	
Medium education	1.50 (1.33 to 1.69)	<0.0001
High education	1.87 (1.50 to 2.32)	<0.0001
p trend	<0.0001	
Vegetable consumption (yes†/no)		
Low education†	1.00	
Medium education	1.35 (1.20 to 1.52)	<0.0001
High education	1.83 (1.48 to 2.28)	<0.0001
p trend	<0.0001	

*Adjusted for education, age, gender and family history of diabetes.
†Indicates reference category.

observed with total cholesterol or total/HDL-cholesterol ratio. Online supplementary table 3 displays the results of mediation step 2 when performed on the original data. Additional results, showing the association between education and potential mediators, obtained using multinomial logistic regression are presented in online supplementary tables 4 and 5 for the original and imputed data, respectively. Furthermore, online supplementary tables 6 and 7 display associations between education and potential continuous mediating factors obtained using linear regression for the original and imputed data, respectively.

Table 4 displays the HRs and associated 95% CIs for the associations between potential mediators and T2DM. The hazard of incident T2DM was significantly greater for individuals who were obese or former/current smokers. Abstainers and individuals who had hypertension were also at a greater risk of T2DM, while participants who exercised vigorously at least once per week were significantly less likely to develop the disease during the follow-up period. Higher levels of fasting triglycerides were associated with a significant increase in T2DM risk. Conversely, T2DM risk was decreased for individuals with higher levels of HDL-cholesterol. Unit increases in total/HDL-cholesterol ratio also proved to be significantly associated with an increase in the hazard of T2DM. The results of step 3 using the original data are presented in supplementary table 8 .

The results of the step 4 of the mediation analysis are displayed in table 5, where only the individual risk factors shown to be mediators were included. To calculate the percentage of the education–T2DM relationship explained by the mediating factors, each mediator was considered one at a time in separate Cox proportional hazards models adjusted for age, gender and family history of diabetes. It was found that BMI contributed the largest effect on the relationship between education and T2DM and cumulatively the mediators explained 32% of the relationship. In the full model, the association between education and incident T2DM was no longer statistically significant: HR (95% CI) high education 0.67 (0.43 to 1.04); medium education 0.92 (0.76 to1.12).

Table 4 Mediation step 3 showing the relationships between potential mediators and incident type 2 diabetes mellitus

Characteristic	HR (95% CI)	p Value*
Alcohol consumption		
Light†	1.00	
Abstainer	1.47 (1.24 to 1.74)	<0.0001
Moderate	0.59 (0.26 to 1.33)	0.2040
Heavy	0.69 (0.09 to 4.97)	0.7152
Body mass index (BMI)		
Overweight (yes/no†)	2.63 (2.13 to 3.26)	<0.0001
Obesity (yes/no†)	2.21 (1.90 to 2.57)	<0.0001
Continuous BMI (per 1 kg/m^2 increase)	1.10 (1.09 to 1.12)	<0.0001
Continuous alcohol (per 1 g increase)	0.98 (0.97 to 0.99)	0.0029
C reactive protein (per 1 mg/L increase)	1.01 (1.00 to 1.01)	0.1037
Current smoker (yes/no†)	1.23 (1.01 to 1.50)	0.0391
Daily consumption of fruit (yes/no†)	0.87 (0.74 to 1.01)	0.0672
Daily consumption of multivitamin supplements (yes/no†)	1.06 (0.86 to 1.30)	0.5689
Daily consumption of vegetables (yes/no†)	1.07 (0.92 to 1.25)	0.3917
Fasting triglycerides (per 1 mmoL/L increase)	1.32 (1.24 to 1.41)	<0.0001
HDL-cholesterol (per 1 mmoL/L increase)	0.53 (0.41 to 0.68)	<0.0001
Hypertension (yes/no†)	1.71 (1.45 to 2.01)	<0.0001
Smoking status		
Never smoker†	1.00	
Former smoker	1.32 (1.11 to 1.57)	0.0021
Current smoker	1.38 (1.12 to 1.71)	0.0027
Total/HDL-cholesterol ratio (per 1 unit increase)	1.10 (1.05 to 1.15)	<0.0001
Total cholesterol (per 1 mmoL/L increase)	0.99 (0.94 to 1.05)	0.8483
Vigorous physical activity (yes/no†)	0.85 (0.73 to 0.99)	0.0340
Weekly consumption of meat (yes/no†)	1.16 (0.89 to 1.52)	0.2676

*Adjusted for education, age, gender and family history of diabetes.
†Indicates reference category where appropriate.

