Intake of artificially sweetened soft drinks and risk of preterm delivery: a prospective cohort study in 59,334 Danish pregnant women[1–3]

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ABSTRACT

Background: Sugar-sweetened soft drinks have been linked to a number of adverse health outcomes such as high weight gain. Therefore, artificially sweetened soft drinks are often promoted as an alternative. However, the safety of artificial sweeteners has been disputed, and consequences of high intakes of artificial sweeteners for pregnant women have been minimally addressed.

Objective: We examined the association between intakes of sugar-sweetened and artificially sweetened soft drinks and preterm delivery.

Design: We conducted prospective cohort analyses of 59,334 women from the Danish National Birth Cohort (1996–2002). Soft drink intake was assessed in midpregnancy by using a food-frequency questionnaire. Preterm delivery (<37 wk) was the primary outcome measure. Covariate information was assessed by telephone interviews.

Results: There was an association between intake of artificially sweetened carbonated and noncarbonated soft drinks and an increased risk of preterm delivery (P for trend: ≤0.001, both variables). In comparison with women with no intake of artificially sweetened carbonated soft drinks, the adjusted odds ratio for women who consumed ≥1 serving of artificially sweetened carbonated soft drinks/d was 1.38 (95% CI: 1.15, 1.65). The corresponding odds ratio for women who consumed ≥4 servings of artificially sweetened carbonated soft drinks/d was 1.78 (95% CI: 1.19, 2.66). The association was observed for normal-weight and overweight women. A stronger increase in risk was observed for early preterm and moderately preterm delivery than with late-preterm delivery. No association was observed for sugar-sweetened carbonated soft drinks (P for trend: 0.29) or for sugar-sweetened noncarbonated soft drinks (P for trend: 0.93).

Conclusions: Daily intake of artificially sweetened soft drinks may increase the risk of preterm delivery. Further studies are needed to reject or confirm these findings. *Am J Clin Nutr* 2010;92:626–33.

INTRODUCTION

Sugar-sweetened soft drinks are currently ranked as the main energy contributor in the US diet (1) and concerns have been raised about their role in the obesity epidemic because of their high content of readily absorbed sugars (2). Previous epidemiologic studies reported positive associations between intakes of sugar-sweetened soft drinks and metabolic syndrome (3, 4), hypertension (5), and type 2 diabetes (2). In the light of such findings, artificially sweetened soft drinks are often promoted as a better alternative (6).

Although artificial sweeteners such as aspartame, acesulfame-K, and saccharine are generally considered safe with respect to acute toxicity, the overall safety of regular consumption is still disputed (7). As an example, recent low-dose animal experiments identified aspartame as a potential carcinogenic agent (8, 9), and short-term side effects such as headaches have frequently been reported in humans (10–13). It has been suggested that low-dose methanol exposure because of the break down of aspartame might be the causal factor. With respect to pregnant women, high consumption of saccharine-containing products is often discouraged because saccharine has been shown to aggregate on the fetal side of the placenta (14). Despite these reports, very few studies have investigated whether regular intakes of foods containing artificial sweeteners are safe during pregnancy (7).

Preterm delivery (<37 wk) is one of the major pregnancy complications and is a leading cause of perinatal morbidity and mortality (15). Preterm infants are also likely to suffer from long-term impairment and social inequality in adult life (16). There is currently some evidence relating dietary factors, such as vitamin C (17) and fish oil (18), with preterm delivery. Recent studies have suggested that both artificially sweetened soft drinks and sugar-sweetened soft drinks might be associated with hypertension (5), which is a known risk factor for preterm delivery (19). There is also further indirect evidence to suggest that sugar-sweetened and artificially sweetened soft drinks might affect the length of gestation because both high blood glucose

concentrations (20) and low-dose methanol exposure (21, 22) have been linked to a shorter duration of gestation. Therefore, it can be hypothesized that both sugar-sweetened and artificially sweetened soft drinks might be related to an increased risk of preterm delivery. The aim of this study was to explore the association between maternal soft drink consumption in pregnancy and preterm delivery.

