Determinants of 20-year non-progression to Type 2 diabetes in women at very high risk: the E3N cohort study

Guy Fagherazzi, G. Gusto, F. Mancini, C. Dow, K. Rajaobelina, Beverley Balkau, M.-C. Boutron-Ruault, F. Bonnet

DR GUY FAGHERAZZI (Orcid ID : 0000-0001-5033-5966)

DR BEVERLEY BALKAU (Orcid ID : 0000-0003-2021-413X)

Article type : Short Report

Title: Diabetic Medicine

Created by: Maria Davie

Email proofs to: guy.fagherazzi@gustaveroussy.fr

Article no.: DME-2018-00208

Article type: Short Report

Short title/*Authors running head*: Non-progression to Type 2 diabetes in women at very high risk • *G. Fagherazzi et al.*

Short Report: Epidemiology

Determinants of 20-year non-progression to Type 2 diabetes in women at very high risk: the E3N cohort study

G. Fagherazzi[1,2], G. Gusto[1,2], F. Romana Mancini[1,2], C. Dow[1,2], K. Rajaobelina[1,2], B. Balkau[1,2,3], M.-C. Boutron-Ruault[1,2] and F. Bonnet[1,2,4]

[1]Inserm U1018, Centre for Research in Epidemiology and Population Health, Villejuif, [2]Paris-South Paris Saclay University, Villejuif, [3]Versailles-Saint Quentin University, Villejuif and [4]CHU Rennes, Rennes 1 University, Rennes, France

Correspondence to: Guy Fagherazzi. Email: guy.fagherazzi@gustaveroussy.fr

What's new?

- Dietary habits play a major role in diabetes prevention in people at risk of Type 2 diabetes.
- The top characteristic found to be associated with not developing Type 2 diabetes was the limiting of foods typical of a Western diet [in the present study population, essentially processed meat, French fries, appetizers (olives, crackers, peanuts, almonds, hazelnuts, pistachios, walnuts), rice/pasta, potatoes, pulses, pizza/pies, canned fish, eggs, alcoholic beverages, cakes, mayonnaise, and butter/cream].
- The second most important characteristic was a high intake of antioxidant-rich foods (such as coffee, tea, fruit and vegetables, and chocolate).
- Our results provide evidence to aid the design of new intervention and prevention strategies in individuals at very high risk of Type 2 diabetes.

Aims To identify the most important determinants associated with not developing Type 2 diabetes in women considered to be at very high risk.

Methods Between 1995 and 2014, we followed 402 women from the E3N cohort study who were considered to be at very high risk of Type 2 diabetes based on the D.E.S.I.R. score. We then computed a classification and regression tree model to identify, among a large set of risk factors, the top risk factors associated with not having Type 2 diabetes at the end of the follow-up.

Results During follow-up**,** 117 women (29%) were diagnosed with Type 2 diabetes, while 285 (71%) were still free of the disease in 2014. A low Western dietary pattern score was the top characteristic associated with not developing Type 2 diabetes, as only 20% of the women at very high risk in the E3N study with that characteristic developed Type 2 diabetes (compared with 29% overall). In women with a moderate or high Western dietary pattern score, the most important characteristic associated with not developing Type 2 diabetes was a high total dietary antioxidant capacity, as only 26% of these women ultimately developed Type 2 diabetes.

Conclusions We showed that the top characteristic associated with not developing Type 2 diabetes, despite being at very high risk, was a healthy diet, characterized by limiting Western dietary habits, but with a high intake of antioxidant-rich foods. This underscores the importance of diet in the prevention of Type 2 diabetes in people at high risk.

Introduction

Identifying key risk factors is key to Type 2 diabetes prevention. It is known that many cases of Type 2 diabetes are preventable through lifestyle modification, with population-attributable fractions related to factors such as diet, excess weight and physical activity of up to 91% [1]. Various Type 2 diabetes risk scores are increasingly used in screening and prevention campaigns all over the world, but many barriers still exist to the uptake of these tools by healthcare practitioners [2]. Previous intervention studies have provided useful, but not optimal strategies to decrease Type 2 diabetes risk in high-risk populations [3]. Insights into the key real-life determinants associated with Type 2 diabetes risk reduction in high-risk individuals would be useful for the design of better interventions. The objective of the present study was to identify the most discriminant factors associated with not developing Type 2 diabetes in women at very high risk of Type 2 diabetes, in the French E3N study.

