Consumption of artificially and sugar-sweetened beverages and incident type 2 diabetes in the Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale–European Prospective Investigation into Cancer and Nutrition cohort[1–4]

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ABSTRACT

Background: It has been extensively shown, mainly in US populations, that sugar-sweetened beverages (SSBs) are associated with increased risk of type 2 diabetes (T2D), but less is known about the effects of artificially sweetened beverages (ASBs).

Objective: We evaluated the association between self-reported SSB, ASB, and 100% fruit juice consumption and T2D risk over 14 y of follow-up in the French prospective Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale–European Prospective Investigation into Cancer and Nutrition cohort.

Design: A total of 66,118 women were followed from 1993, and 1369 incident cases of T2D were diagnosed during the follow-up. Cox regression models were used to estimate HRs and 95% CIs for T2D risk.

Results: The average consumption of sweetened beverages in consumers was 328 and 568 mL/wk for SSBs and ASBs, respectively. Compared with nonconsumers, women in the highest quartiles of SSB and ASB consumers were at increased risk of T2D with HRs (95% CIs) of 1.34 (1.05, 1.71) and 2.21 (1.56, 3.14) for women who consumed >359 and >603 mL/wk of SSBs and ASBs, respectively. Strong positive trends in T2D risk were also observed across quartiles of consumption for both types of beverage ($P = 0.0088$ and $P < 0.0001$, respectively). In sensitivity analyses, associations were partly mediated by BMI, although there was still a strong significant independent effect. No association was observed for 100% fruit juice consumption.

Conclusions: Both SSB consumption and ASB consumption were associated with increased T2D risk. We cannot rule out that factors other than ASB consumption that we did not control for are responsible for the association with diabetes, and randomized trials are required to prove a causal link between ASB consumption and T2D. *Am J Clin Nutr* 2013;97:517–23.

INTRODUCTION

The consumption of sugar-sweetened beverages (SSBs)[5] has been extensively associated with increased risk of type 2 diabetes (T2D) (1) but also with weight gain (2), obesity (3), metabolic syndrome (1), hypertriglyceridemia (4, 5), coronary artery disease (6), and high blood pressure (7). These associations have been attributed to several potential mechanisms as follows: an incomplete compensatory reduction in energy intake at subsequent meals after the intake of liquid calories (8), a glycemic effect with a rapid spike in blood glucose and insulin concentrations (9, 10), which could lead to insulin resistance over time, and a rapid hunger response or a harmful role of fructose (3). In addition, previous studies showed increased risk of T2D related to fruit juice consumption (11, 12), and mechanisms invoked were the same as for the association between SSBs and T2D risk.

In contrast, results for artificially sweetened beverages (ASBs) have been sparse and inconsistent, with some studies that showed increased risk of T2D, weight gain, and cardiometabolic dysfunction (2, 4, 5, 13–15). For instance, Schulze et al (2) failed to find a significant association between ASB consumption and T2D risk. In contrast, Nettleton et al (5) showed a significant association between both T2D and metabolic syndrome risk and ASB consumption, but the significance was lost after adjustment for BMI, which suggested that BMI is an intermediate factor. To

our knowledge, no clear biological mechanism has been proposed to explain positive associations between ASBs and T2D. However, it has been suggested that positive associations might be due to reverse causation because ASB consumption was shown to be higher in individuals with T2D or prediabetic conditions, such as obesity (16). Other authors hypothesized that high ASB consumption could lead to an increase in preference for sweets and be an appetite enhancer (17). A recent study concluded that aspartame, which is one of the most frequently used sweeteners in ASBs, induced a postprandial increase in insulin concentrations that were equivalent to that induced by sucrose (18). This could lead to β cell exhaustion. However, this conclusion is contradicted by the results of another study in which the increase in glucose and insulin concentrations were shown to be lower after ASB than SSB consumption (9). Despite these inconclusive results on the effects of ASB intake, ASB consumption is still considered a healthy alternative and marketed as healthier than SSBs (15).