SUBJECTS AND METHODS

Population and study design

This study was based on data from the Danish National Birth Cohort, the structure of which has been described in detail elsewhere (23). In brief, 91,827 pregnant women from all over Denmark were recruited from January 1996 to October 2002. All pregnant women who were living in Denmark and were fluent in Danish were eligible for recruitment. Women were enrolled by filling out a recruitment form at the first antenatal visit to the general practitioner at ≈6–10 wk gestation. Data were collected via 4 computer-assisted telephone interviews, a food-frequency questionnaire (FFQ), and registry linkages. During the study period, ≈35% of all deliveries in Denmark were recruited into the cohort (23). To investigate the effect of this recruitment rate, Nohr et al (24) analyzed 49,751 women from a source population that included 15,373 cohort participants and showed no indication of attrition bias with respect to exposure-risk associations such as in vitro fertilization and preterm delivery as well as maternal smoking and fetal growth.

Dietary assessment

Dietary information was collected at ≈25 wk gestation through a detailed FFQ that covered intakes during the previous 4 wk gestation (25). Individual food items were quantified into grams per day by using assumptions on standard portion sizes, and intakes of total energy and individual nutrients were quantified by using food-composition tables (26). The FFQ contained a number of questions on beverages such as "How many servings of the following beverages have you consumed during the last month?" Response categories ranged from never to ≥8 servings/d. The 4 beverage items used on our analyses were as follows: carbonated soft drinks/cola (sugar sweetened), carbonated soft drinks/cola (sugar-free, light), noncarbonated soft drinks (sugar sweetened), and noncarbonated soft drinks (sugar-free, light). In the context of soft drinks, it was understood that the words sugar-free and light referred to products that contained artificial sweeteners.

The FFQ was validated against dietary records and biomarkers of particular nutrients (27), but not specifically with respect to soft drink consumption. However, we also asked 103 women to complete the FFQ a second time at 33–35 wk gestation. For each soft drink variable, the observed Spearman's correlation coefficient was ≈0.7 for the frequency of intake reported in the FFQ in weeks 25 and 35 of gestation.

Cohort attrition

A total of 91,827 pregnant women registered into the cohort. Women were allowed to enter the study repeatedly during the study period, which resulted in 101,042 pregnancies in total. To avoid the use of multiple dependent observations, our analyses were restricted to the first pregnancy enrollment ($n = 91,827$) of which 62,374 women filled out the FFQ. The final data set consisted of 59,334 women when we further restricted our analyses to singleton pregnancies ($n = 61,409$) and excluded women who did not answer the questions on soft drinks (≈3%).

The women who entered our final data set did not differ markedly from those women who did not enter the final data set with respect to the following variables: maternal age (29.3 compared with 29.0 y, respectively), prepregnancy body mass index (BMI; in kg/m^2) (23.7 compared with 23.5, respectively), smoking during pregnancy (28.6% compared with 25.1%, respectively), and rate of preterm delivery (<37 wk: 5.0% compared with 4.6%, respectively), whereas the number of nulliparous women (37.1% compared with 53.0%, respectively) differed markedly.

Outcome assessment

Dates of birth of subjects were extracted from the Danish Civil Registration System. Gestational age (in d) was assessed from the last menstrual period on the basis of information recorded in the recruitment form (week 6) and in the first telephone interview (week 12). If this estimate was uncertain because of irregular or abnormally long (>32 d) or short (<24 d) menstrual cycles, gestational age was based on information on the expected date of delivery provided by the women in the second telephone interview (week 30), which was most often based on ultrasound scanning. If this information was missing, we used the gestational age assessed at delivery by the midwife and reported to the Medical Birth Registry. For our estimates of gestational age, 43%, 56%, and 1% were based on information on the last menstrual period, information from the second telephone interview, and the Medical Birth Registry, respectively.