Participants and methods

Study population

The E3N cohort study is an observational study that included 98 995 women aged 40–65 years at baseline in 1990; the study has already been extensively described elsewhere [4], and several Type 2 diabetes risk factors have been studied in this cohort [5]. Type 2 diabetes cases in the E3N study were all validated using a well-defined algorithm that has been described elsewhere [6]. The women in the E3N study did not participate in specific diabetes screening programmes during follow-up. Dietary information was collected in 1993 using a validated semi-quantitative food frequency questionnaire, that was adapted to the French meal pattern [7].

In the present report, we included all participants who answered the 1995 questionnaire where waist circumference was first collected (*n*=69 001). We excluded those who had missing information in 1995 that would be used to calculate their D.E.S.I.R. diabetes risk score (waist circumference, hypertension, diabetes in the family; *n*=13 708), prevalent cases of Type 2 diabetes that occurred before 1995 (*n*=660), and those with missing information on dietary data (*n* =2883). Among the remaining 51 750 women, a total of 402 had a D.E.S.I.R. clinical score of 5 and were thus considered to be at a very high risk of Type 2 diabetes.

Type 2 diabetes risk assessment

The most commonly used risk score in France is still the FINDRISC score [8]; however, in the E3N study, the D.E.S.I.R. score has been shown to perform better than the FINDRISC score [9], therefore we used the clinical D.E.S.I.R. score to identify people at a very high risk of Type 2 diabetes; indeed, for the E3N study, the area under the receiver-operating characteristic curve for incident diabetes with this score was 0.82 [9]. The score ranges from 0 to 5, with a score of 5 indicating very high risk, which corresponds to an average absolute risk of Type 2 diabetes of 32% in the following 9 years. The score for women is based on: waist circumference (70–79 cm: 1 point; 80–89 cm: 2 points; 90–99 cm: 3 points; ≥ 100 cm: 3 points), family history of diabetes (yes: 1 point) and hypertension (yes: 1 point).

Statistical analyses

Dietary patterns were derived from principal components analysis based on the main 57 predefined food groups from the dietary questionnaire, using the SAS 'Proc Factor' procedure (SAS Institute Inc., Cary, NC, USA; see Cottet *et al.* [10] for more details on the food groups). The first two patterns were characterized as: 1) 'Western: essentially processed meat, French fries, appetizers (olives, crackers, peanuts, almonds, hazelnuts, pistachios, walnuts), rice/pasta, potatoes, pulses, pizza/pies, canned fish, eggs, alcoholic beverages, cakes, mayonnaise and butter/cream and 2) 'prudent/Mediterranean:

essentially vegetables, fruits, seafood, olive oil and sunflower oil. For each participant, we calculated the factor score for these two patterns by summing observed consumption from all food groups, weighted by the food group factor loadings. The factor score measures the level of adherence of a woman to the given dietary pattern. These scores were each then divided into three groups, with a low score corresponding to women with a score below the first tertile and a high score corresponding to those with a score above the third tertile.

The most discriminating factors associated with not developing Type 2 diabetes at the end of follow-up were identified using a classification and regression tree (CART) model using R software (ctree() function from the 'partykit' R package). This model explores the structure of data and develops easily visualized decision rules for predicting a categorical outcome (in the present study, diagnosis of Type 2 diabetes, yes/no). Each included variable is examined and the best categorization is made to maximize the sensitivity and specificity of the classification. The procedure is repeated until the stopping criterion (the predicted probability of diabetes does not depend on the non-included variables) is reached. The variables we included in the model are either established risk factors or previously published factors associated with Type 2 diabetes risk in the E3N study, which are listed in the legend for Fig. 1. Variable importance was assessed by the mean decrease in accuracy obtained from 1500 tree iterations.

Variables with <5% missing data were imputed with the median (quantitative variables) or the mode (qualitative variables) of the study population, otherwise, an 'unknown' category was included in the analysis.

Results

Study characteristics

Among the 402 women considered to be at a very high risk of Type 2 diabetes in 1995, 117 (29%) were diagnosed with Type 2 diabetes during follow-up (1995–2014) and 285 (71%) were still free of

the disease in 2014. Women at very high risk who did not develop Type 2 diabetes during follow-up were aged 75 years on average at the end of follow-up (Table 1).

