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ORIGINAL ARTICLE

Association of diet and lifestyle with glycated haemoglobin in type 1 diabetes participants in the EURODIAB prospective complications study

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BACKGROUND/OBJECTIVES: Diet and lifestyle advice for type 1 diabetes (T1DM) patients is based on little evidence and putative effects on glycaemic control. Therefore, we investigated the longitudinal relation between dietary and lifestyle variables and HbA1c levels in patients with type 1 diabetes.

SUBJECTS/METHODS: A 7-year prospective cohort analysis was performed in 1659 T1DM patients (52% males, mean age 32.5 years) participating in the EURODIAB Prospective Complications Study. Baseline dietary intake was assessed by 3- day records and physical activity, smoking status and alcohol intake by questionnaires. HbA1c during follow-up was centrally assessed by immunoassay. Analysis of variance (ANOVA) and restricted cubic spline regression analyses were performed to assess dose–response associations between diet and lifestyle variables and HbA1c levels, adjusted for age, sex, lifestyle and body composition measures, baseline HbA1c, medication use and severe hypoglycaemic attacks.

RESULTS: Mean follow-up of our study population was 6.8 (s.d. 0.6) years. Mean HbA1c level was 8.25% (s.d. 1.85) (or 66.6 mmol/mol) at baseline and 8.27% (s.d. 1.44) at follow-up. Physical activity, smoking status and alcohol intake were not associated with HbA1c at follow-up in multivariable ANOVA models. Baseline intake below the median of vegetable protein (< 29 g/day) and dietary fibre (< 18 g/day) was associated with higher HbA1c levels. Restricted cubic splines showed nonlinear associations with HbA1c levels for vegetable protein (P (nonlinear) = 0.008) and total dietary fibre (P (nonlinear) = 0.0009).

CONCLUSIONS: This study suggests that low intake of vegetable protein and dietary fibre are associated with worse glycaemic control in type 1 diabetes.

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INTRODUCTION

The incidence and prevalence of type 1 diabetes (T1DM) has increased by 3–4% per year in European children during the past 20 years.[1] T1DM patients have a 4–8 times higher risk of cardiovascular disease (CVD) compared with those without diabetes.[2,3] Glycated haemoglobin (HbA1c) level has been associated with CVD risk in T1DM patients.[4,5]

Healthy diet and lifestyle have been associated with an 80% lower risk of CVD in the general population.[6,7] Healthy diet has also been suggested to improve glycaemic control in T1DM patients.[8] Limited number of studies (two cross-sectional studies[9–12] and one prospective cohort study[8,13]) investigated a variety of macronutrients in relation to glycemic control in T1DM. Analyses of cross-sectional EURODIAB data showed higher HbA1c levels in over 2000 T1DM patients (mean age 32 years) with higher carbohydrate[9,10] and lower fibre intakes,[11] while a small cross-sectional study in 253 adolescents (mean age 13 years) with T1DM from the Joslin Pediatric Diabetes Centre (Boston, MA, USA) showed that also high fat intake was important.[12] In 532 intensively treated T1DM patients (mean age 27 years) from the Diabetes Control and Complications Trial (DCCT) inverse associations between HbA1c and carbohydrate, and positive associations with total fat, saturated fatty acids (SAFA) and mono-unsaturated fatty acids (MUFA) intake were shown.[13] Evidence on associations between lifestyle variables and glycaemic control in T1DM patients is not always consistent and a limited number of prospective studies were published. Cross-sectional analysis of FinnDiane data showed in 548 T1DM (mean age 38 years) women with low physical activity (PA) levels a poor glycemic control, but not in men.[14] Another prospective study demonstrated that more strenuous exercise or activity level at work was associated with worse glycemia in T1DM.[13] There is evidence from cross-sectional studies[15–19] and a more recent prospective study that current smoking is associated with poor glycemic control.[20] For alcohol, one large prospective study in $>38\,000$ diabetes patients demonstrated that 2–3 drinks of alcohol per day is associated with better glycemic control, but this study did not distinguish between type 1 and type 2 diabetes patients.[21]

From a clinical point of view, it is important to know how diet and lifestyle variables influence glycaemic control in T1DM, to adapt insulin supply and to prevent vascular complications. However, dietary and lifestyle advice for T1DM patients is based on little evidence and putative effects on glycaemic control.[22] It is not clear which diet is best and what dietary and lifestyle

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measures can help improve glycaemic control. Therefore the aim of this study was to investigate the longitudinal relation between dietary and lifestyle variables and HbA1c levels in T1DM participants in the EURODIAB Prospective Complications Study (PCS).