DISCUSSION

In this population-based cohort study of older adults, we showed that the risk of T2DM increased as the educational level of participants decreased. This educational gradient is consistent with the findings of various other studies. The European Prospective Investigation into Cancer and Nutrition (EPIC) InterAct study[21] showed that the association between low educational level and the higher risk of T2DM was consistent across all examined eight Western European countries. However, a large number of previous studies used self-reported T2DM as the outcome and are thus less reliable than the medically documented T2DM cases obtained in the present study.[4 5 9 22] It has been concluded that self-reported cases of diabetes are reported with a high level of accuracy, where the accuracy improves with increasing levels of education.[23] However, due to high rates of undiagnosed diabetes, a rate which is potentially higher among individuals from low education,[22] the use of self-reported diabetes cases may under-represent undiagnosed individuals or individuals who have been diagnosed but are under-reported.[24] This issue is highlighted in the USA where approximately one-third of adults are undiagnosed.[25] Furthermore, the impact of these issues concerning the under-representation of individuals with diabetes would be observed the most among individuals from low education. This could potentially contribute to educational health disparities being more marked among diagnosed individuals compared with among the whole population of individuals with diabetes.[24]

The next step of the mediation analysis examined the association between education and each of the potential mediators before investigating the impact of the potential mediators on T2DM incidence. Expected differences across education categories were observed for BMI, physical activity and hypertension. Shaw and Spokane[26] found that a steeper decline in physical activity levels existed among individuals with less education. A number of earlier studies have also highlighted educational differences in hypertension.[27–29] Highly educated individuals were more likely to consume fruit and vegetables daily, agreeing with previous research showing that education provides greater knowledge about healthy behaviours.[30] It was shown that individuals within higher levels of education were less likely to be current smokers and a significant increase in mean alcohol consumption was observed with increasing education. Although the relationship between T2DM and fruit and vegetable intake was not significant in ESTHER, a meta-analysis by Li *et al*[31] concluded that higher fruit or green leafy vegetable intake is significantly associated with a reduced risk of T2DM. However, research concerning the association between fruit and vegetable consumption and T2DM in older adults is relatively sparse. It is also important to note that the ESTHER population was born around the time of World War II. Hence, the results of this study may reflect cohort-specific effects. Selection bias may also be an issue. For instance, differential mortality patterns across smoking categories might lead to an under-representation of smokers and thus to an attenuation of the socioeconomic gradient in smoking in older adults.

Table 5 Mediation step 4 showing the percentage of the education–incident type 2 diabetes mellitus association that is explained by the individual mediator

Model	Referent	HR (95% CI), p Value	HR (95% CI), p Value	p trend	Mediated percentage (95% CI)
	Low education	Medium education	High education		
Base*	1.00	0.80 (0.66 to 0.96), 0.0181	0.52 (0.34 to 0.80), 0.0028	0.0002	–
+Body mass index (BMI)	1.00	0.88 (0.73 to 1.06), 0.1821	0.60 (0.39 to 0.93), 0.0219	0.0130	17.7 (8.3 to 65.3)
+Alcohol consumption	1.00	0.83 (0.69 to 1.01), 0.0574	0.55 (0.35 to 0.84), 0.0063	0.0015	6.1 (2.8 to 23.0)
+Hypertension	1.00	0.80 (0.66 to 0.97), 0.0232	0.54 (0.35 to 0.84), 0.0055	0.0006	5.2 (2.4 to 19.1)
+Fasting triglycerides	1.00	0.81 (0.67 to 0.98), 0.0279	0.54 (0.35 to 0.83), 0.0051	0.0006	4.5 (2.1 to 16.8)
+HDL-cholesterol	1.00	0.80 (0.66 to 0.97), 0.0225	0.53 (0.35 to 0.82), 0.0042	0.0004	3.0 (1.4 to 11.2)
+Physical activity	1.00	0.81 (0.67 to 0.98), 0.0278	0.53 (0.34 to 0.82), 0.0042	0.0005	2.9 (1.3 to 10.8)
+Smoking status	1.00	0.79 (0.65 to 0.96), 0.0161	0.52 (0.34 to 0.80), 0.0032	0.0002	1.0 (0.5 to 3.9)
Full†	1.00	0.92 (0.76 to 1.12), 0.3947	0.67 (0.43 to 1.04), 0.0722	0.0699	31.7 (14.7 to 118.1)

*Base model adjusted for age, gender and family history of diabetes.
†Full model adjusted for age, gender, family history of diabetes, BMI, alcohol consumption, hypertension, fasting triglycerides, HDL-cholesterol, physical activity and smoking status.
+ Shows the addition of an additional variable to the base model.