Information from the Medical Birth Registry was also used to distinguish between spontaneous and medically induced deliveries. Medically induced deliveries were defined from information about either induction or cesarean section before the onset of labor (28).

Selection of covariates

A priori, we identified and included as covariates a set of 7 nondietary factors that are well-recognized determinants of preterm delivery: maternal age (20, 20–24, 25–29, 30–34, 35–39, and ≥40 y; 0% missing), height (<160, 160–169, 169–179, and >179 cm; 4.3% missing), prepregnancy BMI (≤18.5, 18.5–24.9, 25–29.9, 30–34.9, and ≥35; 5.8% missing), cohabitant status (single compared with cohabitant; 4.3% missing), parity (0, 1, 2, ≥3; 4.3% missing), smoking during pregnancy (never, occasional smokers, daily smokers of <15 cigarettes/d, and daily smokers of ≥15 cigarettes/d; 0.7% missing), and familial sociooccupational status (6 occupational categories as follows: high occupational status, intermediate occupational status, skilled workers, unskilled workers, students, and not working; 4.5% missing). These covariates were extracted from the 2 prenatal telephone interviews conducted around 12 and 30 wk gestation. Because of the relatively low frequency of missing values for these covariates (range: 0–5.8%), missing values were assigned to a missing category for each covariate. In addition,

we also included the mother's total energy intake (quintiles; 0% missing) as a covariate as it is generally important to distinguish between the separate effects of food and energy intakes (29).

Statistical analyses

We used preterm delivery (<37 wk) as our primary outcome measure, whereas late preterm (34 ≤ wk < 37), moderately preterm (32 ≤ wk < 34), and early preterm delivery (<32 wk) were used as secondary outcomes. In our primary analyses we investigated the association between sugar-sweetened and artificially sweetened soft drinks and preterm delivery. To establish a detailed dose-response relation, soft drink intake was categorized as follows: never, <1 soft drink/wk, 1–6 soft drinks/wk, 1 soft drink/d, 2–3 soft drinks/d, and ≥4 soft drinks/d.

In our secondary analyses we investigated the stability of our finding for the carbonated-soft drinks with respect to late, moderately, and early preterm delivery and prepregnancy weight categorized as underweight (BMI <18.5), normal weight (18.5 ≤ BMI <25), or overweight (BMI ≥25).We also examined spontaneous and medically induced preterm births separately. Because relatively few women reported daily consumption of carbonated soft drinks, the 3 highest-intake categories were merged into one category (≥1/d) in our secondary analyses to reach a sufficient number of cases in each strata.

Univariate and multivariate logistic regression were used for estimating the association between intakes of soft drinks and preterm delivery. We used the chi-square-test (type III) as a measure of an association where the intake of soft drinks was included as a continuous term in the regression model (trend test).

TABLE 1
Selected maternal characteristics in relation to intake of soft drinks in 59,334 women from the Danish National Birth Cohort