Factors associated with not having diabetes in very high risk women

A low score for the Western dietary pattern was the top characteristic associated with not developing Type 2 diabetes in the women at a very high risk (Fig. 1). Indeed, only 20% of the women at very high risk in the E3N study with a low Western dietary pattern score developed Type 2 diabetes (compared with 29% overall). In women with a moderate or high Western dietary pattern score, the next most important characteristic associated with not developing Type 2 diabetes was total dietary antioxidant capacity. Only 26% of those with a moderate or high intake of antioxidant-rich foods developed Type 2 diabetes over the follow-up period.

Then, in order of decreasing impact were the following factors: extreme sleep duration (≤6 h or ≥9 h per night); birth weight; level of education; a prudent/Mediterranean dietary score; and physical activity. These factors had low discriminant capacities, however, and since some were based on small group sizes, they should be interpreted with caution. The two discriminating factors, therefore, were a low Western dietary pattern score (*n*=102) and higher total dietary antioxidant capacity (*n*=193).

Discussion

In the present study in 402 women at very high risk of developing Type 2 diabetes, we were able to isolate the top characteristics associated with not developing diabetes. Our results highlight the importance of diet in Type 2 diabetes prevention. Limiting adherence to a Western diet, characterized in the present study by processed meat, French fries, appetizers, rice/pasta, potatoes, pulses, pizza/pies, canned fish, eggs, alcoholic beverages, cakes, mayonnaise and butter/cream, appeared to be the most important determinant in our study population. In women who had a moderate to high Western dietary pattern score, total dietary antioxidant capacity, characterized by a high consumption

of coffee, tea, fruit and vegetables and chocolate, and a moderate consumption of wine [11], was the second most influential factor associated with not developing the disease. Interestingly, although the sample size was relatively small, we identified extreme sleep duration (≤6 h or ≥9 h per night) as the next most important factor discriminating women who developed Type 2 diabetes from those who did not.

The present study had some limitations, including the fact that the study population only included women. The study should therefore be replicated in men, even though findings related to dietary prevention in the literature have not been shown to be sex-specific. We were also unable to include genetic factors, but we did include family history of diabetes. Dietary information was only assessed at baseline, thus misclassification of exposure is possible as dietary habits may change over time. Because of the study design, measurement error is likely to be non-differential and would tend to attenuate the association.

The study also has several strengths. It included a population with a long follow-up and with information on many health determinants and lifestyle factors. We were able to isolate women at very high risk who were well characterized by a validated risk score that has been shown to perform well in the E3N study. Finally, we used a novel approach, modelling the top factors associated with not developing the disease in a real-life setting, which provides new perspectives from which to identify innovative factors to be included in prevention strategies.

In conclusion, we have shown that, among the main established or suspected diabetes risk factors in the literature, the top characteristic associated with not developing Type 2 diabetes despite being at very high risk was a healthy diet, characterized by both a limiting of Western dietary habits and a high intake of antioxidant-rich foods. The results favour the intensification of targeted interventions with regard to diet in very high risk populations. We also recommend that further intervention studies test new approaches based specifically on these findings.

Funding sources

The E3N cohort is being carried out with the financial support of the *Mutuelle Générale de l'Education Nationale*, the European Community, French League against Cancer, Gustave Roussy,

and the French Institute of Health and Medical Research. The present study was also supported by the French Research Agency (*Agence Nationale de la Recherche*) via an *Investissement d'Avenir* (investment for the future) grant (ANR-10-COHO-0006) that supports the E4N study, and the IDEX Paris Saclay (Nutriperso project).

Conflict of interest

None declared.

Acknowledgements

The authors are grateful to all participants for providing the data used in the E3N cohort Study. G.F. takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

References

1. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG *et al.* Diet, Lifestyle, and the Risk of Type 2 Diabetes Mellitus in Women. *N Engl J Med* 2001;**345**:790–797.

2. Dhippayom T, Chaiyakunapruk N, Krass I. How diabetes risk assessment tools are implemented in practice: a systematic review. *Diabetes Res Clin Pract* 2014;**104**:329–342.

3. Merlotti C, Morabito A, Pontiroli AE. Prevention of type 2 diabetes; a systematic review and meta-analysis of different intervention strategies. *Diabetes Obes Metab* 2014;**16**:719–727.

4. Fagherazzi G, Gusto G, Balkau B, Boutron-Ruault M-C, Clavel-Chapelon F, Bonnet F. Functional gastrointestinal disorders and incidence of type 2 diabetes: Evidence from the E3N-EPIC cohort study. *Diabetes Metab* 2016;**42**:178–183.