METHODS

Study design and population

The EURODIAB PCS is a clinic-based multicentre prospective cohort study. Details on patient selection and the standardized methodology have been described previously.[23] In brief, 3250 individuals with T1DM, aged 15–60 years, were recruited in 31 centres across 16 European countries between 1989 and 1991 (baseline), which was 85% of the invited people. Pregnant women and those with T1DM for less than 1 year were excluded. T1DM was diagnosed as the onset of diabetes before the age of 36 years, with a continuous need of insulin. At each centre, ethical committee approval for the study and informed consent from all participants were obtained. Seven years after baseline examinations (follow-up: 1997–1999), participants were invited for re-examinations. Participants (48%) dropped out from analyses if: they died ($n=82$), four centres did not participate in the follow-up examination ($n=437$) or participants were lost to follow-up because of unknown reasons ($n=840$), had missing data on nutritional intake at baseline ($n=142$) or HbA1c levels at follow-up ($n=90$). This resulted in 1659 participants available for analyses.

Nutritional assessment

Nutritional intake was assessed using a standardized 3-day dietary record[24,25] which provided plausible energy values for 89% of the participants.[24] A high degree of repeatability of the nutrition assessment method was shown in a randomized subsample of the EURODIAB cohort.[24] The three reported days contained two working days (Monday–Friday) and one weekend day (Saturday or Sunday) representing participants' usual diet. The records were checked by a trained local dietician. An experienced nutritionist rechecked the records for completeness and plausibility and coded the records according to the EURODIAB food list. The records were analysed centrally for intake of total energy, carbohydrates, total protein, animal protein, vegetable protein, total fat, SAFA, MUFA, poly-unsaturated fatty acids, total dietary fibre, soluble fibre, insoluble fibre and cholesterol. Energy intake was calculated using Atwater factors.[26] Diet was assessed at baseline and at follow-up. Baseline dietary intake was used for the present study, because minor changes in nutritional intake were found during follow-up.[27]

Lifestyle and body composition measures

Alcohol intake was assessed by the 3-day dietary record and coded as none, $\leqslant 20$ grams per day and >20 grams a day. Baseline questionnaires were used to collect information on leisure-time PA and smoking status. PA was coded as not or mildly active (never-3 times per month), moderately active (1 or 2 times per week) and vigorously active ($\geqslant 3$ times per week).[28] Smoking habits were coded as non-smoker, ex-smoker and current smoker. Weight, height, waist and hip circumferences were measured with indoor clothing without shoes, and body mass index (BMI) (kg/m^2) and waist–hip ratio (WHR) were calculated.[29]

Study outcome

HbA1c levels were measured in a central laboratory, using an enzyme immunoassay (Dako, Ltd, Ely, UK) with a monoclonal antibody raised against HbA1c. HbA1c levels were corrected according to the DCCT method (%) [30] and the International Federation of Clinical Chemistry and Laboratory Medicine (mmol/mol).[31] The follow-up HbA1c level was used as the main study outcome.

Assessment of covariates

Baseline questionnaires were used to collect information on demographic variables, diabetes duration, (family) history of diabetic complications, severe hypoglycaemic attacks and use of medication (such as insulin dose (units/kg body weight), frequency (injections/day) and blood pressure lowering drugs). Severe hypoglycaemic attacks were defined as the number of episodes severe enough to require help of another person over the past year. Blood pressure was measured once in horizontal position, and once after standing up straight using a Hawksley random zero sphygmomanometer and rounded to the nearest 2 mmHg.[23] Fasting blood samples were taken and total cholesterol, high-density lipoprotein cholesterol and triglyceride were assayed by standard enzymatic methods (Boehringer Mannheim, Lewes, UK). low-density lipoprotein cholesterol was calculated from the Friedewald's equation.[32] Albumin excretion rate was calculated from a timed 24-h urine collection, after excluding proteinuria due to urinary tract infection. Microalbuminuria was defined as albumin excretion rate 20–200 μg/min, and macroalbuminuria as albumin excretion rate $\geqslant 200$ μg/min.

Statistical analysis

For descriptive analysis, data were expressed as n (%), mean ± s.d. or median with interquartile range. Baseline dietary and body composition variables were divided into quartiles to investigate potential linear and nonlinear associations. Analysis of variance (ANOVA), adjusted for age and sex, was used to assess the association of the indicated quartiles of dietary and body composition variables, and categories of PA, smoking status and alcohol intake, with HbA1c levels at follow-up, similar to the DCCT study.[13] Quartile and HbA1c estimates were calculated using the general linear model procedure and presented as least square means (s.e.m.). Further adjustments for dietary variables such as fibre, protein, saturated fat and energy intake were performed if ANOVA models showed significant results for the associations between lifestyle variables and HbA1c levels.