	Never	<1/wk	1–6/wk	1/d	2–3/d	≥4/d	P
Sugar-sweetened carbonated soft drinks							
n	9732	15,461	28,580	2902	2015	653	—
Maternal age (y)	29.8 ± 4.4[1]	29.6 ± 4.2	28.7 ± 4.1	28.2 ± 4.2	27.9 ± 4.3	27.2 ± 4.5	<0.001[2]
BMI (kg/m^2)[3]	23.8 ± 4.5	23.2 ± 3.9	23.5 ± 4.1	23.7 ± 4.3	24.0 ± 4.6	24.5 ± 5.2	0.001[2]
Energy intake (MJ/d)	9.4 ± 2.6	9.6 ± 2.4	10.3 ± 2.6	10.8 ± 2.8	11.4 ± 3.0	12.7 ± 3.4	<0.001[2]
Nulliparous women (%)	50.7	51.6	54.5	53.6	52.1	50.8	<0.001[4]
Single women (%)	2.1	1.7	1.8	2.2	3.2	5.6	<0.001[4]
Daily smoking (%)	11.7	9.1	13.1	19.4	27.4	43.3	<0.001[4]
High social status (%)[5]	6.5	6.1	4.9	4.2	2.8	1.8	<0.001[4]
Artificially sweetened carbonated soft drinks							
n	39,923	7437	9678	1122	834	340	—
Maternal age (y)	29.1 ± 4.3	28.9 ± 4.2	28.7 ± 4.0	28.8 ± 3.9	29.0 ± 4.2	29.1 ± 4.0	<0.001[2]
BMI (kg/m^2)[3]	23.1 ± 3.9	23.8 ± 4.3	24.6 ± 4.6	24.8 ± 4.8	25.7 ± 5.1	26.2 ± 5.9	<0.001[2]
Energy intake (MJ/d)	10.2 ± 2.7	9.7 ± 2.6	9.8 ± 2.6	10.0 ± 2.6	9.8 ± 2.8	10.1 ± 3.0	<0.001[2]
Nulliparous women (%)	51.2	57.9	56.6	52.2	52.8	46.3	0.01[4]
Single women (%)	2.0	2.0	1.5	1.4	1.6	2.8	<0.001[4]
Daily smoking (%)	13.8	9.3	11.3	12.9	17.5	31.1	<0.001[4]
High social status (%)[5]	5.5	5.1	5.1	4.9	4.2	2.1	0.03[4]
Sugar-sweetened noncarbonated soft drinks							
n	21,275	8652	16,539	4846	6117	1852	—
Maternal age (y)	28.7 ± 4.3	29.3 ± 4.3	29.4 ± 4.2	29.4 ± 4.2	29.1 ± 4.1	28.0 ± 4.2	<0.001[2]
BMI (kg/m^2)[3]	24.1 ± 4.6	23.3 ± 3.9	23.2 ± 3.9	23.0 ± 3.8	23.1 ± 3.9	23.2 ± 4.1	<0.001[2]
Energy intake (MJ/d)	9.5 ± 2.6	9.7 ± 2.5	10.1 ± 2.6	10.6 ± 2.5	11.1 ± 2.7	12.3 ± 3.1	<0.001[2]
Nulliparous women (%)	60.0	55.1	48.8	43.3	45.5	51.5	0.05[4]
Single women (%)	2.0	2.2	1.9	1.2	1.6	2.6	<0.001[4]
Daily smoking (%)	15.2	10.9	11.6	10.3	12.2	17.6	<0.001[4]
High social status (%)[5]	4.2	6.3	6.2	6.6	5.2	2.8	<0.001[4]
Artificially sweetened noncarbonated soft drinks							
n	39,210	4307	8043	2325	3643	1753	—
Maternal age (y)	29.4 ± 4.3	28.4 ± 4.2	28.3 ± 4.2	28.4 ± 4.1	28.4 ± 4.1	27.8 ± 4.2	<0.001[2]
BMI (kg/m^2)[3]	23.1 ± 3.9	23.8 ± 4.2	24.3 ± 4.5	24.3 ± 4.6	24.7 ± 4.8	24.9 ± 5.0	<0.001[2]
Energy intake (MJ/d)	10.1 ± 2.7	9.7 ± 2.6	9.8 ± 2.6	10.1 ± 2.7	10.1 ± 2.7	10.6 ± 3.0	0.08[2]
Nulliparous women (%)	51.7	58.6	55.5	51.7	53.0	57.5	<0.001[4]
Single women (%)	2.0	2.3	2.0	1.7	1.3	2.0	<0.001[4]
Daily smoking (%)	12.2	12.5	14.3	14.2	14.8	18.7	<0.001[4]
High social status (%)[5]	6.4	4.0	3.6	3.6	2.4	1.8	<0.001[4]

[1] Mean ± SD (all such values).
[2] Determined by using a test for linear trend.
[3] Prepregnancy BMI.
[4] Determined by using the chi-square test.
[5] Familial sociooccupational status: high status refers to a management-level job that required a university education.