We examined the associations between the consumption of SSBs, ASBs, and 100% fruit juice and T2D risk over a 14-y follow-up in the large French Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale (E3N)–European Prospective Investigation into Cancer and Nutrition cohort data.

SUBJECTS AND METHODS

Study cohort

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

Of the 98,995 women in the cohort, we excluded women who did not complete the dietary questionnaire ($n = 24,466$), women who did not complete any questionnaires after inclusion ($n = 6097$), prevalent cases of diabetes ($n = 879$), and women with extreme values for the ratio between energy intake and required energy (ie, the lowest and highest one percentile for the cohort) ($n = 1435$). A total of 66,118 women were finally included in the current analysis, of whom 1369 women had a validated diagnosis of T2D during the follow-up (1993–2007).

Assessment of beverage consumption and covariates

The usual diet over the previous year was assessed by using a validated 208-item diet-history questionnaire in 1993 that was structured according to the French meal pattern. Questions were asked about all times of the day when food or drinks were consumed from breakfast to after-dinner snacks, and thus, all intake consumption between meals, such as appetizers before lunch or dinner, was included. Another important feature of the questionnaire was that it was divided into 2 parts. The first part included questions on consumption frequency and portion sizes of 66 food types or items grouped by meal as follows: 38 items for breakfast and snacks between meals, 50 items for lunch and dinner, and 13 items for appetizers. To quantify the frequency of consumption, the following 11 categories were used: never or <1 time/mo; 1, 2 or 3 times/mo; and 1–7 times/wk. For beverages, contents of glasses were estimated by using a photo booklet. The validity and reproducibility of our dietary-assessment questionnaire has been previously described (19). Regarding beverages, study participants were asked to report the frequency and usual serving sizes of 100% fruit juice and sweetened beverages that they consumed just before lunch, afternoon snack, just before dinner, and after dinner and to provide information about the type of beverages consumed (soda or water with added fruit syrup). Women could also specify if their soda or fruit drinks were sugar or artificially sweetened. Participants could report consumption of 100% fruit juice at breakfast as well.

Ascertainment of diabetes

The algorithm used to validate diabetes cases used 2 steps. A first set of potential cases of diabetes included women who had self-reported either diabetes, a diabetes diet plan, the use of diabetic drugs, or a hospitalization for diabetes in ≥1 of the 8 questionnaires sent up until July 2005. A total of 4289 self-reported potential cases were identified. Among them, 2315 cases were validated because women were identified from the drug-reimbursement file provided by the health insurance records as having been reimbursed for a diabetes drug between 1 January 2004 (date when the file became available) and 30 June 2007 (date of the current study endpoint). In the 1974 women without diabetes drug reimbursement, women alive and with an accurate address ($n = 1735$) were mailed a questionnaire that was specifically designed to validate diabetes. Of the 1480 women who completed this questionnaire (response rate: 84%), 342 potential cases were confirmed if glucose concentrations at diagnosis were reported to comply with WHO recommendations (fasting glucose concentration ≥7.0 mmol/L or random glucose concentration ≥11.1 mmol/L) or if women reported taking diabetes drugs or their last values of fasting glucose or glycated hemoglobin concentrations were reported to be ≥7.0 mmol/L or ≥7% respectively. Thus, a total of 2657 self-reported diabetes cases were validated.

A second set of potential cases of diabetes was identified exclusively from the drug-reimbursement file ($n = 1216$) without a previous report of diabetes in any of the 8 study questionnaires. We mailed the diabetes-specific questionnaire to 1139 women, and 734 women completed it. We considered women who declared they were nondiabetic and had been reimbursed for diabetes drugs only once before 30 June 2007 as noncases ($n = 233$) and women who confirmed diabetes in the diabetes-specific questionnaire($n = 458$) and women who did not answer the diabetes-specific questionnaire but had diabetic drugs reimbursed at least twice ($n = 381$)as validated diabetic cases. Other potential cases were considered nonvalidated ($n = 144$).