To investigate potential nonlinear associations, restricted cubic spline (RCS) regression analyses as described by Desquilbet *et al.*[33] were performed for those variables which were significantly associated with HbA1c at follow-up in the prior ANOVA. RCS is a sum of polynomials, which hold a high degree of smoothness at points called knots and allows the use of all data points to estimate change in HbA1c at all levels of exposure.[33] Three knots were placed at the 5th, 50th and 95th percentiles of the exposure variables and the medians of the exposure variables were used as the references value.[34] RCS models were adjusted for age, sex, diet (energy intake), lifestyle (PA, smoking, alcohol intake) and body composition variables (BMI, WHR), baseline HbA1c, medication use (blood pressure lowering drugs, insulin dose) and severe hypoglycaemic attacks. Further analyses were performed by adjusting for diabetes duration instead of age, since both were highly correlated (Spearman correlation $r=0.65$, $P<0.0001$). Adjustments for total protein, fat and fibre intake were checked in separate models. Linear and nonlinear P-values were calculated from RCS.

For variables nonlinearly associated with HbA1c, change in HbA1c for low and high values was examined. The medians of quartiles 1 and 4 for diet and body composition variables were compared with the median dietary intake or body composition variables of the whole study population and presented as differences in HbA1c with 95% confidence intervals.

Statistical analyses were performed using SAS (version 9.2, SAS Institute, Cary, NC, USA). RCS analyses were performed using the %RCS_reg macro for SAS.[33,35] A P-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of T1DM participants in the EURODIAB PCS are described in Table 1. Among the 1659 participants, 52.1% were men; participants had a mean age of 32.5 years, a diabetes duration of 14.5 years and a mean follow-up time of 6.8 years. The mean HbA1c level was 8.25% (or 66.6 mmol/mol) at baseline and 8.27% (s.d. 1.44) at follow-up. At baseline, mean nutrient intakes were 2317.1 kcal/day for energy, 250.2 g/day for carbohydrates, 102.4 g/day for protein, 99.4 g/day for fat and 18.1 g/day for total dietary fibre.

A comparison between participants included and excluded in this study showed a worse clinical profile in those who were excluded, that is, with more micro- and macrovascular complications, more CVD risk factors (smoking, blood pressure and cholesterol) and a lower energy and macronutrient intake (Table 1).

Table 1. Baseline characteristics of the EURODIAB Prospective Complications Study participants ($n = 1659$) and those lost to follow-up ($n = 1591$).

Variable	*Included* (n = *1659)*	*Lost to follow-up* (n = *1591)*	P-*value*
Baseline HbA1c (%; mmol/mol)	8.25 ± 1.85; 66.6 ± 20.2	8.65 ± 1.98; 71.1 ± 21.6	< 0.0001
Follow-up HbA1c (%; mmol/mol)	8.27 ± 1.44; 66.9 ± 15.7	8.45 ± 1.46; 68.9 ± 16.0	0.15
Men	865 (52.1)	725 (50.3)	0.30
Age (years)	32.5 ± 9.8	33.0 ± 10.5	0.17
Diabetes duration (years)	14.5 ± 9.1	14.9 ± 9.6	0.28
Body mass index (kg/m^2)	23.6 ± 2.8	23.4 ± 3.0	0.10
Waist–hip ratio	0.85 ± 0.12	0.86 ± 0.13	0.10
Smoking			0.001
Non	869 (52.5)	741 (47.3)	
Ex	302 (18.3)	274 (17.5)	
Current	483 (29.2)	552 (35.2)	
Physical activity			0.19
Not or mildly active	565 (34.7)	587 (37.6)	
Moderately active	546 (33.5)	514 (32.9)	
Vigorously active	518 (31.8)	461 (29.5)	
Alcohol intake			0.44
None	790 (47.6)	678 (57.2)	< 0.0001
⩽ 20 g/week	661 (39.8)	392 (33.1)	
> 20 g/week	208 (12.5)	115 (9.7)	
Total energy (kcal/day)[a]	2317.1 (1936.5–2865.5)	2245.2 (1832.2–2764.0)	0.0005
Carbohydrate (g/day; en%)	250.2 ± 81.6; 42.4 ± 7.3	240.4 ± 76.9; 42.6 ± 7.4	0.001
Total protein (g/day; en%)	102.4 ± 30.5; 17.6 ± 3.5	99.2 ± 31.4; 17.6 ± 3.5	0.006
Animal protein	70.7 ± 25.3; 12.2 ± 3.7	68.3 ± 26.4; 12.2 ± 3.7	0.01
Vegetable protein	30.6 ± 11.2; 5.2 ± 1.2	29.9 ± 11.9; 5.3 ± 1.3	0.11
Total fat (g/day; en%)	99.4 ± 36.4; 37.9 ± 7.2	97.4 ± 39.4; 38.0 ± 7.4	0.15
SAFA	37.6 ± 15.9; 13.9 ± 3.5	37.0 ± 16.3; 14.1 ± 3.4	0.32
PUFA[a]	13.7 (9.3–20.0); 5.2 (3.9–7.2)	13.8 (9.3–20.7); 5.5 (4.1–7.8)	0.36
MUFA	40.2 ± 15.3; 15.1 ± 4.1	38.3 ± 16.5; 14.7 ± 3.9	0.002
Total dietary fibre (g/day; g/1000 kcal)[a]	18.1 (13.9–23.5); 7.8 (6.1–9.9)	16.6 (13.0–21.6); 7.4 (5.9–9.5)	< 0.0001
Insoluble fibre[a]	12.3 (9.4–16.0); 5.3 (4.1–6.7)	11.2 (8.7–14.5); 5.0 (3.9–6.5)	< 0.0001
Soluble fibre[a]	5.7 (4.3–7.5); 2.5 (1.9–3.1)	5.4 (4.2–6.8); 2.4 (1.9–3.1)	0.0003
Cholesterol (g/day; g/1000 kcal)[a]	333.6 (234.9–455.9);140.1 (108.9–185.6)	339.1 (237.4–472.7);148.2 (110.8–199.2)	0.33
Insulin frequency (injections/day)	2.6 ± 0.8	2.5 ± 0.7	0.22
Insulin dose (units/kg/day)	0.68 ± 0.22	0.67 ± 0.24	0.44
Severe hypoglycaemic attacks[b]	537 (32.4)	509 (32.0)	0.82
Blood pressure lowering drugs	141 (8.6)	186 (11.8)	0.01
Cardiovascular disease	134 (8.2)	177 (11.3)	0.003
Neuropathy	497 (30.4)	652 (42.3)	< 0.0001
Retinopathy			0.002
Non-proliferative	501 (36.0)	381 (35.0)	
Proliferative	120 (8.6)	142 (13.0)	
Albuminuria			0.0009
Microalbuminuria (AER 20–200 μg/min)	335 (21.0)	330 (22.7)	
Macroalbuminuria (AER > 200 μg/min)	115 (7.2)	155 (10.6)	
Systolic blood pressure (mmHg)	120.1 ± 16.7	122.6 ± 18.9	< 0.0001
Diastolic blood pressure (mmHg)	75.0 ± 11.4	75.9 ± 11.4	0.03
Total cholesterol (mmol/l)	5.3 ± 1.1	5.4 ± 1.2	0.01
Fasting triglycerides (mmol/l)[a]	0.9 (0.7–1.2)	1.0 (0.7–1.4)	< 0.0001
HDL-cholesterol (mmol/l)	1.5 ± 0.4	1.4 ± 0.4	< 0.0001
LDL-cholesterol (mmol/l)	3.3 ± 1.0	3.4 ± 1.1	0.01