The mediation analysis highlighted seven risk factors that explained a proportion of the relationship between education and T2DM with BMI providing the largest contribution. Previously, Lee *et al*[9] also found that BMI explained the largest proportion of the association between education and T2DM. Previous studies have adopted several statistical approaches to demonstrate mediation, some more robust than others.[10 11] However, Williams *et al*[8] used the Baron and Kenny method to conclude that 27% of the relationship could be explained by health behaviours in a population consisting of adults aged 25 years and above. Our study adds to this research by providing a mediation analysis of the relationship in older adults and by exploring a greater number of potential mediators. It is clear that BMI remains a vital factor in the development of T2DM in older adults. Our results also showed that alcohol consumption and hypertension play considerable roles in explaining the relationship in older adults. This is consistent with the findings from the Women's Health Study. However, there are also some contrasting results between the two studies. For example, CRP explained 18% of the relationship in the study by Lee *et al*,[9] whereas it was not shown to mediate the relationship in the present study. Furthermore, the potential mediators considered by Lee *et al*[9] explained 92% of the relationship between education and T2DM. However, as highlighted previously, this study did not use a robust methodology to infer mediation meaning that this percentage could overestimate the true contribution of the risk factors. In our study, only 32% of the relationship was explained. This highlights that additional pathways must exist with regard to how SEP influences T2DM and factors such as neighbourhood conditions, working conditions, income, race, stress and depression have been suggested.[30 32] Another possible explanation for the reduced mediated percentage is that some of the potential mediators were not assessed in sufficient detail due to the nature in which the data were collected. For instance, physical activity was included in this analysis as a dichotomous variable representing vigorous physical activity at least once per week (yes/no). However, this categorisation of the variable does not capture the influence that different levels of exercise may have.

A possible shortcoming of our analysis is that using the Baron and Kenny approach to mediation does not explicitly invoke the modern counterfactual framework that distinguishes controlled direct and indirect effects. Under such a framework, the causal effects of interest are defined as contrasts of potential outcomes or a contrast of outcomes that would be observed under different exposure and mediator values.[33] However, serious questions have been raised about the utility for policy of this counterfactual approach to mediation.[34] To the extent that any method must rely on untestable assumptions about the absence of exposure-outcome, mediator-outcome and exposure-mediator confounding, the superiority and utility of counterfactual mediation models are not obvious.[35]

We believe that the results of this analysis can help identify possible targets of intervention that may help to reduce socioeconomic inequalities in T2DM in older adults. Given our findings, it would be reasonable to surmise that public health programmes designed to prevent obesity in the population might have a beneficial effect on socioeconomic disparities in T2DM incidence. The total incidence of T2DM would fall, as demonstrated in a study by Franco *et al*[36] looking at the special case of Cuba after their economic crisis in the 1990s, but even if the relative decline from a population-level BMI intervention was equal in each SEP group, the lowest SEP groups would gain most in absolute terms. However, we must emphasise that generalising about intervention effects from observational studies is fraught

with difficulties. While the literature on the disparate effects of vitamin supplements on cardiovascular health is telling in this regard,[37] there may be some circumstances when the public health effects of observational and intervention studies are in reasonable accord.[38 39] While observational studies may lack internal validity for imputing intervention effects, intervention trials may lack external validity or be dependent on context[40] and, with due circumspection, both can have value.[41] In addition, just as it is impossible to have certainty about mediation in an individual subject, targeted behavioural interventions for individuals to reduce BMI come with a risk of intervention-generated inequality.[42] However, it is likely that population programmes to maintain healthy weight will have beneficial effects on other biological risk factors and putative mediators of diabetes incidence.[43]

Author affiliations
[1]UKCRC Centre of Excellence for Public Health, Queen's University Belfast, Belfast, UK
[2]Centre for Statistical Science and Operational Research (CenSSOR), Queen's University Belfast, Belfast, UK
[3]German Cancer Research Center (DKFZ), Heidelberg, Germany
[4]Institute of Health Care and Social Sciences, FOM Hochschule, Essen, Germany
[5]Social Research, University of Helsinki, Helsinki, Finland
[6]Faculty in Wroclaw, SWPS University of Social Sciences and Humanities, Wroclaw, Poland
[7]The Tisch Cancer Institute and Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[8]Hellenic Health Foundation, Athens, Greece
[9]Department of Hygiene and Epidemiology, University of Athens, Medical School, Athens, Greece
[10]Network Aging Research, University of Heidelberg, Heidelberg, Germany

Contributors CJS directed the implementation of the study, performed the data analysis and drafted the article. BS contributed invaluable feedback and guidance on the direction of the study and was highly influential in the data collection process. The paper comprises joint first authorship between CJS and BS. BS, UM, KUS and HB contributed to the acquisition of data. BS, AHM, AK, MGO'D, UM, PB, AT, HB and FK contributed to designing the study, interpreting findings, reviewing the article and revising it critically for important intellectual content. All authors approved the manuscript submission for publication.