Altogether, a total of 3496 diabetes cases diagnosed until 30 June 2007 were validated in the E3N cohort. Although this procedure did not systematically allow differentiation between type 1 diabetes

and T2D, the age range of our population implied that incident cases considered in our analyses were almost all T2D. Prevalent diabetes cases were excluded from analyses (*see* Study cohort).

Statistical analysis

Each type of beverage consumption (in mL/wk) was categorized into 5 categories that corresponded to quartiles, defined among consumers of sweetened beverages, plus a nonconsumer category, which was systematically taken as the reference in the models. Cox multivariate regression models with age as the timescale were used to estimate HRs and 95% CIs. The time at entry was the age at the beginning of follow-up, and the exit time was the age when participants were diagnosed with diabetes, died, lost to follow-up, or censored at the end of the follow-up period, whichever came first. Models were adjusted for years of education (continuous), smoking status (nonsmoker, exsmoker, or current smoker), physical activity [continuous (in metabolic equivalent task hours per week)], hypertension [self-reported or use of antihypertensive drugs (yes or no)], hypercholesterolemia [self-reported blood cholesterol concentration >5.172 mmol/L or use of cholesterol-lowering drugs (yes or no)], use of hormone replacement therapy (ever or never), family history of diabetes (yes or no), self-reported use of antidiabetic drugs (yes or no), alcohol intake [continuous (g/d)], omega-3 fatty acid intake [continuous (g/d)], carbohydrate intake [continuous (g/d)], total energy intake [excluding alcohol and carbohydrates; continuous (kcal/d)], coffee [continuous (mL/d)], fruit and vegetables and processed-meat consumption

[continuous (g/d)], and dietary pattern [Western or Mediterranean; details on dietary patterns are available in Cottet et al (20)].

We also computed a quadratic spline regression model to evaluate the continuous relation between the consumption of different beverages and risk of T2D. For all models, no consumption was chosen as the reference, and 2 knots at 560 and 1330 mL/wk were selected.

All statistical analyses were conducted with SAS 9.2 software (PHREG procedure for Cox models; SAS Institute Inc). All statistical tests were 2-sided and considered significant at $P < 0.05$.

Sensitivity analyses

Because adiposity has been shown to be a key factor in the relation between SSBs and T2D (1), we tested models further adjusted for total energy intake and BMI (models 2 and 3 in **Table 1**). To test a reverse-causation hypothesis, we evaluated the associations between ASBs, SSBs, fruit juice, and T2D by excluding cases in the first 5 y of follow-up. We also stratified analyses by BMI categories to test if associations were similar in the different strata.

RESULTS

Baseline characteristics

As shown in **Table 2**, the mean (±SD) age of participants at baseline was 52.6 ± 6.6 y. Approximately 10% of the study population had a family history of diabetes, 66% of study participants had BMI between 20 and 25, and only 3.2% of study

TABLE 1
Risk of type 2 diabetes according to categories of consumption of sugar-sweetened and artificially sweetened beverages and 100% fruit juice (E3N cohort data; $n = 66,118$)[1]