Abbreviations: AER, albumin excretion rate; en%, energy percentage; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MUFA, mono-unsaturated fatty acids; PUFA, poly-unsaturated fatty acids; SAFA, saturated fatty acids. Numbers may vary because of missing values. *P*-values were calculated with the students' *t*-test for parametric continuous variables, Kruskal–Wallis test for nonparametric continuous variables and chi-square test for categorical variables. [a]Values are expressed as mean ±s.d., *n* (%), or Median (interquartile range). [b]Severe hypoglycaemic attacks defined as any episode severe enough to require help of another person in the past year.

Diet and HbA1c

Age and sex adjusted estimates of mean HbA1c levels at follow-up for quartiles of baseline dietary variables (Table 2) showed that lower intake of total dietary fibre, soluble and insoluble fibre and higher intake of animal protein were significantly associated with higher HbA1c (all ANOVA *P*-values < 0.03). For energy and vegetable protein both low and high intakes were associated with higher HbA1c levels (all ANOVA *P*-values < 0.05). Total protein, carbohydrates, total fat, SAFA, poly-unsaturated fatty acids, MUFA and cholesterol were not associated with HbA1c.

Table 2. Age and sex adjusted estimates of HbA1c at follow-up, by quartiles of dietary and body composition variables (Q) ($n = 1659$)[a]

