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Functional Gastrointestinal Disorders and Incidence of Type 2 Diabetes: Evidence from the E3N-EPIC Cohort Study

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Abbreviations:

- BMI: body mass index
- E3N: *Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Éducation Nationale*
- FGID: functional gastrointestinal disorder
- T2D: type 2 diabetes

ABSTRACT

OBJECTIVE. Functional gastrointestinal disorders (FGID) such as diarrhea or constipation can reflect intestinal dysfunction, especially with regard to the intestinal microbiota, which in turn has been associated with chronic conditions including obesity and insulin resistance. However, little is known on the association between FGID and type 2 diabetes risk.

DESIGN & METHODS. We analyzed the influence of diarrhea, constipation and alternation diarrhea-constipation on T2D risk in 62 683 women from the prospective E3N-EPIC cohort.

RESULTS. We recorded 1 795 T2D cases during follow-up. Compared to women with a normal gastrointestinal transit, women with chronic diarrhea or alternation diarrhea-constipation were at increased risk of T2D (HR=1.29, 95%CI:[1.00-1.65] and 1.32, 95%CI: [1.15-1.52] respectively), whereas women with constipation were at decreased risk (HR=0.67, 95%CI: [0.57-0.78]). There was no interaction between FGID and BMI for the risk of diabetes. The associations were independent of dietary habits such as coffee, fruit and vegetable consumption, and even of the use of laxatives and psychotropic drugs.

CONCLUSIONS. The study showed for the first time an association between some FGID and T2D risk in a large prospective cohort and supports the hypothesis of a relationship between gastrointestinal functions and diabetes. The presence of gastrointestinal transit disorders could assist in the screening of subjects at higher risk of diabetes, beyond conventional risk factors.

KEYWORDS: functional gastrointestinal disorders, type 2 diabetes, cohort, risk factor

Type 2 diabetes (T2D) is one of the most frequent chronic diseases worldwide and its prevalence keeps increasing.¹ The International Diabetes Federation predicts an increase in the worldwide prevalence of T2D from 8.3% to 8.8% in people aged 20 to 79 years between 2013 and 2035, with 382 million people having T2D in 2013 and 592 million in 2035.² Diabetes has a high social and economic burden and even though primary and secondary preventions of diabetes are constantly improving, there is still a need for a better understanding of this disease. Similarly, functional gastrointestinal disorders (FGID) such as irritable bowel syndrome (IBS) are highly prevalent conditions,³⁻⁵ and frequently accompanied with diarrhea or constipation.⁵ The worldwide pooled prevalence of chronic idiopathic constipations has been estimated to be 14%.³ The rate is higher in women and in individuals with low socioeconomic status. It increases with age and is country-dependent, with France ranking among the top countries.³ In 1998, about 26 million French individuals were affected by at least one type of FGID.⁶ A French study in 1998, based on a representative sample of the general population aged over 15 years, reported that among those with FGID, 35% had constipation and 28% had diarrhea, and that symptoms lasted 6 months to 5 years for 38% of subjects, and over 5 years for another 52%.⁵

It is known that individuals with T2D have more frequent occurrences of diarrhea and constipation than the general population.⁷⁻⁹ An estimated 76% of diabetic patients suffer from FGID,¹⁰ which are partly attributed to the side effects of T2D treatments such as metformin¹¹ or insulin,¹⁰ or to complications of T2D. Population studies have also shown that obesity is associated with a wide range of chronic gastrointestinal complaints,¹²⁻¹⁷ which supports the hypothesis that obesity and FGID are physiologically related.^{4, 10, 11} To date, little is known on the longitudinal association of gastrointestinal disorders such as diarrhea and constipation and the risk of incident T2D. Hypotheses relating FGID and the microbiota have recently been proposed.¹⁸ FGID and the microbiota are thought to share common features such as a genetic predisposal, which could then be involved in the genesis of immune-related disorders and diabetes.¹⁹ Further, specific features of the microbiota have been associated with the development of T2D.^{20, 21}

However, to our knowledge, no study has ever evaluated whether FGID such as diarrhea and constipation could be associated with the risk of developing T2D. Therefore we analyzed the relation between FGID and incident T2D in the large prospective E3N-EPIC cohort study.