Type of beverage	No. of cases/noncases	Person-years	Age adjusted	Model 1	Model 2	Model 3
Sugar sweetened						
Nonconsumers	1046/52,492	679,281	1 (reference)[2]	1 (reference)	1 (reference)	1 (reference)
<86 mL/wk	125/4357	56,559	1.54 (1.28, 1.86)	1.32 (1.09, 1.59)	1.32 (1.09, 1.59)	1.28 (1.06, 1.55)
86–164 mL/wk	61/2638	34,329	1.21 (0.94, 1.57)	1.16 (0.90, 1.51)	1.16 (0.90, 1.51)	1.12 (0.86, 1.45)
165–359 mL/wk	64/2636	34,230	1.31 (1.02, 1.68)	1.24 (0.96, 1.59)	1.24 (0.96, 1.60)	1.22 (0.94, 1.57)
>359 mL/wk	73/2626	33,696	1.49 (1.18, 1.89)	1.32 (1.04, 1.69)	1.34 (1.05, 1.71)	1.30 (1.02, 1.66)
P-trend			0.0002	0.0118	0.0088	0.0206
Artificially sweetened						
Nonconsumers	1046/52,492	679,281	1 (reference)	1 (reference)	1 (reference)	1 (reference)
<99 mL/wk	252/10,604	137,517	1.27 (1.10, 1.45)	1.20 (1.04, 1.38)	1.21 (1.05, 1.39)	1.19 (1.03, 1.37)
99–221 mL/wk	17/557	7157	1.67 (1.03, 2.70)	1.16 (0.72, 1.89)	1.17 (0.72, 1.90)	1.25 (0.77, 2.01)
222–603 mL/wk	20/555	7205	1.95 (1.25, 3.03)	1.37 (0.88, 2.15)	1.37 (0.88, 2.14)	1.27 (0.81, 1.98)
>603 mL/wk	34/541	6936	3.50 (2.49, 4.93)	2.18 (1.53, 3.09)	2.21 (1.56, 3.14)	1.68 (1.19, 2.39)
P-trend			<0.0001	<0.0001	<0.0001	0.0057
100% fruit juice						
Nonconsumers	522/23,126	299,619	1 (reference)	1 (reference)	1 (reference)	1 (reference)
<180	200/10,417	136,050	0.89 (0.76, 1.05)	0.87 (0.73, 1.03)	0.84 (0.71, 0.99)	0.90 (0.76, 1.07)
180–447 mL/wk	199/10,419	135,111	0.87 (0.74, 1.02)	0.86 (0.73, 1.02)	0.83 (0.70, 0.98)	0.95 (0.81, 1.12)
448–967 mL/wk	246/10,372	134,251	1.08 (0.93, 1.26)	1.08 (0.92, 1.25)	1.05 (0.90, 1.23)	1.18 (1.01, 1.38)
>967 mL/wk	202/10,415	133,066	0.89 (0.76, 1.05)	0.84 (0.71, 0.99)	0.83 (0.70, 0.98)	0.93 (0.78, 1.10)
P-trend			0.5964	0.2823	0.3570	0.9125

[1] Model 1 was adjusted for years of education; smoking status; physical activity (metabolic equivalent task hours per week); hypertension; hypercholesterolemia; use of hormone replacement therapy; family history of diabetes; self-reported use of antidiabetic drugs; alcohol intake (g/d); omega-3 fatty acid intake; carbohydrate intake (g/d); coffee (mL/d), fruit and vegetables, and processed-meat consumption (g/d); and dietary pattern (Western or Mediterranean). Model 2 was adjusted as for model 1 and for total energy intake [excluding energy from alcohol and carbohydrates (kcal/d)]. Model 3 was adjusted as for model 2 and for BMI (in kg/m^2; <20, 20 to <25, 25–30, and >30). E3N, Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale.

[2] HR; 95% CI in parentheses (all such values).

TABLE 2
Baseline characteristics of the study population (E3N cohort data;
$n = 66,118$)[1]