Competing interests None declared.

Ethics approval The ESTHER study was approved by the ethics committees of the Medical Faculty, University of Heidelberg and of the Medical Association of Saarland and is conducted in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available.

REFERENCES

1. International Diabetes Federation. *IDF diabetes*. 7 ed. Brussels, Belgium: International Diabetes Federation, 2015. http://www.diabetesatlas.org.
2. International Diabetes Federation. *IDF diabetes atlas update poster*. 6th edn. Brussels, Belgium: International Diabetes Federation, 2014. http://www.idf.org/sites/default/files/Atlas-poster-2014_EN.pdf
3. Mokdad AH, Ford ES, Bowman BA, *et al*. Diabetes trends in the U.S.: 1990-1998. *Diabetes Care* 2000;23:1278–83.
4. Maty SC, Everson-Rose SA, Haan MN, *et al*. Education, income, occupation, and the 34-year incidence (1965-99) of type 2 diabetes in the alameda county study. *Int J Epidemiol* 2005;34:1274–81.
5. Demakakos P, Marmot M, Steptoe A. Socioeconomic position and the incidence of type 2 diabetes: the ELSA study. *Eur J Epidemiol* 2012;27:367–78.
6. Robbins JM, Vaccarino V, Zhang H, *et al*. Socioeconomic status and diagnosed diabetes incidence. *Diabetes Res Clin Pract* 2005;68:230–6.
7. Agardh E, Allebeck P, Hallqvist J, *et al*. Type 2 diabetes incidence and socio-economic position: a systematic review and meta-analysis. *Int J Epidemiol* 2011;40:804–18.
8. Williams ED, Tapp RJ, Magliano DJ, *et al*. Health behaviours, socioeconomic status and diabetes incidence: the australian diabetes obesity and lifestyle study (AusDiab). *Diabetologia* 2010;53:2538–45.
9. Lee TC, Glynn RJ, Peña JM, *et al*. Socioeconomic status and incident type 2 diabetes mellitus: data from the women's Health Study. *PLoS One* 2011;6:e27670.
10. Kumari M, Head J, Marmot M. Prospective study of social and other risk factors for incidence of type 2 diabetes in the whitehall II study. *Arch Intern Med* 2004;164:1873–80.
11. Krishnan S, Cozier YC, Rosenberg L, *et al*. Socioeconomic status and incidence of type 2 diabetes: results from the black women's Health Study. *Am J Epidemiol* 2010;171:564–70.
12. Raum E, Rothenbacher D, Löw M, *et al*. Changes of cardiovascular risk factors and their implications in subsequent birth cohorts of older adults in Germany: a life course approach. *Eur J Cardiovasc Prev Rehabil* 2007;14:809–14.
13. Schöttker B, Haug U, Schomburg L, *et al*. Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study. *Am J Clin Nutr* 2013;97:782–93.
14. Schöttker B, Raum E, Rothenbacher D, *et al*. Prognostic value of haemoglobin A1c and fasting plasma glucose for incident diabetes and implications for screening. *Eur J Epidemiol* 2011;26:779–87.
15. Lynch JW, Kaplan GA. Socioeconomic Factors. In: Berkman LF, Kawachi I, eds. *Social epidemiology*. New York: Oxford University Press, 2000:p. 13–35.
16. Liberatos P, Link BG, Kelsey JL. The measurement of social class in epidemiology. *Epidemiol Rev* 1988;10:87–121.
17. Schöttker B, Herder C, Rothenbacher D, *et al*. Serum 25-hydroxyvitamin D levels and incident diabetes mellitus type 2: a competing risk analysis in a large population-based cohort of older adults. *Eur J Epidemiol* 2013;28:267–75.
18. World Health Organisation. Global database on body mass index. 2015 http://apps.who.int/bmi/index.jsp?introPage=intro_3.html
19. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986;51:1173–82.
20. Royston P. Multiple imputation of missing values: update of ice. *Stata J* 2005;5:527–36.
21. Sacerdote C, Ricceri F, Rolandsson O, *et al*. Lower educational level is a predictor of incident type 2 diabetes in european countries: the EPIC-InterAct study. *Int J Epidemiol* 2012;41:1162–73.
22. Smith JP. Nature and causes of trends in male diabetes prevalence, undiagnosed diabetes, and the socioeconomic status health gradient. *Proc Natl Acad Sci U S A* 2007;104:13225–31.
23. Okura Y, Urban LH, Mahoney DW, *et al*. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol* 2004;57:1096–103.
24. Dray-Spira R, Gary-Webb TL, Brancati FL. Educational disparities in mortality among adults with diabetes in the u.s. *Diabetes Care* 2010;33:1200–5.
25. Cowie CC, Rust KF, Byrd-Holt DD, *et al*. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: national health and nutrition examination survey 1999-2002. *Diabetes Care* 2006;29:1263–8.
26. Shaw BA, Spokane LS. Examining the association between education level and physical activity changes during early old age. *J Aging Health* 2008;20:767–87.
27. Wang Y, Chen J, Wang K, *et al*. Education as an important risk factor for the prevalence of hypertension and elevated blood pressure in chinese men and women. *J Hum Hypertens* 2006;20:898–900.
28. Sear AM, Weinrich M, Hersh JE, *et al*. The relationship between income, education and hypertension. *J Biosoc Sci* 1982;14:213–21.