RESEARCH DESIGN & METHODS

Study population

The E3N study (*Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale*) is a French prospective cohort study of 98 995 female teachers initiated in 1990²². E3N is the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC). Participants returned mailed questionnaires to update health-related information and newly diagnosed diseases every 2 to 3 years and a drug reimbursement claims database has been available since 2004 from their medical insurance records (*Mutuelle Générale de l'Education Nationale (MGEN)*). Average follow-up per questionnaire cycle has been 83% and overall, the total loss to follow-up since 1990 is less than 3%. All women signed an informed consent letter to comply with the French National Commission for Computerized Data and Individual Freedom (CNIL).

Of the 98 995 women in the cohort, we excluded those who did not complete the dietary questionnaire (n = 24 466), those who did not complete any questionnaire after inclusion (n = 926), prevalent cases or non-validated cases of diabetes (n = 3 356), prevalent cases of cardiovascular diseases (stroke and myocardial infarction, n=127), prevalent cancer cases (n=4 169), those with missing baseline information on gastrointestinal transit (n=1 893) and those with extreme values for the ratio between energy intake and required energy (i.e. the lowest and highest percentiles in the cohort) (n = 1 375). A total of 62 683 women were finally included in the analysis, amongst whom 1 795 had a validated diagnosis of T2D during follow-up (1993-2008). Mean follow-up was 8.81 years (STD=2.59) for cases, and 13.58 years (STD=3.94) for non-cases.

Assessment of functional gastrointestinal disorders

Updated information on FGID was requested in the baseline questionnaire (1993) and in the four subsequent follow-up questionnaires (1995, 1997, 2000 and 2002). Study participants answered the question “Which of the following best describes your bowel movements: normal, diarrhea, constipation, alternation diarrhea-constipation”. Baseline characteristics of the study population according to this variable are provided in Table 1.

Ascertainment of diabetes

Potential diabetes cases were identified first through self-reporting of diabetes in any of the 9 follow-up questionnaires, diabetes diet, antidiabetic drugs, hospitalization for diabetes or through the drugs reimbursement file obtained from the insurance every three months since 01/01/2004. All potential cases were sent a specific questionnaire that included questions on the circumstances of diagnosis (year of diagnosis, symptoms, biological exams, fasting or random glucose concentrations at diagnosis), present diabetes therapy (prescription of a medical diet or physical activity, list of antidiabetic treatments), last measurement of fasting glucose and HbA1c levels. Cases were considered validated when positive for at least two of the following three sources: self-reported diabetes in the follow-up questionnaires and/or positive answer to the specific diabetes questionnaire (i.e. fasting plasma glucose ≥ 1.26 g/l or random glucose ≥ 2.00 g/l at diagnosis and/or current fasting plasma glucose ≥ 1.26 g/l and/or current HbA1c $\geq 7\%$ and/or reporting of antidiabetic drug use) and/or antidiabetic drugs reimbursed by the health insurance in the 1/1/2004-1/1/2012 period. Cases identified through the drug reimbursement file but who were reimbursed for antidiabetic drugs only once in the period and had declared to be non-diabetic were considered as non-cases.

For the present analysis, prevalent and non-validated diabetes cases were excluded from the analyses, leaving 1 795 validated incident cases during follow-up.

Statistical analysis

Association between gastrointestinal transit and type 2 diabetes risk

Descriptive data were presented as mean (STD) and N (%). Cox multivariable regression models with age as the time scale were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) and are tabulated in Table 2. Time at entry was the age at the beginning of follow-up, exit time was the age when participants were diagnosed with diabetes, died, were lost to follow-up, or were censored at the end of the follow-up period, whichever occurred first. The main exposure variable was FGID (normal/diarrhea/constipation/alternation diarrhea-constipation), which was modeled as a time-dependent variable, considering the “normal” category as the reference. Both age-adjusted (M_0) and multivariable models (M_1) were computed. Multivariable models were adjusted for established T2D risk factors: smoking status (nonsmoker/ ex-smoker/ current smoker, time-dependent), physical activity (continuous in Met-h/week, time-dependent), treated hypertension (yes, no, time-dependent), treated hypercholesterolemia (yes, no, baseline), family history of diabetes (yes/no, baseline).