	Study population ($n = 66,118$)
Age (y)	52.6 ± 6.6[2]
Birth cohort [n (%)]	
Before 1930	4701 (7.1)
Between 1930 and 1934	8214 (12.4)
Between 1935 and 1939	12,355 (18.7)
Between 1940 and 1944	15,941 (24.1)
After 1944	24,907 (37.7)
Education [n (%)]	
Undergraduate	9071 (13.7)
Graduate/postgraduate	57,047 (86.3)
Hypertension (yes)	8569 (13.1)
Cholesterolemia [n (%)]	
Use of hypolipidemic drug	3160 (4.8)
Untreated cholesterolemia <6.2 mmol/L	5717 (8.6)
Untreated cholesterolemia ≥6.2 mmol/L	12,826 (19.4)
Missing	44,415 (67.2)
Family history of diabetes (yes)	6783 (10.3)
Use of HRT [n (%)]	
Nonuser	45,187 (68.3)
Current	12,732 (19.3)
Past	6923 (10.5)
Unknown recency	1276 (1.9)
BMI [n (%)]	
<20 (kg/m^2)	9903 (15.0)
20 to <25 (kg/m^2)	43,792 (66.2)
25–30 (kg/m^2)	10,290 (15.6)
>30 (kg/m^2)	2133 (3.2)
Sugar-sweetened beverage (mL/wk)	328.3 ± 485.8
Artificially sweetened beverage (mL/wk)	567.7 ± 906.5
100% fruit juice (mL/wk)	686.7 ± 730.8
Physical activity (MET-h/wk)	54.8 ± 30.2
Coffee (mL/d)	291.8 ± 267.5
Alcohol (g/d)	11.1 ± 14.1
Fruit and vegetables (g/d)	468.0 ± 225.7
Processed meat (g/d)	23.9 ± 19.3
Omega-3 fatty acids (g/d)	0.4 ± 0.3
Carbohydrates (g/d)	231.0 ± 74.2
Energy (kcal/d)	2170.5 ± 574.45

[1] E3N, Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale; HRT, hormone replacement therapy; MET-h, metabolic equivalent task hours.
[2] Mean ± SD (all such values).

participants were obese. Mean SSB, ASB, and 100% fruit juice consumptions were 328.3, 567.7 and 686.7 mL/wk, respectively, in consumers. The variation in consumption was larger for ASBs than for SSBs (SD: 129.5 compared with 69.4 mL/wk). We also observed a higher proportion of obese women in ASB consumers than in SSB and 100% fruit juice consumers (6.8% compared with 3.6% and 3.1%, respectively).

T2D risk in the overall population

As presented in Table 1, SSB consumption was positively associated with increased T2D risk in both the age-adjusted model (P-trend = 0.0002) and multivariate model (P-trend = 0.0088 in model 2, which was adjusted for all covariates except BMI), women who reported consumption > 359 mL/wk were

significantly at higher risk [HR: 1.34 (95% CI: 1.05, 1.71) in model 2] than were nonconsumers.

ASB consumption was also positively associated with greater risk of T2D in both age-adjusted model (P-trend < 0.0001) and multivariate model (P-trend < 0.0001 in model 2). A high consumption of ASBs (>603 mL/wk) was associated with significant greater risk of diabetes [HR: 2.21 (95% CI: 1.56, 3.14) in model 2] compared with that for nonconsumers.

High 100% fruit juice consumption was not associated with risk of T2D in the age-adjusted model 1. Instead, a high consumption of 100% fruit juice (>967 ml/wk) was associated with significant decreased risk of T2D [HR: 0.83 (95% CI: 0.70, 0.98) in model 2] compared with that for nonconsumers. No significant trend was observed.

On the basis of spline regression modeling (**Figure 1**), we described the continuous relation between SSBs, ASBs, and 100% fruit juice and T2D risk. We observed a linear, and mostly significant, positive relation with T2D risk of SSB and ASB consumption <500 and 1000 mL/wk, respectively. Above these thresholds, CIs were wide because of a low frequency of consumers in the study population and a limited statistical power. No association was seen for 100% fruit juice and T2D risk.

Additional adjustment

We tested models with and without adjustment for total energy intake or BMI. Associations between SSBs, ASBs, and 100% fruit juice and T2D risk were very similar in models with or without adjustment for total energy intake (models 1 and 2 in Table 1). However, BMI appeared to be an effect modifier. With an additional adjustment for BMI (model 3), associations remained significant for SSB and ASB consumption, although their magnitude was attenuated with a high consumption of SSBs and ASBs, which yielded HRs (95% CIs) of T2D of 1.30 (1.02, 1.66) and 1.68 (1.19, 2.39), respectively, in model 3, whereas tests for trend remained significant (P-trend = 0.0206 and P-trend = 0.0057 for SSBs and ASBs, respectively, in model 3). However, the inverse association between a high consumption of 100% fruit juice and T2D risk disappeared after adjustment for BMI in women who consumed between 448 and 967 mL 100% fruit juice/wk in model 3.