All analyses were performed with SAS version 9.1 software (SAS Institute Inc, Cary, NC).

RESULTS

The mean age and prepregnancy BMI in our study population was 29.0 y and 23.5, respectively. Only 1.9% of the women were single. The number of women who reported smoking daily during pregnancy was 12.5%.

The prevalence of preterm delivery in our study population was 4.62%, and 33.3% of all preterm deliveries were medically induced. The prevalence of late, moderately, and early preterm delivery was 3.56%, 0.61%, and 0.45%, respectively.

The association between selected maternal characteristics and soft drink intake is shown in **Table 1**. In general, the observed associations were rather similar. A lower social status, a higher percentage of single women, and a higher percentage of daily smokers were observed with increased intakes for all types of soft drinks. However, a greater BMI and more modest differences in energy intake were observed for the artificially sweetened compared with the sugar-sweetened soft dinks.

For carbonated soft drinks (**Table 2**), no association with preterm delivery was observed for sugar-sweetened soft drinks (adjusted P for trend: 0.29). However, the intake of artificially sweetened soft drinks was strongly associated with an increased risk of preterm delivery (adjusted P for trend: 0.0001). For the artificially sweetened carbonated soft drinks the odds ratios increased monotonically with increased intakes, with adjusted odds ratio of 1.78 (95% CI: 1.19, 2.66) for women who consuming ≥4 servings of artificially sweetened carbonated soft drinks/d compared with women with no intake of artificially sweetened carbonated soft drinks. To put this effect estimate into perspective, the adjusted odds ratio for daily smoking compared with nonsmoking in the same multivariate analyses was 1.21 (95 CI: 1.05, 1.38) in our data.

For the noncarbonated soft drinks (**Table 3**), a positive association was observed for artificially sweetened soft drinks (adjusted P for trend: 0.001). However, the effect size was more modest, and the adjusted odds ratio for women who consumed ≥4 servings of artificially sweetened soft drinks/d compared with women with no intake of artificially sweetened soft drinks was 1.29 (95% CI: 1.05, 1.59). After covariate adjustment, no association was observed for sugar-sweetened soft drinks (P for trend: 0.93), and the apparent inverse association with preterm delivery in the unadjusted analyses disappeared after adjustment for parity.

For the results shown in Tables 2 and 3, the correlation between artificially sweetened carbonated and noncarbonated soft drinks was relatively modest (Spearman's $r = 0.3$), and significant associations were observed for both variables after mutual adjustment (data not shown). Previous studies have linked the intake of artificially sweetened soft drinks with the development of type 2 diabetes (2). The elimination of women who were diagnosed with gestational diabetes (1%) did not change our findings for artificially sweetened carbonated soft drinks (adjusted P for trend: 0.0004) or noncarbonated soft drinks (adjusted P for trend: 0.002)

In the secondary analyses, the stability of the association for artificially sweetened carbonated soft dinks was explored further. To reach a sufficient statistical power in our stratified analyses, the 3 highest-intake categories were merged into one. On the basis of this categorization, women who consumed artificially sweetened carbonated soft drinks ≥1 time/d had an adjusted odds ratio of 1.38 (95% CI: 1.15, 1.65) for having preterm delivery compared with women with no intake of artificially sweetened carbonated soft drinks (**Table 4**). A dose-response relation was observed for both late and moderately preterm delivery (P for trend: <0.05). No dose response was observed for early preterm delivery despite a significantly higher risk in

