



Chronic Consumption of Artificial Sweetener in Packets or Tablets and Type 2 Diabetes Risk: Evidence from the E3N-European Prospective Investigation into Cancer and Nutrition Study

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Keywords

Diabetes · Artificial sweeteners · Risk · Cohort · Epidemiology

Abstract

Background: The influence of artificial sweeteners on metabolic diseases is controversial. Artificially sweetened beverages have been associated with an increased risk of type 2 diabetes (T2D) but biases and reverse causation have been suspected to have influenced the observed association. In addition, it has been suggested that investigation into the relationship between the frequency and duration of the consumption of packet or tablet artificial sweeteners and T2D risk is necessary. **Methods:** We used data from 61,440 women in the prospective E3N-European Prospective Investigation into Cancer and Nutrition study, conducted between 1993 and 2011. We estimated hazards ratios (HRs) and 95% CIs of T2D risk associated with both the frequency and the duration of use of artificial sweeteners consumed in packets or tablets. **Results:** Compared to “never or rare” consumers of artificial sweeteners, those using them “always or almost always” had an increased risk of T2D (HR = 1.83 [95% CI 1.66–

2.02] in the multivariate model [MM], HR = 1.33 [95% CI 1.20–1.47] when further adjusted for body mass index, BMI). Women consuming artificial sweeteners in packets or tablets for more than 10 years also had an increased risk of T2D compared to never or rare users (HR = 2.10 [95% CI 1.83–2.40] in the MM and HR = 1.15 [95% CI 1.00–1.33] when adjusted for BMI, respectively). **Conclusions:** Our data suggest that both a higher frequency and a longer consumption of artificial sweeteners in packets or tablets was associated with T2D risk, independently of major T2D risk factors, but partially mediated by adiposity. A precautionary principle should be applied to the promotion of these products that are still largely recommended as healthy sugar substitutes.

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Introduction

The influence of artificial sweeteners on metabolic diseases is controversial. Studies focused on artificially sweetened beverage consumption have found a direct association with type 2 diabetes (T2D) risk [1], while others have reported that associations disappeared when

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controlling for adiposity [2]. In a recent meta-analysis, artificial sweetener consumption was associated with increased T2D risk but the association was considered likely to be due to reverse causation biases because of a likely higher consumption of artificially sweetened beverages among overweight individuals [3].

Moreover, most studies have only been able to study diet drinks [4]; so little is known about the overall influence of artificial sweeteners in the diet, particularly those in the form of packets or tablets that can be added to coffee or yoghurt as a substitute for sugar. In an intervention study on the postprandial insulin response to preloads of sucrose, aspartame, and stevia extract, there was no reduction in postprandial insulin levels with aspartame despite reduced glycemia, which might contribute to hyperinsulinism. The authors suggested that the use of artificial sweeteners could result in metabolic abnormalities [5]. In addition, it has been suggested that diet drinks could increase the craving for and consumption of high sugar, energy-dense foods and drinks, or could cause consumers to underestimate their energy intake, and result in a positive energy balance leading to weight gain [6]. Finally, a large intake of artificial sweeteners may be associated with glucose intolerance by altering the gut microbiota [7].

Consumption of sweeteners has increased significantly in recent years [8] as their presence have become increasingly higher in everyday products, not only as tabletop packets and diet drinks, but also in breakfast cereals, snack foods, dairy products, and medications. There is a need for careful evaluation of the risk–benefit balance of these products. There is especially a need for studies that investigate a potential cumulative effect of artificial sweetener consumption over long periods, which has never been reported thus far.

Our aim was therefore to study the associations between the frequency and the duration of use of artificial sweeteners in packets or tablets and the risk of T2D, based on very detailed data from the E3N-European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Material and Methods

Study Population

E3N-EPIC is a prospective French cohort study of 98,995 women recruited in 1990 and born between 1925 and 1950 [9]. It is the French contribution to the large EPIC and the EPIC substudy devoted to diabetes with respect to interaction of genetic and lifestyle factors on the incidence of T2D (InterAct) [10]. Data are available

from mailed questionnaires that participants returned every 2–3 years, in addition to a drug-reimbursement claims database that has been available since 2004 from the participants' medical records. The average follow-up per questionnaire cycle has been 83%, and to date, the total loss to follow-up since 1990 is 3%. All women signed letters of informed consent, in compliance with the French National Commission for Computerized Data and Individual Freedom (CNIL).