Variable	*Q1*	*Q2*	*Q3*	*Q4*	P *(ANOVA)*
Energy (kcal/day)	1644 (14)	2142 (13)	2566 (13)	3354 (14)	
HbA1c by energy quartiles	8.4 (0.1)	8.2 (0.1)	8.2 (0.1)	8.4 (0.1)	0.03
Carbohydrate (g/day)	157.8 (1.6)	217.7 (1.6)	266.8 (1.6)	358.4 (1.7)	
HbA1c by carbohydrate quartiles	8.4 (0.1)	8.2 (0.1)	8.2 (0.1)	8.3 (0.1)	0.07
Total protein (g/day)	68.2 (0.7)	90.8 (0.6)	108.5 (0.6)	142.0 (0.7)	
HbA1c by total protein quartiles	8.2 (0.1)	8.2 (0.1)	8.3 (0.1)	8.4 (0.1)	0.12
Animal protein (g/day)	42.4 (0.5)	60.7 (0.5)	76.1 (0.5)	103.6 (0.6)	
HbA1c by animal protein quartiles	8.2 (0.1)	8.2 (0.1)	8.3 (0.1)	8.4 (0.1)	0.03
Vegetable protein (g/day)	18.5 (0.2)	25.9 (0.2)	32.4 (0.2)	45.5 (0.2)	
HbA1c by vegetable protein quartiles	8.4 (0.1)	8.1 (0.1)	8.2 (0.1)	8.3 (0.1)	0.047
Total fat (g/day)	59.2 (0.7)	84.1 (0.7)	106.6 (0.7)	147.8 (0.7)	
HbA1c by total fat quartiles	8.3 (0.1)	8.3 (0.1)	8.2 (0.1)	8.3 (0.1)	0.47
Saturated fatty acids (g/day)	20.4 (0.3)	30.6 (0.3)	40.4 (0.3)	59.1 (0.3)	
HbA1c by saturated fatty acids quartiles	8.3 (0.1)	8.2 (0.1)	8.2 (0.1)	8.3 (0.1)	0.61
Poly-unsaturated fatty acids (g/day)	7.2 (0.2)	11.4 (0.2)	16.5 (0.2)	28.6 (0.2)	
HbA1c by poly-unsaturated fatty acids quartiles	8.3 (0.1)	8.2 (0.1)	8.3 (0.1)	8.3 (0.1)	0.85
Mono-unsaturated fatty acids (g/day)	23.1 (0.3)	33.8 (0.3)	43.3 (0.3)	60.7 (0.3)	
HbA1c by mono-unsaturated fatty acids quartiles	8.3 (0.1)	8.2 (0.1)	8.3 (0.1)	8.3 (0.1)	0.66
Total dietary fibre (g/day)	11.0 (0.2)	16.1 (0.2)	20.5 (0.2)	29.3 (0.2)	
HbA1c by total dietary fibre quartiles	8.5 (0.1)	8.4 (0.1)	8.2 (0.1)	8.1 (0.1)	< 0.001
Insoluble fibre (g/day)	7.4 (0.1)	10.9 (0.1)	14.0 (0.1)	20.0 (0.1)	
HbA1c by insoluble fibre quartiles	8.5 (0.1)	8.3 (0.1)	8.1 (0.1)	8.1 (0.1)	< 0.001
Soluble fibre (g/day)	3.4 (0.1)	5.0 (0.1)	6.5 (0.1)	9.4 (0.1)	
HbA1c by soluble fibre quartiles	8.5 (0.1)	8.3 (0.1)	8.2 (0.1)	8.1 (0.1)	< 0.001
Dietary cholesterol (g/day)	179.7 (4.8)	285.0 (4.7)	387.8 (4.7)	624.6 (4.8)	
HbA1c by cholesterol quartiles	8.1 (0.1)	8.3 (0.1)	8.3 (0.1)	8.3 (0.1)	0.19
Body mass index (kg/m^2)	20.3 (0.1)	22.5 (0.1)	24.3 (0.1)	27.3 (0.1)	
HbA1c by body mass index quartiles	8.2 (0.1)	8.1 (0.1)	8.2 (0.1)	8.6 (0.1)	< 0.001
Waist–hip ratio	0.72 (0.004)	0.80 (0.003)	0.87 (0.003)	1.02 (0.003)	
HbA1c by waist–hip ratio quartiles	8.1 (0.1)	8.1 (0.1)	8.3 (0.1)	8.6 (0.1)	< 0.001

[a]Quartiles are presented for all variables. Quartile and HbA1c estimates were calculated using the general linear model procedure and presented as least square means (s.e.m.).

Lifestyle and body composition variables and HbA1c

HbA1c levels were significantly higher in the highest BMI and WHR quartiles (both ANOVA *P*-values < 0.001) (Table 2). There was no statistically significant association between PA and HbA1c levels, although HbA1c levels decreased from no to vigorous PA (mean (s.e.m.) HbA1c (%): 8.35 (0.06), 8.18 (0.06) and 8.24 (0.07), age and sex adjusted ANOVA model $P = 0.1$ respectively). There was a borderline significant relation between smoking and HbA1c. HbA1c increased from no, ex to currently smoking (8.21 (0.05), 8.20 (0.08) and 8.40 (0.07), ANOVA $P = 0.05$ respectively) in age and sex adjusted models. However, after adjustments for dietary fibre, protein, saturated fat and energy intake, we found that the association between smoking status and HbA1c attenuated. There was no significant association between alcohol consumption and HbA1c(%) levels, with HbA1c levels 8.33 (0.05), 8.18 (0.06), 8.32 (0.10) from none to $\leqslant 20$ g or > 20 g alcohol per week (ANOVA $P = 0.1$).

HbA1c levels were significantly raised in participants with prior known CVD, neuropathy, retinopathy and/or nephropathy compared with participants with no previous complication. However, exclusion of participants with previous complications did not alter the results between the diet, lifestyle or body composition variables and HbA1c levels. The trends of HbA1c in the quartiles remained similar (data not shown).