5. Fagherazzi G, Vilier A, Affret A, Balkau B, Bonnet F, Clavel-Chapelon F. The association of body shape trajectories over the life course with type 2 diabetes risk in adulthood: a group-based modeling approach. *Ann Epidemiol* 2015; **25**:785–787.

6. Mancini FR, Affret A, Dow C, Balkau B, Bonnet F, Boutron-Ruault M-C *et al*. Dietary antioxidant capacity and risk of type 2 diabetes in the large prospective E3N-EPIC cohort. *Diabetologia* 2018; **61**:308–316.

7. van Liere MJ, Lucas F, Clavel F, Slimani N, Villeminot S. Relative validity and reproducibility of a French dietary history questionnaire. *Int J Epidemiol* 1997; **26** (Suppl. 1):S128–136.

8. Meijnikman AS, De Block CEM, Verrijken A, Mertens I, Corthouts B, Van Gaal LF. Screening for type 2 diabetes mellitus in overweight and obese subjects made easy by the FINDRISC score. *J Diabetes Complications* 2016;**30**:1043–1049.

9. Balkau B, Lange C, Fezeu L, Tichet J, de Lauzon-Guillain B, Czernichow S *et al.* Predicting diabetes: clinical, biological, and genetic approaches: data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR). *Diabetes Care* 2008;**31**:2056–2061.

10. Cottet V, Touvier M, Fournier A, Touillaud MS, Lafay L, Clavel-Chapelon F *et al.* Postmenopausal breast cancer risk and dietary patterns in the E3N-EPIC prospective cohort study. *Am J Epidemiol* 2009;**170**:1257–1267.

11. Mancini FR, Affret A, Dow C, Balkau B, Bonnet F, Boutron-Ruault M-C *et al.* Dietary antioxidant capacity and risk of type 2 diabetes in the large prospective E3N-EPIC cohort. *Diabetologia* 2018;**61**:308–316.

FIGURE 1 Top characteristics* of women at very high risk of Type 2 diabetes who do not develop the disease (E3N cohort study; *N*=402).

Table 1 Baseline characteristics of participants at very high risk of Type 2 diabetes (D.E.S.I.R. clinical risk score = 5, E3N Cohort study; *N*=402)

		Diagnosis of Type 2 diabetes at the end of follow-up (2014)		
	All (*n*=402)	**Yes (*n*=117)**	**No (*n*=285)**	***P***
D.E.S.I.R. clinical risk score components				
Waist circumference, cm	96.9 (7.40)	97.3 (6.58)	96.7 (7.71)	0.97
Hypertension: yes, *n* (%)	402 (100.0)	117 (29.1)	285 (70.9)	-
Family history of diabetes: yes, *n* (%)	402 (100.0)	117 (29.1)	285 (70.9)	-
Other characteristics				
Age, years	55.7 (6.65)	54.5 (6.32)	56.3 (6.72)	0.52
Smoker: yes, *n* (%)	23 (5.7)	7 (6.0)	16 (5.6)	0.98
BMI, kg/m²	30.5 (3.96)	31.1 (3.69)	30.3 (4.04)	0.49
Years of schooling	13.2 (3.35)	13.4 (3.18)	13.1 (3.42)	0.15
Alcohol, g ethanol/day	11.6 (16.37)	11.4 (14.72)	11.7 (17.02)	0.02
Energy intake, kcal/day	2245.8 (599.44)	2247.67 (548.10)	2245.0 (620.21)	0.12
Recreational physical activity, MET-h/week	21.4 (24.48)	20.2 (18.99)	21.9 (26.39)	0.62
Deprivation index, FDep	–0.1 (0.96)	–0.1 (0.99)	–0.1 (0.95)	0.91
Western pattern adherence score	0.3 (1.11)	0.4 (1.10)	0.2 (1.11)	0.83
Prudent pattern adherence score	0.3 (1.07)	0.2 (1.11)	0.3 (1.05)	0.48
Dietary acid load score (PRAL)	–2.5 (20.30)	0.1 (20.54)	–3.5 (20.14)	0.05
Total dietary antioxidant capacity	13.0 (6.11)	12.8 (6.13)	13.1 (6.11)	0.59