For this analysis, women were excluded if they did not complete the dietary questionnaire ($n = 24,466$), had pre-existing diabetes ($n = 803$) or a prevalent major chronic disease (cancer and cardiovascular disease; $n = 8,463$), did not complete any questionnaire after the dietary questionnaire ($n = 161$), had extreme values for the ratio between energy intake and required energy (i.e., below the 1st or above the 99th percentiles of the distribution in the population; $n = 1,236$), or had not answered the question on the frequency of use of artificial sweeteners ($n = 2,426$). Thus, the analysis included 61,440 women, of whom 2,152 had a validated incident T2D diagnosed during follow-up (June 1993–December 2011).

Assessment of the Consumption of Artificial Sweeteners in Packets or Tablets

Dietary data were collected in 1993 using a validated diet history questionnaire [11]. The frequencies and quantities of 208 food items consumed over the past year were reported for 8 periods during the day, from breakfast to after-dinner snacks (including the aperitif, before lunch and dinner).

Participants were asked, “Do you usually use artificial sweeteners, either in packets or tablets (for coffee, tea, etc.)? at the following meals: breakfast, morning snacks, lunch, afternoon snacks, dinner, and after-dinner snacks.” These 6 “yes or no” questions were combined into a daily frequency index ranging from 0 to 6, which was categorized as the following: 0, the reference category; 1; 2; ≥ 3 times per day.

The frequency of the use of artificial sweeteners as a substitute for sugar was also ascertained in the same questionnaire from the question, “How often do you replace sugar by artificial sweeteners?” Possible answers were “never or rarely,” “half the time,” and “always or almost always”.

Finally, participants who responded “half the time” or “always or almost always” were asked to report the year they started to consume artificial sweeteners in packets or tablets; the duration of use was calculated and categorized by quartiles (<3, 3–5, 5–10, and ≥ 10 years).

Ascertainment of T2D

The validation algorithm for T2D cases has already been described elsewhere [12] but briefly, potential cases of T2D were first identified either in follow-up questionnaires (with declaration of at least one of the following: T2D, a diabetes diet, use of a glucose lowering medication, or hospitalization due to diabetes), or they were identified as receiving a glucose-lowering medication reimbursement from health insurance records, at least once between January 2004 and March 2012. Those who were identified in both manners were considered validated. All participants were mailed a diabetes-specific questionnaire that included questions on the circumstances of the diagnosis (year, symptoms, biological examinations, etc.), management (diabetes diet, physical activity, medications), and results of their most recent concentrations of fasting

glucose and glycated hemoglobin (HbA1c). Cases that were not validated by the first algorithm were validated if one of the following criteria was met: fasting plasma glucose ≥ 7.0 mmol/L, random glucose ≥ 11.1 mmol/L at diagnosis, report of glucose-lowering medication use, or last values of fasting glucose or HbA1c concentrations ≥ 7.0 mmol/L or $\geq 7\%$, respectively. In total, 2,152 validated cases of incident diabetes and 59,288 non-cases were analyzed in the present study.

Statistical Analyses

Cox multivariable regression models, with age as the time scale, were used to estimate hazards ratios (HRs) and 95% CIs of T2D risk. The time at entry was the age at the start of follow-up and the exit time was the age when participants were diagnosed with T2D, died, were lost to follow-up, or were censored at the end of the follow-up period, whichever occurred first. We first performed univariate analysis (model 1), then adjusted for baseline alcohol consumption (g/day), carbohydrate intake (g/day), daily energy intake from protein and lipids (kcal/day), level of education (less than high school diploma vs. high school diploma or more), smoking status (never vs. current/former), hypertension (yes vs. no), hypercholesterolemia (yes vs. no), family history of diabetes (yes vs. no), and physical activity (in metabolic equivalents, MET hours/week; model 2). Model 3 was further adjusted for body mass index (BMI; <20 , 20–25, 25–30, or ≥ 30 kg/m²).