Nonlinear associations between diet, lifestyle, body composition variables and HbA1c

RCS regression was performed to describe the nonlinear dose–response association of animal protein, vegetable protein, total dietary fibre, insoluble fibre and soluble fibre, energy, BMI and WHR with HbA1c. After adjustment for age, sex, lifestyle, body composition variables, baseline HbA1c, medication use and severe hypoglycaemic attacks, we found that vegetable protein, total dietary fibre, insoluble fibre, soluble fibre, BMI and WHR were significantly nonlinearly associated with HbA1c (Figures 1a–f). Adjustment for diabetes duration instead of age, and adjustments for other macronutrient intake (protein, fat and fibre) did not alter the results. Low intake of vegetable protein, total dietary fibre, insoluble fibre and soluble fibre, and high BMI and WHR were associated with higher HbA1c. High intake of animal protein was associated with higher HbA1c when adjusted for age and sex (spline regression *P*-value for linearity = 0.02), but this association did not remain statistically significant after additional adjustment for WHR (figure not shown, spline regression *P*-value for linearity = 0.09). Vegetable protein, total dietary fibre, insoluble fibre and soluble fibre intake in the lowest quartile compared to the median intake were associated with positive HbA1c differences of 0.17% (95% confidence interval: 0.02, 0.31), 0.27% (0.14, 0.39), 0.23% (0.12, 0.35) and 0.29% (0.18, 0.41), respectively (Supplementary Table 1). High intake of soluble fibre compared with the median intake was associated with a HbA1c difference of −0.12% (−0.23, −0.02). High intake of total dietary fibre and insoluble fibre compared with the median intake were borderline significantly associated with negative HbA1c differences of −0.10% (−0.19, −0.01) and −0.08% (−0.18, 0.02), respectively. High BMI and WHR compared to the median BMI or WHR were associated with positive HbA1c differences of 0.28% (0.17, 0.38) and 0.08% (0.01, 0.18), respectively.