Sensitivity analyses

We excluded the first 5 y of follow-up to test a reverse-causation hypothesis between the consumption of ASBs, SSBs, and 100% fruit juice and T2D risk. A total of 353 cases were omitted for the current analysis, which left 1016 cases. Similar associations were shown for the different types of beverages. A high consumption of SSBs was still associated with significant increased T2D risk [HR: 1.36 (95% CI: 1.03, 1.80)]. Also, high ASB consumption was associated with a significant 81% increase in T2D risk [HR: 1.81 (95% CI: 1.19, 2.73)]. Positive trends of T2D risk were observed for both SSBs and ASBs (P-trend = 0.0336 and P-trend = 0.0063, respectively). As in the analysis with the whole population, no association was shown for 100% fruit juice consumption [HR: 0.90 (95% CI: 0.74, 1.10)] for the highest category compared with nonconsumers; P-trend = 0.8909. When analyses were stratified by BMI categories, it appeared that there was a negative gradient in the strength of
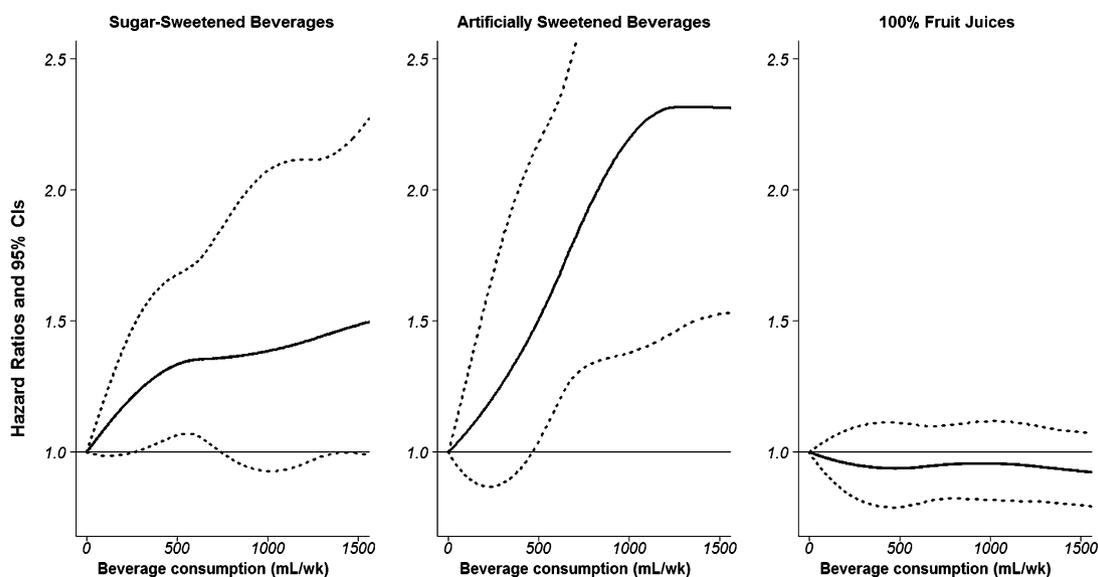
FIGURE 1. Quadratic spline regression models for risk of type 2 diabetes according to the consumption of sugar-sweetened and artificially sweetened beverages and 100% fruit juice. Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale cohort data ($n = 66,118$; reference: 0 mL/wk; 2 knots at 560 and 1330 mL/wk). Solid lines correspond to HRs, and dashed lines correspond to 95% CIs.

associations between SSB and ASB consumption and T2D risk throughout BMI categories. For SSB consumption, HRs (95% CIs) of T2D for the highest category of consumption were 1.61 (1.12, 2.32), 1.22 (0.79, 1.88), and 0.94 (0.56, 1.57) in the categories of BMI (in kg/m^2) <25, between 25 and 30, and >30, respectively. In the same BMI categories, HRs (95% CIs) for the highest category of ASBs were 2.23 (1.14, 4.36), 2.17 (1.27, 3.68), and 1.00 (0.52, 1.92), respectively. In obese women, high ASB or SSB consumption was not associated with T2D risk, but the statistical power was limited.