A similar analysis has been performed with overweight as the outcome instead of T2D to quantify the potential mediation by adiposity between FGID and T2D.

Sensitivity analyses

We fitted additional models (M_2) adjusted for dietary factors, considered as continuous variables: intake of ethanol (g/day), omega 3 fatty acids (g/day), carbohydrates (g/day), and energy from fat and protein (kcal/day), and consumption of coffee (mL/day), fruits and vegetables(g/day), and processed meat (g/day). Finally, as adiposity is a key factor in T2D etiology, we tested models (M_3) additionally adjusted for BMI (continuous, kg/m²). We also tested a potential interaction between FGID and BMI, which was shown to be not statistically significant ($P_{inter}=0.45$).

To investigate potential reverse causation, we also evaluated the associations between FGID and T2D by excluding cases in the first five years of follow-up. We also computed Cox models starting in 1995 instead of 1993, where information on the use of laxatives and psychotropic drugs was available.

All statistical analyses used SAS 9.3 (SAS Institute Inc., Cary, NC, PHREG procedure for Cox models). All statistical tests were two-sided and considered as significant if the P-value<0.05.

RESULTS

Baseline characteristics

Compared to women with a normal gastrointestinal transit, those with chronic diarrhea were more frequently current smokers (15.6 vs. 13.3%), had a higher intake of carbohydrates (240.4 vs. 236.1 g/day), drank more alcohol (13.9 vs. 11.4 g/day), had a higher energy intake from fat and protein (1 214.4 vs. 1 191.0 kcal/day), drank less coffee (277.0 mL/day vs. 290.7 mL/day), ate less fruits and vegetables (462.7 vs. 488.9 g/day) and had a higher processed meat consumption (26.5 vs. 24.4 g/day) (Table 1).

Women with chronic constipation had a lower BMI than women with a normal gastrointestinal transit (22.4 vs. 22.9 kg/m²). They were more frequently treated for hypercholesterolemia (7.2 vs. 6.8%), had less physical activity (46.6 vs. 50.1 Met-hr/week), had a lower intake of carbohydrates (228.7 vs. 236.1 g/day,) and had lower energy intake from fat and protein (1 174.0 vs. 1 191.0 kcal/day).

Finally, women who had alternation diarrhea-constipation were characterized by a higher coffee consumption than those with normal gastrointestinal transit (295.0 vs. 290.7 mL/day).

Functional gastrointestinal disorders and type 2 diabetes risk

In age-adjusted models (M_0 , Table 2), there was a positive association between chronic diarrhea and T2D risk, when compared to women with normal gastrointestinal transit ($HR=1.36$, 95%CI: [1.07-1.74]). In contrast, women with chronic constipation were at a decreased risk of T2D (0.68 [0.58-0.79]). Women with alternation diarrhea-constipation were at an increased risk of T2D (1.42 [1.23-1.63]).

Further adjustment for T2D risk factors (M_1 models) did not materially change the magnitude of the associations (HR [95%CI]: 1.31 [1.03-1.68], 0.67 [0.57-0.78] and 1.37 [1.18-1.57] for women with chronic diarrhea, constipation and alternation of diarrhea and constipation respectively, as compared to women with normal gastrointestinal transit). Similarly, adjustment for dietary data (models M_2) did not modify the associations (respectively 1.29 [1.00-1.65], 0.67 [0.57-0.78] and 1.32 [1.15-1.52] for women with diarrhea, constipation, and alternation diarrhea-constipation, as compared to women with normal gastrointestinal transit) suggesting alternative mechanisms.

Mediation by body mass index

The associations between constipation and alternation of diarrhea and constipation, and risk of T2D were slightly reduced after adjustment for BMI ($HR=0.85$ [0.73-0.99] and 1.26 [1.09-1.45] respectively), while there was no longer any association with chronic diarrhea (1.04 [0.81-1.32]) (M_3 models).

In addition, we have seen similar patterns of risk regarding the associations between diarrhea, constipation, and alternation diarrhea-constipation and the risk of incident overweight (data not shown). When compared to women with normal gastrointestinal transit, women with constipation were associated with a decreased risk of overweight ($HR=0.84$ [0.80-0.89]), women with diarrhea were at increased risk ($HR=1.13$ [1.01-1.26]) and without influence among women with alternation diarrhea-constipation ($HR=1.01$ [0.95-1.08]).