(FRAP, mmol/day)				
Body shape trajectory from 8 years to 35–40 years (Fagherazzi *et al.* [5])				0.41
Trajectory 1	10 (2.5)	2 (1.7)	8 (2.8)	
Trajectory 2	135 (33.6)	45 (38.5)	90 (31.6)	
Trajectory 3	110 (27.4)	31 (26.5)	79 (27.7)	
Trajectory 4	11 (2.6)	1 (0.9)	10 (3.5)	
Trajectory 5	114 (28.4)	34 (29.1)	80 (28.1)	
Trajectory 6	22 (5.5)	4 (3.3)	18 (6.3)	
ABO blood group and rhesus				0.92
O–	127 (31.6)	41 (35.0)	86 (30.2)	
O+	26 (6.5)	8 (6.8)	18 (6.3)	
A+	23 (5.7)	6 (5.1)	17 (6.0)	
A–	131 (32.6)	38 (32.5)	93 (32.5)	
B+	6 (1.5)	1 (0.9)	5 (1.8)	
B–	44 (10.9)	10 (8.6)	34 (11.9)	
AB+	5 (1.2)	2 (1.7)	3 (1.1)	
AB–	8 (2.0)	3 (2.6)	5 (1.8)	
Unknown	32 (8.0)	8 (6.8)	24 (8.4)	
Laterality				0.58
Right-handed	353 (87.8)	102 (87.1)	251 (88.1)	
Left-handed or mixed	36 (9.0)	12 (10.3)	24 (8.4)	
Unknown	13 (3.2)	3 (2.6)	10 (3.5)	
Birth weight				0.44

Light: <2.5 kg	33 (8.2)	11 (9.4)	22 (7.7)	
Medium: 2.5–4 kg	269 (66.9)	85 (72.6)	184 (64.6)	
Heavy: > 4 kg	67 (16.7)	16 (13.7)	51 (17.9)	
Unknown	33 (8.2)	5 (4.3)	28 (9.8)	
Age at menarche				0.75
<13 years	213 (53.0)	61 (52.1)	152 (53.3)	
≥ 13 years	176 (43.8)	53 (45.3)	123 (43.2)	
Unknown	13 (3.2)	3 (2.6)	10 (3.5)	
Number of children, age at first full-term pregnancy				0.38
Nulliparous	57 (14.2)	15 (12.8)	42 (14.6)	
One child, age < 30 years	40 (10.0)	9 (7.7)	31 (10.9)	
One child, age >30 years	12 (3.0)	6 (5.1)	6 (2.1)	
At least two children, age <30 years	261 (64.8)	79 (67.5)	182 (63.9)	
At least two children, age >30 years	30 (7.5)	7 (6.0)	23 (8.1)	
Unknown	2 (0.5)	1 (0.9)	1 (0.4)	
Breastfeeding				0.60
Never	180 (44.8)	50 (42.7)	130 (45.6)	
Yes for at least one pregnancy	222 (55.2)	67 (57.3)	155 (54.4)	
Menopausal status				0.08
Premenopause	121 (30.1)	44 (37.6)	77 (27.0)	
Postmenopause at <50 years	153 (38.1)	37 (31.6)	116 (40.7)	
Postmenopause at >50 years	128 (31.8)	36 (30.8)	92 (32.3)	
Number of hours of sleep per night				0.34

≤ 6 h	72 (17.9)	19 (16.2)	53 (18.6)	
7–8 h	245 (61.0)	79 (67.5)	166 (58.2)	
≥ 9 h	74 (18.4)	18 (15.4)	56 (19.7)	
Unknown	11 (2.7)	1 (0.9)	10 (3.5)	
Treated hypercholesterolaemia				0.43
No	342 (85.1)	97 (82.9)	245 (86.0)	
Yes	60 (14.9)	20 (17.1)	40 (14.0)	
Intestinal transit				0.18
Normal	282 (70.1)	90 (76.9)	192 (67.4)	
Diarrhoea	24 (6.0)	6 (5.2)	18 (6.3)	
Constipation	39 (9.7)	6 (5.2)	33 (11.6)	
Alternating diarrhoea constipation	47 (11.7)	13 (11.1)	34 (11.9)	
Unknown	10 (2.5)	2 (1.7)	8 (2.8)	
Marital status				
Single	85 (21.1)	27 (23.1)	58 (20.4)	
In couple	295 (73.4)	86 (73.5)	209 (73.3)	
Unknown	22 (5.5)	4 (3.4)	18 (6.3)	

**n* (%) and *P* values of chi-squared tests for categorical variables.

Means (SD) and logistic regression tests for continuous variables.

FDep, xxx; PRAL, xxx.