DISCUSSION

We showed a direct association between SSBs and ASBs and risk of T2D in French women of the E3N cohort that persisted after adjustment for BMI and energy intake. Results remained significant even after cases that occurred early during follow-up were excluded . No association was observed between 100% fruit juice intake and T2D risk.

Results for SSBs were in agreement with the existing literature. A review by Malik et al (3) in 2012 concluded that SSB consumption was directly and indirectly related to an increased T2D risk, directly because of the glycemic effects of the large amounts of absorbed sugars or metabolic effects of fructose and indirectly because of weight gain. In our study, associations were shown to be partly mediated by BMI but were still significant when BMI was adjusted for, which indicated an independent, direct effect of large SSB consumption on T2D risk.

Conclusions of existing studies that focused on ASB consumption were less consistent (2, 4, 5, 14, 15), but some studies showed positive associations (4, 5, 14) with risk of T2D, weight gain, or cardiometabolic dysfunction. Our findings weigh in favor of a positive association between ASBs and T2D risk.

Lower risk of T2D was shown for a high consumption of 100% fruit juice in our population, unlike in other studies that suggested a positive association (11, 12). However, in our study, the significant association disappeared after adjustment for BMI.

Biological mechanisms

A recent review (3) on SSBs and T2D risk synthesized the main hypotheses. An increase in SSB consumption is associated with increased risk of weight gain (21) because of decreased satiety and incomplete compensatory reduction in energy intake. Alternatively, a postprandial spike in blood glucose and, consequently, in insulin concentrations, may lead to hyperinsulinemia and insulin resistance over time. Also, the fructose present in SSBs may lead to increased lipogenesis, atherogenic dyslipidemia, and insulin resistance (22).

Mechanisms that might explain the positive relation between ASBs and T2D risk are less-well identified. Increases in sweet preference and appetite enhancement have already been linked with increased ASB consumption (17). Another likely hypothesis was proposed by Anton et al (18) in 2010 , whereby they showed that aspartame, which was the most frequently used sweetener in ASBs, generates a similar body response in terms of postprandial glucose and insulin concentrations to those induced by the sucrose present in SSBs. Indeed, in their study, which included 31 subjects, there was no significant difference in glucose and insulin concentrations 30 min after ingestion of a load of aspartame compared with after a similar ingestion of sucrose. However, participants who ingested preloads of stevia (herbs with natural sweeteners) had significantly reduced insulin concentrations 30 and 60 min after the test meal compared with those of participants who ingested aspartame preloads. In France, it has been shown that users of sweeteners other than sugar, such as ASBs, had higher glycemia than did nonusers, and the use of low-sugar products was accompanied by an increase in diet density of certain micronutrients, including cholesterol (23). The recent population-based San Antonio Heart Study suggested that ASB consumption might be fueling the obesity epidemic instead of fighting it, but the results should be interpreted with caution (17).

Contrary to most studies in the literature, we showed no positive association between fruit juice consumption and T2D risk. That result might be explained by the fact that women were required to report their consumption of freshly squeezed fruit and

pure fruit juice only and not sweetened fruit juices, which were considered SSBs. The consumption of sweetened fruit juices, which are rich in dietary fructose, but not freshly squeezed fruit or pure fruit juice has already been associated with an impaired glucose tolerance in another population (24).

Associations mediated by adiposity?