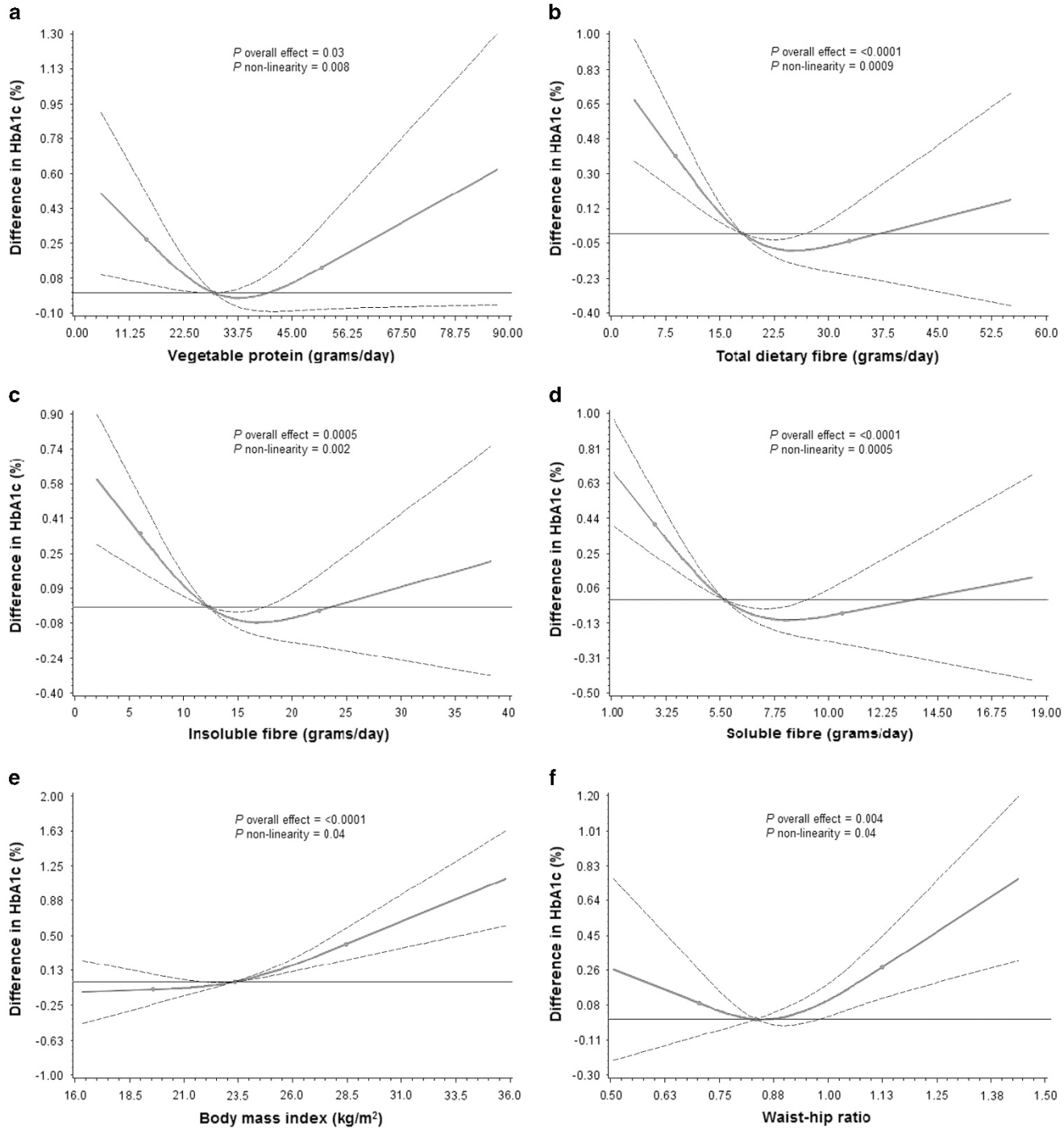

Figure 1. Associations of baseline (**a**) vegetable protein, (**b**) total dietary fibre, (**c**) insoluble fibre, (**d**) soluble fibre, (**e**) body mass index and (**f**) waist–hip ratio with HbA1c at 7 years of follow-up ($n = 1633$). RCS regression with three knots located at the 5th, 50th and 95th percentiles of dietary intake or body composition variables. The *y* axis represents the difference in HbA1c for all levels of dietary intake and body composition variables compared with the reference (median) value of dietary intake or body composition variables. Models were adjusted for age, sex, energy intake, physical activity, body mass index, waist–hip ratio, smoking, alcohol intake, baseline HbA1c, use of blood pressure lowering drugs, insulin dose and severe hypoglycaemic attacks. Dashed lines indicate 95% confidence intervals. Reference values: vegetable protein 28.8 g/day; total dietary fibre 18.1 g/day; insoluble fibre 12.3 g/day; soluble fibre 5.7 g/day; body mass index 23.3 kg/m2; and waist–hip ratio 0.83.

DISCUSSION

In this study of T1DM patients, we showed a nonlinear association of baseline vegetable protein, total dietary fibre, insoluble fibre, soluble fibre, BMI and WHR with HbA1c at 7 years of follow-up. No associations between carbohydrate, total or animal protein, fat, PA, smoking status or alcohol intake and HbA1c were found.

The null association for total protein intake and HbA1c is in line with previous studies in T1DM[12,13] and in the general population.[36] However, these studies did not differentiate between animal protein and vegetable protein. In our study, we found a nonlinear inverse association for vegetable protein and a nonsignificant positive association for animal protein and HbA1c,

this may explain why together as total protein a null association with HbA1c was shown. In the general British population, a low intake of protein was predictive of high HbA1c levels.[37] In an earlier publication of the EURODIAB PCS and a case–control study of T1DM patients, no association between protein intake or vegetable protein and microalbuminuria was found.[38,39] Our results on vegetable protein indicate that a low intake is related to higher HbA1c levels. Studies have not examined malnutrition of total or vegetable protein, because most populations are able to reach the recommendation of 10–15% of total energy intake.[40,41] In our population, 77% reached this recommendation.[25]

The nonlinear association of dietary fibre and HbA1c, especially the association of low intake of dietary fibre with high HbA1c, is in line with previous observational research.[11,12] Previous cross-sectional analysis of EURODIAB data showed an inverse association of both insoluble and soluble fibre with HbA1c at baseline[11] and a cross-sectional study in adolescents also showed that low dietary fibre intake was associated with higher HbA1c levels.[12] Studies have shown a decreased risk of fatal and non-fatal CVD with high intake of dietary fibre in T1DM [42] and healthy populations.[43] However, Delahanty *et al.*[13] did not show an association between dietary fibre and HbA1c in T1DM. This can be due to the higher levels of dietary fibre at baseline of 26 g/day which remained constant during the trial.[44] In the EURODIAB study the mean intake was 18 g/day and the recommended dietary fibre intake of at least 30 g/day was only achieved by 7% of the study population.[25] The results of this study indicate that there is potential of reducing HbA1c levels and CVD risk by increasing dietary fibre to current recommendations of at least 30 g/day or 20 g per 1000 kcal,[41] although an intake of dietary fibre above 25 g/day did not seem to have an additional beneficial effect. To support a preventive role for dietary fibre, dietary fibre was also indicated for treatment of type 2 diabetes in a meta-analysis of 15 randomized intervention trials, with similar overall differences in HbA1c levels as in our study.[45]

Carbohydrate has been a key nutrient in medical nutritional therapy for T1DM and for insulin use to improve glycaemic control. In this study, we did not find an association between carbohydrates and HbA1c. Previous research showed that carbohydrate intake did influence HbA1c levels. Previous cross-sectional analysis of the EURODIAB showed a modest tendency of an increased HbA1c with high intakes of carbohydrates,[9] the DCCT and a cross-sectional study in adolescents showed an inverse association with HbA1c,[12,13] and more recently in the SEARCH Nutrition Ancillary Study also suggested that increased total carbohydrate intake raised HbA1c levels in young T1DM patients.[46] These discrepancies with our results on the association of carbohydrates and HbA1c could be explained by the exchange of carbohydrate for fat,[27,47] high fibre content[13] or the source of carbohydrates.[9] The differences between the DCCT results and our results can also be due to the follow-up time and study population. The DCCT followed 532 intensively treated subjects for 5 years, while our study population was larger and had a longer follow-up ($n = 1659$, 7-years follow-up).