TABLE 2
Association between intake of carbonated soft drinks during pregnancy and preterm delivery (<37 wk) in 59,334 women from the Danish National Birth Cohort[1]

	n	Cases	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[2]
		n (%)		
Sugar-sweetened carbonated soft drinks				
Never	9723	503 (5.2)	1.00	1.00
<1 serving/wk	15,461	709 (4.6)	0.88 (0.78, 0.99)	0.90 (0.80, 1.02)
1–6 servings/wk	28,580	1232 (4.3)	0.83 (0.74, 0.92)	0.83 (0.75, 0.93)
1 serving/d	2902	144 (5.0)	0.96 (0.79, 1.16)	0.95 (0.78, 1.15)
2–3 servings/d	2015	111 (5.5)	1.07 (0.87, 1.32)	1.03 (0.83, 1.28)
≥4 servings/d	653	40 (6.1)	1.20 (0.86, 1.67)	1.08 (0.77, 1.52)
P for trend	—	—	0.59	0.29
Artificially sweetened carbonated soft drinks				
Never	39,923	1767 (4.4)	1.00	1.00
<1 serving/wk	7437	351 (4.7)	1.07 (0.95, 1.20)	1.06 (0.94, 1.19)
1–6 servings/wk	9678	481 (5.0)	1.13 (1.02, 1.25)	1.12 (1.01, 1.25)
1 serving/d	1122	62 (5.5)	1.26 (0.97, 1.64)	1.27 (0.98, 1.65)
2–3 servings/d	834	51 (6.1)	1.41 (1.06, 1.87)	1.35 (1.01, 1.80)
≥4 servings/d	340	27 (7.9)	1.86 (1.25. 2.77)	1.78 (1.19, 2.66)
P for trend	—	—	<0.0001	0.0001

[1] OR, odds ratio. P values were determined by using the chi-square test.
[2] Adjusted for maternal age, height, prepregnancy BMI, total energy intake, cohabitant status, parity, smoking during pregnancy, and familial socio-occupational status.

TABLE 3
Association between intake of noncarbonated soft drinks during pregnancy and preterm delivery (<37 wk) in 59,281 women from the Danish National Birth Cohort[1]

	n	Cases	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[2]
		n (%)		
Sugar-sweetened noncarbonated soft drinks				
Never	21,275	1076 (5.1)	1.00	1.00
<1 serving/wk	8652	386 (4.5)	0.88 (0.78, 0.99)	0.93 (0.83, 1.05)
1–6 servings/wk	16,539	690 (4.2)	0.82 (0.74, 0.90)	0.90 (0.81, 0.99)
1 serving/d	4846	202 (4.2)	0.82 (0.70, 0.95)	0.93 (0.80, 1.09)
2–3 servings/d	6117	280 (4.6)	0.90 (0.79, 1.03)	1.0 (0.87, 1.14)
≥4 servings/d	1852	102 (5.5)	1.09 (0.89, 1.35)	1.16 (0.93, 1.43)
P for trend	—	—	0.04	0.93
Artificially sweetened noncarbonated soft drinks				
Never	39,210	1729 (4.4)	1.00	1.00
<1 serving/wk	4307	216 (5.0)	1.15 (0.99, 1.32)	1.12 (0.97, 1.30)
1–6 servings/wk	8043	376 (4.7)	1.06 (0.95, 1.19)	1.05 (0.93, 1.18)
1 serving/d	2325	113 (4.9)	1.11 (0.91, 1.35)	1.11 (0.91, 1.35)
2–3 servings/d	3643	197 (5.4)	1.24 (1.07, 1.44)	1.22 (1.04, 1.42)
≥4 servings/d	1753	105 (6.0)	1.38 (1.13. 1.69)	1.29 (1.05, 1.59)
P for trend	—	—	<0.0001	0.001

[1] OR, odds ratio. P values were determined by using the chi-square test.
[2] Adjusted for maternal age, height, prepregnancy BMI, total energy intake, cohabitant status, parity, smoking during pregnancy, and familial socio-occupational status.

the highest-intake group. At daily intake, the effect size was slightly stronger for moderately and early preterm compared with late preterm delivery.