For variables with $<5\%$ of values missing during follow-up, missing values were imputed with the median of the study population (quantitative variables) or the mode (qualitative variables), as preliminary analyses demonstrated that results were similar to those where missing values were replaced through multiple imputation. In the case of $\geq 5\%$ of missing values, a “missing” category was created. T2D Kaplan–Meier curves were also computed according to the duration of use of artificial sweeteners (Fig. 1).

As sensitivity analyses, we computed additional multivariate models adjusted for the consumption of artificially sweetened beverages and dietary patterns (i.e., “Western” and “Mediterranean”), which were derived from a principal component analysis (PCA) as a surrogate for the overall diet quality, as previously described [13]. In order to test for a potential reverse causation bias, analyses were also performed on a subpopulation excluding participants who had developed diabetes in the first 5 years after inclusion in the study. All statistical analyses used SAS 9.4 software (PHREG procedure for Cox models and LIFETEST for Kaplan–Meier curves; SAS Institute Inc.). All statistical tests were 2-sided and considered significant at $p < 0.05$.

Results

Study Population Characteristics

The baseline characteristics of the study population are shown in Table 1, according to the frequency of consumption of artificial sweeteners. We observed a gradient between the frequency of consumption of artificial sweeteners and several unhealthy behaviors while comparing

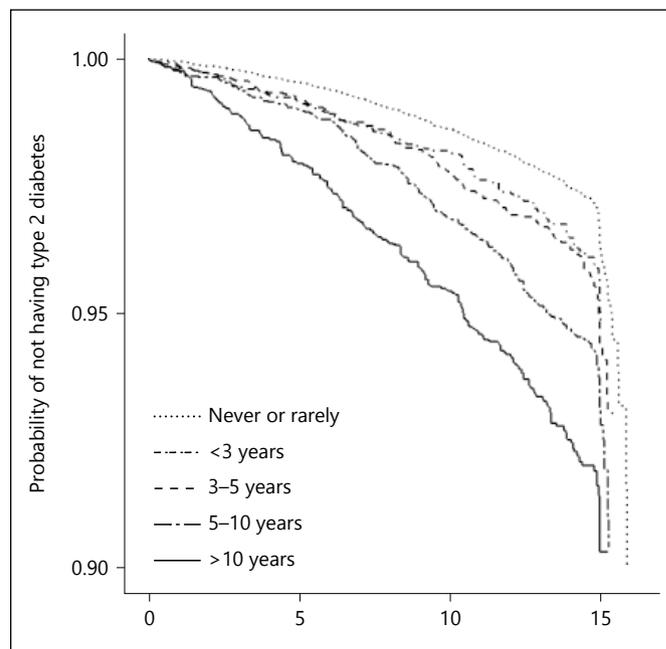


Fig. 1. Kaplan–Meier curves of type 2 diabetes (T2D) according to the duration of use of artificial sweeteners in packets or tablets (E3N-EPIC cohort data, $n = 61,440$). Kaplan–Meier curves of incident T2D according to the duration of use of artificial sweeteners in packets or tablets (never or rarely, <3 , 3–5, 5–10, ≥ 10 years). log-rank test, $p < 0.0001$. About 5% of users of artificial sweeteners for more than 10 years at baseline had developed T2D after 10 years of follow-up vs. only 1.5% for never users.

never or rare users with those who reported “always or almost always” for the consumption of artificial sweeteners such as the latter group having a higher BMI (23.9 vs. 22.5 kg/m²), being less physically active (47.5 vs. 49.4 MET-h/week), more frequently had a family history of diabetes (13.0 vs. 10.8%), a personal history of hypertension (40.1 vs. 35.4%) or hypercholesterolemia (8.8 vs. 6.1%), were more frequently smokers (16.4 vs. 12.8%), and consumed more alcohol (12.1 vs. 11.5 g/day). They also tended to consume fewer carbohydrates (215.8 vs. 220.1 g/day), and had a lower daily energy intake (2,140.0 vs. 2,229.2 kcal/day) than never or rare users. No difference was observed for the mean age at baseline or the level of education.