29. Dyer AR, Stamler J, Shekelle RB, *et al*. The relationship of education to blood pressure: findings on 40,000 employed chicagoans. *Circulation* 1976;54:987–92.
30. Braveman P, Egerter S, Williams DR. The social determinants of health: coming of age. *Annu Rev Public Health* 2011;32:381–98.
31. Li M, Fan Y, Zhang X, *et al*. Fruit and vegetable intake and risk of type 2 diabetes mellitus: meta-analysis of prospective cohort studies. *BMJ Open* 2014;4:e005497.
32. Chida Y, Hamer M. An association of adverse psychosocial factors with diabetes mellitus: a meta-analytic review of longitudinal cohort studies. *Diabetologia* 2008;51:2168–78.
33. Vanderweele TJ. Controlled direct and mediated effects: definition, identification and bounds. *Scand J Stat* 2011;38:551–63.
34. Kaufman JS. Commentary: gilding the black box. *Int J Epidemiol* 2009;38:845–7.
35. Naimi AI, Kaufman JS, MacLehose RF. Mediation misgivings: ambiguous clinical and public health interpretations of natural direct and indirect effects. *Int J Epidemiol* 2014;43:1656–61.
36. Franco M, Orduñez P, Caballero B, *et al*. Obesity reduction and its possible consequences: what can we learn from Cuba's Special Period? *Cmaj* 2008;178:1032–4.
37. Prentice RL. Clinical trials and observational studies to assess the chronic disease benefits and risks of multivitamin-multimineral supplements. *Am J Clin Nutr* 2007;85:308S–13.
38. Berger M, Mamdani M, Atkins D. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using. *Value Heal* 2009;12:1044–52.
39. Dreyer NA, Tunis SR, Berger M, *et al*. Why observational studies should be among the tools used in comparative effectiveness research. *Health Aff* 2010;29:1818–25.
40 Schillaci G, Battista F, Pucci G. Are observational studies more informative than randomized controlled trials in Hypertension?Response to are observational studies more informative than randomized controlled trials in hypertension? con side of the argument. *Hypertension* 2013;62:470–6.
41. Broadbent A. Causation and prediction in epidemiology: a guide to the “Methodological Revolution”. *Studies Hist Philos Sci Part C: Stud Hist Philos Biol Biomed Sci* 2015;54:72–80.
42. Lorenc T, Petticrew M, Welch V, *et al*. What types of interventions generate inequalities? evidence from systematic reviews. *J Epidemiol Community Health* 2013;67:190–3.
43. O'Doherty MG, Jørgensen T, Borglykke A, *et al*. Repeated measures of body mass index and C-reactive protein in relation to all-cause mortality and cardiovascular disease: results from the consortium on health and ageing network of cohorts in Europe and the united states (CHANCES). *Eur J Epidemiol* 2014;29:887–97.

BMJ Open

Education achievement and type 2 diabetes ––what mediates the relationship in older adults? Data from the ESTHER study: a population-based cohort study

Christopher J Steele, Ben Schöttker, Adele H Marshall, Anne Kouvonen, Mark G O'Doherty, Ute Mons, Kai-Uwe Saum, Paolo Boffetta, Antonia Trichopoulou, Hermann Brenner and Frank Kee

BMJ Open 2017 7:
doi: 10.1136/bmjopen-2016-013569