The association between the intake of artificially sweetened carbonated soft drinks and preterm delivery was also relatively stable with respect to underweight, normal weight, and

TABLE 4
Intake of artificially sweetened carbonated soft drinks with respect to timing of preterm delivery (n = 59,334)[1]

	n	Cases	OR (95% CI)[2]
		n (%)	
All preterm (<37 wk)			
Never	39,923	1767 (4.4)	1.00
<1 serving/wk	7437	351 (4.7)	1.06 (0.94, 1.19)
1–6 servings/wk	9678	481 (5.0)	1.12 (1.01, 1.25)
≥1 serving/d	2296	140 (6.1)	1.38 (1.15, 1.65)
P for trend[3]	—	—	0.0004
Late preterm (34 ≤ wk < 37) vs nonpreterm (≥37 wk)			
Never	39,518	1362 (3.5)	1.00
<1 serving/wk	7360	274 (3.7)	1.06 (0.93, 1.21)
1–6 servings/wk	9573	376 (3.9)	1.13 (1.00, 1.27)
≥1 serving/d	2258	102 (4.5)	1.31 (1.06, 1.61)
P for trend	—	—	0.003
Moderately preterm (32 ≤ wk < 34) vs nonpreterm (≥37 wk)			
Never	38,383	227 (0.6)	1.00
<1 serving/wk	7127	41 (0.6)	1.00 (0.72, 1.41)
1–6 servings/wk	9265	68 (0.7)	1.31 (0.99, 1.73)
≥1 serving/d	2176	20 (0.9)	1.61 (1.02, 2.57)
P for trend	—	—	0.01
Early preterm (<32 wk) vs nonpreterm (≥37 wk)			
Never	38,334	178 (0.5)	1.00
<1 serving/wk	7112	36 (0.5)	1.06 (0.74, 1.52)
1–6 servings/wk	9234	37 (0.4)	0.83 (0.58, 1.19)
≥1 serving/d	2174	18 (0.8)	1.67 (1.02, 2.74)
P for trend	—	—	0.62

[1] OR, odds ratio. P values were determined by using the chi-square test.
[2] Adjusted for maternal age, height, prepregnancy BMI, total energy intake, cohabitant status, parity, smoking during pregnancy, and familial socio-occupational status.

TABLE 5
Intake of artificially sweetened carbonated soft drinks in relation to preterm delivery ($n = 59,334$) stratified by prepregnancy BMI (in kg/m^2)[1]

	n	Cases	OR (95% CI)[2]
		n (%)	
Underweight women (BMI < 18.5)			
Never	4289	223 (5.2)	1.00
<1 serving/wk	619	28 (4.5)	0.63 (0.30, 1.32)
1–6 servings/wk	772	47 (6.1)	1.09 (0.60, 2.01)
≥1 serving/d	173	12 (6.9)	2.07 (0.78, 5.46)
P for trend	—	—	0.51
Normal-weight women (18.5 ≤ BMI < 25)			
Never	26,787	1140 (4.6)	1.00
<1 serving/wk	4784	239 (5.0)	1.17 (1.01, 1.35)
1–6 servings/wk	5600	253 (4.5)	1.07 (0.93, 1.23)
≥1 serving/d	1176	69 (5.9)	1.38 (1.07, 1.77)
P for trend	—	—	0.02
Overweight women (BMI ≥ 25)			
Never	8847	404 (4.6)	1.00
<1 serving/wk	2034	84 (4.1)	0.86 (0.67, 1.09)
1–6 servings/wk	3306	181 (5.5)	1.18 (0.98, 1.41)
≥1 serving/d	947	59 (6.2)	1.36 (1.02, 1.81)
P for trend	—	—	0.02

[1] OR, odds ratio. P values were determined by using the chi-square test.

[2] Adjusted for maternal age, height, prepregnancy BMI (continuous variable), total energy intake, cohabitant status, parity, smoking during pregnancy, and familial sociooccupational status.

overweight women (**Table 5**). An increase in risk was observed in all strata, although a dose-response relation was not observed in the strata for underweight women, which contained relatively few observations.