Habitual Frequency of Use of Artificial Sweeteners and T2D Risk

Because adjustment for covariates had little impact on the observed associations between models 1 and 2, we will only comment on the associations from model 2 in the following paragraph (Table 2). A gradient of risk was ob-

Table 1. Baseline characteristics, mean (SD) or *n* (%), by frequency of use of artificial sweeteners in packets or tablets (E3N-EPIC cohort data, *n* = 61,440)

Frequency of use of artificial sweeteners in packets or tablets	Overall population	Never or rarely	Half the time	Always or almost always
Variables, <i>n</i>	61,440	47,250	4,240	9,950
Age, years	52.6 (6.6)	52.5 (6.6)	52.4 (6.6)	52.9 (6.6)
BMI, kg/m ²	22.8 (3.1)	22.5 (3.0)	23.4 (3.1)	23.9 (3.5)
Physical activity, Met-h/week	49.0 (49.2)	49.4 (47.9)	48.6 (50.0)	47.5 (54.8)
Family history of diabetes (yes)	6,932 (11.3)	5,111 (10.8)	527 (12.4)	1,294 (13.0)
Hypertension (yes)	22,312 (36.3)	16,722 (35.4)	1,597 (37.7)	3,993 (40.1)
Smoking status (current)	8,273 (13.5)	6,064 (12.8)	582 (13.7)	1,627 (16.4)
Hypercholesterolemia (yes)	4,075 (6.6)	2,890 (6.1)	309 (7.3)	876 (8.8)
Education level (high school diploma or more)	52,584 (85.6)	40,454 (85.6)	3,664 (86.4)	8,466 (85.1)
Alcohol, g/day	11.6 (13.9)	11.5 (13.7)	11.7 (13.9)	12.1 (14.6)
Carbohydrates, g/day	235.6 (71.3)	220.1 (74.7)	239.5 (70.9)	215.8 (70.6)
Energy, kcal/day	2,217.2 (557.3)	2,229.2 (554.0)	2,264.1 (563.3)	2,140.0 (563.6)
Artificially sweetened beverages, mL/week*	101.9 (446.9)	51.5 (282.7)	170.0 (723.9)	278.2 (702.7)

* Among consumers only.

Table 2. Hazards ratios (95% CI) of type 2 diabetes according to the frequency and duration of use of artificial sweeteners in packets or tablets (E3N-EPIC cohort data, *n* = 61,440)

Artificial sweeteners	N cases	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 3, HR (95% CI)
Frequency of use				
Never or rarely	1,372	Reference	Reference	Reference
Half the time	172	1.42 (1.21–1.66)	1.31 (1.12–1.53)	1.09 (0.93–1.28)
Always or almost always	608	2.17 (1.97–2.38)	1.83 (1.66–2.02)	1.33 (1.20–1.47)
Frequency and duration of use*				
Never or rarely	1,372	Reference	Reference	Reference
Half the time or always or almost always, years				
<3	96	1.39 (1.13–1.71)	1.26 (1.03–1.55)	1.24 (1.01–1.53)
3–5	142	1.59 (1.34–1.89)	1.47 (1.23–1.74)	1.30 (1.10–1.55)
5–10	222	1.97 (1.71–2.26)	1.70 (1.48–1.96)	1.33 (1.15–1.53)
≥10	248	2.65 (2.32–3.04)	2.10 (1.83–2.40)	1.15 (1.00–1.33)

Model 1: univariate.

Model 2: model 1 + alcohol consumption, carbohydrates intake, energy intake from protein and lipids, level of education, smoking status, hypertension, hypercholesterolemia, family history of diabetes, and physical activity.

Model 3: model 2 + body mass index.