In the present study, no association between fat and HbA1c was found. Two cross-sectional studies and one prospective study in T1DM patients found a positive association between fat and HbA1c, especially for SAFA and MUFA.[12,13,47] The positive association with SAFA was also found in children and adolescents with T1DM, while MUFA intake was negatively correlated with HbA1c.[48] Schoenaker *et al.*[42] showed that SAFA was not associated with either CVD or all-cause mortality in T1DM patients in the EURODIAB PCS. It has also been found that T1DM patients have a high-fat atherogenic diet,[27,47,49] in which especially recommended SAFA intake is exceeded. In the DCCT, more participants reached the recommended intake of SAFA of maximum 10% of total energy intake (28 versus 14% of EURODIAB PCS participants),[25,50] which unlikely explains the association between SAFA and HbA1c found in the DCCT, but not in EURODIAB. Additionally, there is a large day-to-day variation in fat intake.[51] This variation was reduced in the DCCT, because of the prescribed meals and the high adherence to these meals.[8] Although not confirmed in the current analysis, SAFA intake should be restricted in line with current recommendations.

Our results showed that body composition variables (BMI and WHR) were associated with HbA1c. A direct increase in HbA1c levels was seen from a BMI $>24\ kg/m^2$, whereas lower BMI levels were not associated with HbA1c. Similarly, a significant increase in HbA1c levels was demonstrated from a WHR >0.97, whereas lower WHR levels showed no association with HbA1c. This is consistent with previous research.[13,15] Lifestyle variables PA, and alcohol intake were not significantly associated with HbA1c in this study. Results indicated a tendency towards improved glycemic control with higher levels of PA which is what we expected. These results are not in line with the previously published DCCT study[8] that showed that more strenuous exercise or activity level at work was associated with worse glycemia. This discrepancy may be explained by the type of PA which differed in both studies, leisure-time PA was measured in EURODIAB, whereas work-related PA was measured in DCCT. Previous cross-sectional analysis of the EURODIAB study showed a moderate significant decrease in HbA1c when alcohol consumption increased,[52] but after age and sex adjustment in our current analyses this association was no longer present. We are not aware of previous studies that have examined the association between alcohol consumption and HbA1c specifically in T1DM. Several cross-sectional studies, and a prospective study in over 700 T1DM patients followed for 16 years, showed that smoking was associated with poor glycemic control.[15,20] We also found initially an association with poor glycemic control in current smokers, as was shown previously in EURODIAB cross-sectionally.[16] Further adjustments for dietary components, however, attenuated these results.

This study has several strengths and limitations. To the best of our knowledge, our study is the first to assess the shape of associations between diet and lifestyle variables and HbA1c in a large cohort of T1DM patients. Current research in this area have been dominated by studies in patients with type 2 diabetes with limited generalisability to T1DM. We used standardized 3-day dietary records, one of the better methods to collect dietary data. Our nutrient intakes are comparable to intakes reported in other type 1 diabetic populations [13] as described previously.[27] Reverse causation may not likely explain our results, since the EURODIAB study population had stable nutrient intakes over 7 years.[27] Limitations are the large number of participants lost to follow-up. Although these participants had a worse clinical profile than the included participants, the direction of the associations between diet and lifestyle and HbA1c are unlikely to be affected. Furthermore, in our study only macronutrients were analysed and no foods or dietary patterns. Investigating foods and dietary patterns in relation to HbA1c in T1DM patients are important in future studies.[53]

In conclusion, our results in European individuals with T1DM show nonlinear associations between low vegetable protein and low dietary fibre intake and higher HbA1c. Low intake of especially vegetable protein and dietary fibre should be avoided as well as a high BMI or WHR. These results are in line with dietary advice of the American Diabetes Association, the European Association for the Study of Diabetes and the general advice to consume a diet rich in fruits, vegetables and wholegrain cereals and to achieve or maintain a healthy BMI and WHR.[41] Further research is recommended in other study populations and study designs including intervention studies to further elucidate the associations between dietary and lifestyle variables and HbA1c levels in T1DM. It is important to further study which foods containing dietary fibre or vegetable protein influence HbA1c levels. Furthermore, foods and dietary patterns should be assessed in relation to HbA1c.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

SNB and SSS-M were responsible for conception and design. SNB was responsible for drafting of the manuscript. SNB, DAJMS and SSS-M contributed to the analysis and interpretation of the data. DAJMS, GDM, MT, NC, JHF and SSS-M contributed to critical revision of the manuscript for important intellectual content. All authors approved the final version.

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