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Original article

Functional gastrointestinal disorders and incidence of type 2 diabetes: Evidence from the E3N–EPIC cohort study

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Abstract

Objective. – Functional gastrointestinal disorders (FGID) such as diarrhoea and constipation can reflect intestinal dysfunction, especially with regard to intestinal microbiota, which, in turn, have been associated with chronic conditions, including obesity and insulin resistance. However, little is known of the association between FGID and type 2 diabetes (T2D) risk.

Design and methods. – This analysis aimed to determine the influence of diarrhoea, constipation and alternating bouts of diarrhoea/constipation on T2D risk in 62,683 women from the prospective E3N–EPIC cohort.

Results. – A total of 1795 T2D cases were recorded during follow-up. Compared with women who had normal gastrointestinal transits, women with chronic diarrhoea or alternating diarrhoea/constipation were at increased risk of T2D (HR: 1.29, 95% CI: 1.00–1.65 vs. HR: 1.32, 95% CI: 1.15–1.52, respectively), whereas women with constipation had a decreased risk (HR: 0.67, 95% CI: 0.57–0.78). There was no interaction between FGID and body mass index for risk of T2D. Also, these associations were independent of dietary habits such as coffee, fruit and vegetable consumption, and even of the use of laxatives and psychotropic drugs.

Conclusion. – The present analysis showed, for the first time, a limited association between FGID and T2D risk in a large prospective cohort, and supports the hypothesis of a relationship between gastrointestinal function and diabetes. The presence of gastrointestinal transit disorders may assist in screening for subjects at higher risk of diabetes beyond the conventional risk factors.

Keywords: Cohort; Functional gastrointestinal disorders; Risk factor; Type 2 diabetes

1. Introduction

Type 2 diabetes (T2D) is one of the most common chronic diseases seen worldwide, and its prevalence continues to increase [1]. The International Diabetes Federation predicts an increase in T2D worldwide prevalence 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 by 2035 [2]. Diabetes brings a high social and economic burden and, although its primary and secondary prevention is constantly improving, there is still a need for better understanding of the disorder. Similarly, functional gastrointestinal disorders (FGID) such as irritable bowel syndrome (IBS) are highly prevalent conditions [3–5], and frequently accompanied by diarrhoea and/or constipation [5]. The worldwide-pooled prevalence of chronic idiopathic constipation has been estimated to be 14% [3]. The rate is higher in women and in those of low socioeconomic status. It increases with age and is country-dependent, with France being among

Abbreviations: BMI, body mass index; E3N, *Étude Épidémiologique auprès des femmes de la Mutuelle Générale de l'Éducation Nationale*; FGID, functional gastrointestinal disorders; T2D, type 2 diabetes.

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the top-ranked countries [3]. In 1998, around 26 million French citizens were affected by at least one type of FGID [6]. A French study done in 1998, based on a representative sample of the general population aged > 15 years, reported that, among those with FGID, 35% had constipation and 28% had diarrhoea, and these symptoms lasted from 6 months to 5 years in 38% of subjects and for > 5 years in a further 52% [5].

It is accepted that patients with T2D have more frequent bouts of diarrhoea and constipation than the general population [7–9]. An estimated 76% of diabetic patients suffer from FGID [10], which is partly attributed to the side effects of T2D treatments, such as metformin [11] and insulin [10], and to complications of T2D. Population studies have also shown that obesity is associated with a wide range of chronic gastrointestinal (GI) complaints [12–17], thereby supporting the hypothesis that obesity and FGID are physiologically related [4,10,11]. To date, little is known of the longitudinal association of GI disorders, such as diarrhoea and constipation, and the risk of incident T2D. Hypotheses associating FGID and the microbiota have recently been proposed [3]. FGID and the microbiota are thought to share common features, including a genetic predisposition, which might then be involved in the genesis of immune-related disorders and diabetes [18,19]. Furthermore, specific features of the microbiota have been associated with the development of T2D [20,21]. However, to our knowledge, no study thus far has ever evaluated whether FGID such as diarrhoea and constipation could be associated with the risk of developing T2D. Therefore, this analysis of the relationship between FGID and incident T2D was carried out in a group of women from the large-scale prospective E3N–EPIC cohort study.

2. Research design and methods

2.1. Study population

The E3N study (*Étude Épidémiologique auprès des femmes de la Mutuelle Générale de l'Éducation Nationale*) is a French prospective cohort study of 98,995 female teachers that began in 1990 [22]. The study is also the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC). Participants returned mailed questionnaires to update their 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'Éducation Nationale* (MGEN)]. The average follow-up per questionnaire cycle has been 83% and, overall, the total proportion of patients lost to follow-up since 1990 is < 3%. All women signed an informed consent letter to comply with the French National Commission for Computerized Data and Individual Freedoms (CNIL).

Of the 98,995 women in the cohort, those who failed to complete the dietary questionnaire ($n = 24{,}466$) or any questionnaire after inclusion ($n = 926$), and prevalent or non-validated cases of diabetes ($n = 3356$), prevalent cases of cardiovascular diseases [stroke and myocardial infarction ($n = 127$)], prevalent cancer cases ($n = 4169$), those missing baseline information on GI transit ($n = 1893$) and those with extreme ratios of energy intake to required energy (those in the lowest and highest percentiles in the cohort; $n = 1375$) were excluded. Ultimately, a total of 62,683 women were included in our analysis, of whom 1795 had a validated diagnosis of T2D during follow-up (1993–2008). Mean follow-up duration was 8.81 years (SD = 2.59) for cases, and 13.58 years (SD = 3.94) for non-cases.

2.2. Assessment of functional gastrointestinal disorders

Updated information on FGID was requested by the baseline questionnaire (1993) as well as the four subsequent follow-up questionnaires (in 1995, 1997, 2000 and 2002). Study participants had to answer the question: "Which of the following best describes your bowel movements: normal, diarrhoea, constipation, alternating diarrhoea/constipation?" Baseline characteristics of the study population according to this variable are presented in Table 1.

2.3. Ascertainment of diabetes

Potential diabetes cases were identified first through self-reporting of diabetes on any of the nine follow-up questionnaires, and also by diabetes diet, antidiabetic drugs, hospitalization for diabetes and antidiabetic drug-reimbursements obtained from insurance records every 3 months since 1st January 2004. All potential cases were sent a specific questionnaire that included questions on the circumstances of the diagnosis (year of diagnosis, symptoms, biological examinations, fasting or random glucose concentrations at diagnosis), current diabetes therapy (prescription of a medical diet or physical activity, list of antidiabetic treatments), and latest values for fasting glucose and HbA_{1c} levels. Cases were considered validated if positive for at least two of the following three sources: self-reported diabetes on follow-up questionnaires and/or a positive answer to the specific diabetes questionnaire (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 $HbA_{1c} \geq 7\%$, and/or report of antidiabetic drug use), and/or antidiabetic drug-reimbursements by the health insurance company during the period 1st January 2004 to 1st January 2012. Cases identified through drug-reimbursement files, but with reimbursement for antidiabetic drugs only once during the period, and declared to be nondiabetic were considered non-cases.

Thus, for the present analysis, prevalent and non-validated diabetes cases were excluded, leaving 1795 validated incident cases during follow-up.

2.4. Statistical analysis

2.4.1. Association between gastrointestinal transit and type 2 diabetes risk

Descriptive data are presented as means (SD) and as *n* (%). Cox multivariable regression models with age as the timescale were used to estimate the hazard ratio (HR) and 95% confidence interval (95% CI), and are presented in Table 2. Time at entry was patient's age at the beginning of follow-up, and exit time was the age at which the participant was either diagnosed with diabetes,