Other sensitivity analyses

To test the hypothesis of potential reverse causation, we evaluated the associations between FGID and T2D by excluding cases in the first five years of follow-up and results were similar. Similarly, we also computed Cox models starting in 1995 instead of 1993, where information on the use of laxatives and psychotropic drugs was available. Adjustment for these potential confounders did not alter the associations observed.

CONCLUSIONS

In the large prospective E3N-EPIC cohort study, we showed for the first time an association between FGID and T2D risk. Women with chronic diarrhea were found to be at increased risk of T2D when compared to those with normal gastrointestinal transit, whereas those with chronic constipation had a marked decrease in T2D risk. These associations were found to be independent of established T2D risk factors, of dietary habits such as coffee or fruit and vegetable consumption, and even of the use of laxatives and psychotropic drugs. The association with diarrhea was found to be mediated partly by adiposity since, after controlling for BMI, only chronic constipation and alternation diarrhea-constipation were still associated with a respectively decreased and increased T2D risk. Moreover, we have found consistent patterns of risk for diarrhea and constipation when looking at overweight as the outcome instead of T2D. These results are in favor of both a direct mechanism between FGID and T2D and an indirect one through adiposity.

Potential mechanisms

To our knowledge, this is the first study to investigate the association between FGID and T2D risk. Mechanisms in relation to the gut microbiota and inflammation could explain, at least partly, our results. An altered gut microbiota has been linked to obesity and T2D.^{23,24} Individuals with chronic FGID are suggested to have a different microbial ecology compared to those with normal gastrointestinal transit, which could in turn result in different risks for T2D.¹⁹

The intestinal microbial community can affect the rate of deposition and utilization of fat, insulin resistance and diabetes, as well as an inflammation state.^{19,25} It is known that the gut microbiota participates in the overall body metabolism by affecting energy balance, glucose metabolism and low-grade inflammation associated with obesity and related metabolic disorders such as T2D.²⁶ It has been shown that transfer of intestinal microbiota can modulate insulin sensitivity in individuals with metabolic syndrome.²⁷ Translocation of gut microbiota, particularly endotoxins or lipopolysaccharides on the surface of gram-negative bacteria to the systemic circulation, has been proposed to induce inflammation and insulin resistance.²⁴ In mouse, commensal gut bacteria translocate to mesenteric adipose tissue, initiating low-grade inflammation before the onset of insulin resistance and type 2 diabetes.²⁸

However, the present epidemiological study was not designed to properly address the impact of gut microbiota on both FGID and the risk of diabetes. Further complimentary studies are warranted to test this hypothesis.

Limitations and advantages

This study has some limitations. Although we adjusted for many type 2 diabetes risk factors, some residual confounding cannot be completely ruled out. Our study population included only women. Even if some previous studies have reported a higher prevalence of FGID in women,³ there is no biological ground to suggest indicate that the association with T2D is restricted to women.

This study has also numerous strengths. The large number of cases enabled us to have a high statistical power to detect associations. The dietary questionnaire of the E3N-EPIC cohort study provided detailed information on the women's diet, thus enabling us to adjust for potential confounders. Moreover, we analyzed validated incident type 2 diabetes cases only, based on a well-defined validation algorithm, which reduced the risk of missing cases or of false-positive cases. Some residual misclassifications with respect to diabetes status may exist, but it is likely to be non-differential with regard to FGID.

Lastly, the prospective design and the long follow-up in the E3N-EPIC cohort allowed us to perform sensitivity analyses while maintaining sufficient statistical power, making a reverse causation hypothesis unlikely.

Conclusion

The study showed for the first time an association between some FGID and T2D risk in a large prospective cohort study, which supports the hypothesis of a relationship between gastrointestinal functions and the development of diabetes. The presence of gastrointestinal transit disorders could assist in the screening of subjects at higher risk of diabetes, independently of classical risk factors. These findings need to be confirmed in other populations and these results may prompt future research, in particular the assessment of the influence of microbiota on the risk of diabetes in individuals with FGID.