As mentioned previously, it has been suggested that the association between SSBs and T2D risk is probably mediated, at least in part, by adiposity (3), which has been confirmed by our results. The review by Malik et al (3) listed the studies that showed a strong positive association between SSBs and weight gain or risk of overweight and obesity (1, 21, 25–27). The authors mentioned that positive associations were mostly shown in models without adjustment for possible mediating factors, such as BMI. Our results were also in favor of a detrimental effect of SSBs and ASBs independent of BMI. We also stratified analyses by BMI categories to test if the associations were similar in the different strata. There was a negative gradient in the strength of the associations between both SSB and ASB consumption and T2D risk throughout BMI categories, which suggested that the negative effects of consumption of these beverages were attenuated in women already overweight or obese.

Reverse causation

The suggestion that the positive association between ASBs and T2D risk is due to reverse causation deserves additional consideration. Indeed, ASB consumption was shown to be more frequent in people with T2D (16). People also tend to drink ASBs in preference to SSBs when they have prediabetic conditions, such as obesity. To test this hypothesis, we censored, in a sensitivity analysis, the first 5 y of follow-up of the study to ensure the temporality between exposures and the incidence of the disease. We showed very similar results between this analysis and that with the complete follow-up, which made reverse causation unlikely in our study.

Strengths and limitations

The current study had some limitations. First, questions on the consumption of SSBs, ASBs, and 100% fruit juice were not asked at all meals during the day in the food-frequency questionnaire. The relatively low mean daily consumption of these beverages in the study population might have been because this information was only requested in the morning, just before lunch, afternoon snack, just before dinner, and after dinner. Nevertheless, a supplementary question on beverage consumption at lunch and dinner would only have increased the variability in reports and should, in no way, have differentially affected reports on beverage consumption between cases and noncases. Therefore, it is unlikely that a wider declaration of SSBs or ASBs would have attenuated the associations. We could distinguish which types of SSBs, ASBs or 100% fruit juice the women consumed. Consequently, we had no information on the sweeteners that could have been implicated in the relation between these beverages and risk of T2D. Another limitation was that information on beverage consumption was not updated during the follow-up, and dietary habits may have changed over time. Some confounders may still have been unmeasured, even if we adjusted for most of the known

and potential T2D risk factors. Finally, we faced a limited statistical power in some subcategories when stratified by BMI. Therefore, stratified analyses, especially for ASB consumption, should be interpreted with caution. Finally, our study population was composed exclusively of women. This limitation should have been minor because no difference in biological mechanisms has been reported between men and women.

In contrast, our study had several strengths. To our knowledge, we are the first non-US study to highlight an increase in risk of T2D for both SSBs and ASBs. Moreover, we analyzed validated T2D cases only on the basis of a well-defined validation algorithm, which strongly diminished risk of missing or false-positive cases. Individuals might have been misclassified with respect to their diabetes status, but this potential error was also likely to be nondifferential. Finally, to test a reverse-causation hypothesis, the prospective design and the long follow-up in the E3N cohort allowed us to perform sensitivity analyses while keeping sufficient statistical power to detect associations and discredit the hypothesis of a reverse causation.

Public health implications

SSB and ASB consumption were shown to be directly and indirectly (possibly mediated by adiposity) linked with increased risk of T2D. Extensive and lasting changes in public policy are required to curb the worldwide diabetes and obesity epidemics, and limiting the consumption of SSBs and ASBs may be an important strategy to do so. Even if some studies in the literature had paradoxical conclusions regarding the effects of ASB consumption, ASBs are still considered, and marketed, as healthier than SSBs (15, 28). Our results, in accordance with a recent joint scientific statement of the American Heart Association and the American Diabetes Association (13), strongly suggest the need to conduct randomized trials that evaluate metabolic consequences of ASB components, such as artificially sweeteners, to prove a causal link between ASB consumption and T2D. Meanwhile, a precautionary principle could be applied to the promotion of ASBs, which are still largely recommended as a healthy substitute to SSBs.

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