* These models were computed using *n* = 60,150 participants with available data on the duration of use of artificial sweeteners.

served with the frequency of consumption of artificial sweeteners used as a substitute for sugar. When compared to participants who never or rarely used artificial sweeteners, those using them “half the time” or “always or almost always” had a higher T2D risk, HR = 1.31 (95% CI 1.12–1.53) and HR = 1.83 (95% CI 1.66–2.02), respectively.

Duration of Use of Artificial Sweeteners and T2D Risk

Figure 1 shows the Kaplan–Meier curves of T2D by the duration of use of artificial sweeteners. Women who reported a longer duration of use had a greater chance of developing diabetes. After 10 years of follow-up, about 5% of those who reported having used artificial sweeteners as a sugar substitute for more than 10 years prior to

baseline had developed T2D, whereas less than 1.5% of those who never or rarely used them developed T2D.

In the multivariable models (Table 2), women who had used artificial sweeteners for less than 3 years were at a higher risk of T2D than never or rare users (HR = 1.26 [95% CI 1.03–1.55]), and the strength of the association increased with the duration of use, HR = 1.47 (95% CI 1.23–1.74), 1.70 (95% CI 1.48–1.96), and 2.10 (95% CI 1.83–2.40) for 3–5 years, 5–10 years, and more than 10 years of use of artificial sweeteners, respectively.

Daily Frequency of Consumption of Artificial Sweeteners in Packets or Tablets and T2D Risk

There was a positive trend between the number of times artificial sweeteners were consumed per day and the risk of developing T2D, with “no intake” used as the reference (Fig. 2). Those who reported use once a day had a 32% increased risk (HR = 1.32 [95% CI 1.15–1.52]), those who reported use twice a day had a 67% increased risk (HR = 1.67 [95% CI 1.43–1.95]), and those who reported use 3 or more times per day had a 63% increased risk of T2D (HR = 1.63 [95% CI 1.37–1.94]).

Influence of Adiposity

To test the influence of adiposity on the relationship between artificial sweetener consumption in packets or tablets and T2D risk, we further adjusted models for BMI (model 3 in Table 2). The magnitude of the associations decreased but remained statistically significant, suggesting that consumption of artificial sweeteners have both a direct and a potential indirect effect, mediated by adiposity, on T2D risk. Those who reported consumption of artificial sweeteners in packets or tablets “always or almost always” were still at highest risk (HR = 1.33 [95% CI 1.20–1.47]). Participants with 5–10 years, and more than 10 years of use still had risks of developing T2D (HR = 1.33 [95% CI 1.15–1.53] and HR = 1.15 [95% CI 1.00–1.33], respectively) in BMI-adjusted models.

Sensitivity Analyses

Adjustment for the consumption of artificially sweetened beverages had no impact on the associations between the frequency and the duration of use of artificial sweeteners and T2D risk (in model 2 further adjusted for artificially sweetened beverages: HR = 1.80 [95% CI 1.63–1.98] for “always or almost always” compared to “never or rare” users and HR = 2.03 [95% CI 1.77–2.33] for a duration of use of artificial sweeteners of more than 10 years compared to “never” users, respectively). Similarly, when further controlling for the “Western” and