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Table 1. Baseline characteristics by gastrointestinal transit. E3N Cohort data (N = 62 683).

Mean (STD) or N(%)	Gastrointestinal transit				P-value*
	Normal (N = 44 711)	Diarrhea (N = 1 752)	Constipation (N = 8 719)	Alternation Diarrhea - Constipation (N = 7 501)	
Age (years)	52.6 (6.6)	52.8 (6.6)	52.9 (6.6)	52.6 (6.5)	0.0012
Body Mass Index (kg/m²)	22.9 (3.1)	23.0 (3.7)	22.4 (2.8)	23.0 (3.3)	<0.0001
Smoking					
<i>Non smoker</i>	24 668 (55.2)	901 (51.4)	4 769 (54.7)	3 846 (51.3)	<0.0001
<i>Former smoker</i>	14 112 (31.6)	577 (32.9)	2 784 (31.9)	2 503 (33.4)	
<i>Current smoker</i>	5 931 (13.3)	274 (15.6)	1 166 (13.4)	1 152 (15.4)	
Treated hypercholesterolemia (yes)	3 032 (6.8)	118 (6.7)	626 (7.2)	481 (6.4)	<0.0001
Family history of diabetes (yes)	4 965 (11.1)	191 (10.9)	955 (11.0)	799 (10.7)	0.0058
Treated hypertension (yes)	661 (1.5)	32 (1.8)	128 (1.5)	121 (1.6)	0.0768
Physical activity (met-hr/week)	50.1 (49.5)	49.7 (65.7)	46.4 (48.9)	47.5 (48.7)	<0.0001
Carbohydrates (g/day)	236.1 (71.3)	240.4 (73.1)	228.7 (70.3)	237.9 (72.4)	<0.0001
Alcohol (g/day)	11.4 (13.5)	13.9 (18.4)	11.1 (13.3)	12.2 (14.7)	<0.0001
Energy from fat and protein (kcal/day)	1 191.0 (322.1)	1 214.4 (339.5)	1 174.0 (327.3)	1 212.4 (339.9)	<0.0001
Coffee (ml/day)	290.7 (264.1)	277.0 (264.6)	293.0 (277.2)	295.0 (271.8)	<0.0001
Fruits & Vegetables (g/day)	488.9 (230.0)	462.7 (238.1)	477.4 (229.9)	461.9 (223.7)	<0.0001
Omega 3 fatty acids intake (g/day)	1.5 (0.5)	1.5 (0.6)	1.5 (0.5)	1.5 (0.6)	<0.0001
Processed meat (g/day)	24.4 (18.8)	26.5 (20.8)	24.7 (19.3)	26.3 (20.3)	<0.0001

* P-values were derived from Khi-2 tests for categorical variables and Kruskal-Wallis tests for continuous variables

Table 2. Hazard-ratios (HR) and 95% confidence intervals (95% CI) for type 2 diabetes by gastrointestinal transit. E3N Cohort data (N = 62 683)

HR (CI 95%)	Gastrointestinal transit			
	<i>Normal</i>	<i>Diarrhea</i>	<i>Constipation</i>	<i>Alternation Diarrhea - Constipation</i>
Cases	N = 1325	N = 67	N = 178	N = 225
Models M ₀ : Age-adjusted	1 (Ref)	1.36 (1.07-1.74)	0.68 (0.58-0.79)	1.42 (1.23-1.63)
M ₁ : M ₀ + established T2D risk factors [†]	1 (Ref)	1.31 (1.03-1.68)	0.67 (0.57-0.78)	1.37 (1.18-1.57)
M ₂ : M ₁ + dietary information [‡]	1 (Ref)	1.29 (1.00-1.65)	0.67 (0.57-0.78)	1.32 (1.15-1.52)
M ₃ : M ₂ + body mass index	1 (Ref)	1.05 (0.82-1.35)	0.85 (0.73-0.99)	1.26 (1.09-1.46)

[†] adjusted for age, smoking status, physical activity, hypertension, hypercholesterolemia, family history of diabetes

[‡] further adjusted for alcohol intake, omega 3 fatty acids intake, carbohydrate intake, total energy intake (excluding alcohol and carbohydrate), coffee, fruits and vegetables and processed meat consumption