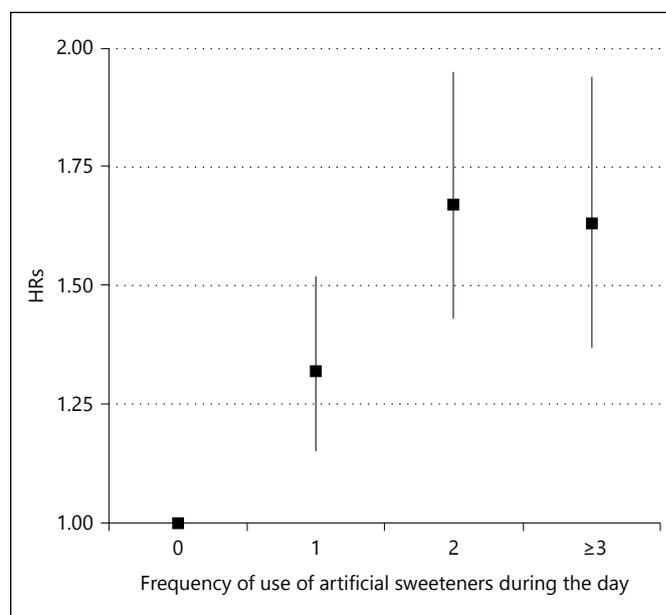


Fig. 2. Hazards ratios (HRs) of type 2 diabetes risk associated with the frequency of use of artificial sweeteners in packets or tablets during a day (E3N-EPIC cohort data, $n = 61,440$). HRs were estimated from a Cox model with age as the time scale and adjusted for alcohol consumption, carbohydrate intake, energy intake from protein and lipids, level of education, smoking status, hypertension, hypercholesterolemia, family history of diabetes, and physical activity.

“Mediterranean” dietary patterns, we did not observe any difference in the magnitudes of the associations: HR = 1.75 (95% CI 1.59–1.94) for “always or almost always” compared to “never or rare” users and HR = 1.99 (95% CI 1.73–2.29) for a duration of use of artificial sweeteners of more than 10 years compared to “never” users, respectively. Another sensitivity analysis was performed to test for a potential reverse causality bias, excluding T2D cases diagnosed in the first 5 years of follow-up. Results for the frequency of use and the duration of use were similar, that is, HR = 1.76 (95% CI 1.59–1.96) for “always or almost always” users compared to “never or rare” users and HR = 1.72 (95% CI 1.32–2.23) for a duration of use of artificial sweeteners of more than 10 years.

Discussion

In the large E3N-EPIC cohort study, with a population of more than 60,000 women followed for 18 years, we observed that both the frequency of habitual use and the number of times per day that artificial sweeteners were

consumed in packets or tablets were directly associated with an increased risk of T2D. The magnitude of the association also depended on the duration of use, suggesting a cumulative effect of artificial sweeteners on T2D development. These results have been found to be independent of the main T2D risk factors, and in particular, independent of the consumption of artificially sweetened beverages and the overall diet quality, evaluated thanks to PCA-derived dietary patterns.

Analyses adjusted for BMI suggest that the relationship between artificial sweeteners and T2D risk could be both direct and indirect, as we observed potential partial mediation by adiposity (but still with significant associations after controlling for BMI). Finally, excluding the cases that occurred in the first 5 years of follow-up did not modify the findings, suggesting that reverse causation is unlikely to explain the observed associations between intake of artificial sweeteners and T2D risk.

There is growing evidence in the literature for potential harmful effects associated with the consumption of artificial sweeteners [14]; most articles published to date have focused on artificially sweetened beverages [15]. A recent meta-analysis concluded that they were associated with higher odds of developing diabetes, but that some biases could partly explain the observed associations [1]. Nevertheless, the authors concluded that artificially sweetened beverages could not be considered healthy alternatives for the prevention of T2D. Consumption of artificially sweetened beverages is positively associated with BMI and percentage of body fat increase in children [16]. Current evidence is controversial [17], but suggests that reducing the intake of any sweetener, whether high or low calorie, is a better strategy for limiting metabolic disorders than using artificial sweeteners [18]. In our study, the magnitudes of the observed associations were only moderately decreased after controlling for the main T2D risk factors, suggesting an independent association with artificial sweeteners. Moreover, we also observed that the increased risk associated with higher frequency or longer duration of use of artificial sweeteners remained after adjusting for BMI.

Biological Pathways

It has been suggested that the use of artificial sweeteners could lead to overeating, diminished release of hormones such as GLP-1, impaired blood glucose regulation [18] and therefore could ultimately lead to T2D. A high consumption of artificial sweeteners can also activate sweet taste receptors T1R2 and T1R3, which may be involved in the regulation of metabolic processes such as

sugar sensing, glucose homeostasis, and satiety hormone release [19]. This could partly explain why a high consumption of artificial sweeteners over a long period could lead to a higher intestinal absorption of glucose, higher energy intake, and increased risks of obesity and T2D. Some artificial sweeteners additionally have metabolic effects on adipocyte differentiation and metabolism, and effects on adipose tissue could be independent of the classical sweet taste receptors, T1R2, and T1R3, which could also lead to some metabolic disorders [20].

In addition, artificial sweeteners have previously been shown to alter the gut microbiota in rodents and humans, which could contribute to impaired glucose regulation [7]. A recent review has also shown that a long-term consumption of low-dose, low-calorie sweeteners could lead to obesity and insulin resistance through disruption of the gut microbiota [21]. These results are in agreement with our findings of a cumulative association with T2D development due to a consumption of artificial sweeteners over time.

Strengths and Limitations

Our study has some limitations. Our study population included only women. However, no difference has been reported between men and women with regard to associations with the consumption of artificial sweeteners and potential biological mechanisms. Our questions on the use of artificial sweeteners as a whole prevent us from making conclusions about a specific sweetener. However, our study started in 1993, and the artificial sweeteners in packets or tablets on the market at that time were predominantly composed of aspartame. Information on BMI was self-reported, which could lead to potential biases due to error measurements, but weight and height measurements were proved to be reliable measures in the E3N-EPIC study (correlation coefficients 0.94 and 0.89, respectively, in the validation study) [22]. Another limitation is that information on artificial sweeteners was not updated during follow-up, while dietary habits could have changed over time. This could have induced an attenuation of the observed associations. Some confounders may remain unmeasured, even though we adjusted for most of the known and potential T2D risk factors.

Our study has also numerous strengths. We analyzed validated T2D cases only, based on a well-defined validation algorithm that reduces the risk of false-negatives or false-positives. Individuals might have been misclassified with respect to their diabetes status but this potential error is likely to be non-differential, resulting in a dilution of the association. The prospective design and the long follow-up

in the E3N-EPIC cohort allowed us to perform sensitivity analyses while keeping sufficient statistical power to detect associations and dismiss reverse causation. Most of the previous articles on artificial sweeteners and metabolic disorders are focused on the consumption of artificially sweetened beverages. We are the first to study associations with the consumption of artificial sweeteners consumed in packets or tablets and to provide a comprehensive analysis with the frequency of use during the day, the usual frequency of use in the previous year, and the duration of consumption of artificial sweeteners in packets or tablets with regards to T2D risk in a large population. These findings complement and extend our previous results on the associations between artificially sweetened beverages and T2D risk [15].

Conclusion

Curbing the worldwide diabetes and obesity epidemics requires extensive and long-term changes in public policies. Limiting the consumption of artificial sweeteners may be an important strategy. Even if studies in the literature have had paradoxical conclusions regarding the effects of artificial sweeteners, they are still considered – and marketed – as a healthy sugar substitute. Moreover, there is an increase in their consumption [8], as they are now present in many everyday products (diet drinks, grains, snack foods, dairy products, and medications). Given the economic and industrial stakes related to artificial sweeteners, a better evaluation of the health benefits and harms of such components should be a public health priority.

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Our study reports a cumulative association of high frequency and chronic use of artificial sweeteners in packets or tablets on the risk of developing T2D, independently of major T2D risk factors. There is an urgent need for large and independent studies evaluating metabolic consequences of chronic consumption of artificial sweeteners and to properly assess the potential causality with T2D occurrence. Meanwhile, a precautionary principle should be applied to the promotion of foods and drinks containing sweeteners that are still largely recommended as healthy substitutes for sugar.

Author Contributions

G.F. designed the research; F.C.-C. contributed to the data collection; G.G. performed the statistical analysis; G.F. wrote the paper and has primary responsibility for the final content; and G.G., A.A., C.D., F.R.M., B.B., M.-C.B.-R., F.B., and F.C.-C. interpreted the data, reviewed the paper, and revised it critically. All authors read and approved the final manuscript.

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Disclosure Statement

The authors have no conflicts of interest to declare for this work.

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