Additional stability analyses revealed that the association for artificially sweetened carbonated soft drinks was primarily driven by medically induced delivery rather than spontaneous preterm delivery (**Table 6**). As medically induced deliveries are often driven by endothelial dysfunction and hypertensive disorders (19), we explored adjustment for hypertension in pregnancy (self-reported measures). With respect to all preterm deliveries (Table 6), further adjustment for pregnancy hypertension had a minor effect on the overall association, and the adjusted odds ratio for the highest-intake group was reduced from 1.38 (95% CI: 1.15, 1.65) to 1.35 (95% CI: 1.12, 1.62). Additional exclusion of women diagnosed with preeclampsia (2.8%) did not change the effect estimate further, and the intake of artificially sweetened carbonated soft drinks was not a predictor of preeclampsia in the data (data not shown).

For artificially sweetened noncarbonated soft drinks, similar stability analyses revealed that the association with preterm delivery was present for both normal weight and overweight women, and the overall association was also primarily driven by medically induced deliveries (data not shown).

DISCUSSION

In this large prospective cohort of pregnant women, we observed a positive association between the intake of artificially sweetened soft drinks and the risk of preterm delivery. No association was observed for sugar-sweetened soft drinks. The associations for the artificially sweetened soft drinks were robust to stratification by prepregnancy BMI and were primarily driven by medically induced delivery rather than spontaneous delivery.

The different associations observed for artificially sweetened compared with sugar-sweetened soft drinks are particularly noteworthy. A chance finding would seem unlikely because consistent results were observed for both types of artificially sweetened soft drinks, and no association was observed for both types of sugar-sweetened soft drinks. Subjects answered the 4 questions on soft drinks independent of each other, and the results for the 2 types of artificially sweetened soft drinks were stable after mutual adjustment.

Hypertensive disorders in pregnancy have been identified as a strong risk factor for medically induced preterm delivery (19). Intakes of sugar-sweetened and artificially sweetened soft drinks in middle-aged nonpregnant subjects were also associated with hypertension and metabolic disorders (3–5). These findings suggest that the association for artificially sweetened soft drinks in our study might have been driven by hypertensive disorders or endothelial dysfunction. However, the exclusion of women diagnosed with preeclampsia in our study did not change our effect estimates, and relatively small changes were observed when adjustments were made for hypertension in pregnancy. These results suggest that preeclampsia and pregnancy hypertension are not likely to be important confounders with respect to our findings.

It has been suggested that previous findings on artificially sweetened soft drinks and metabolic disorders might be due to reverse causality (4) because the disease develops over a substantial period of time, and individuals might shift their intake from sugar-sweetened to artificially sweetened soft drinks before diagnosis. Although it cannot be excluded, inverse causality does not seem to be the most likely explanation for our findings. First, the pregnancy period covered a relatively short time window, and information on diet was collected well before the expected time of delivery. Second, the stability of our findings with respect to stratification by prepregnancy BMI and with respect to the exclusion of women diagnosed with gestational diabetes does not suggest that our findings were limited to women who might have shifted their soft drink intake because of weight changes or the development of gestational diabetes.

TABLE 6
Intake of artificially sweetened carbonated soft drinks (servings/wk or servings/d) in relation to overall, spontaneous, and medically induced preterm delivery (n = 59,334)[1]

	n	Cases	OR (95% CI)[2]
		n (%)	
All preterm deliveries (<37 wk)			
Never	39,923	1767 (4.4)	1.00
<1 serving/wk	7437	351 (4.7)	1.06 (0.94, 1.19)
1–6 servings/wk	9678	481 (5.0)	1.12 (1.01, 1.25)
≥1 serving/d	2296	140 (6.1)	1.38 (1.15, 1.65)
P for trend	—	—	0.0004
Only spontaneous preterm deliveries (<37 wk)			
Never	39,357	1201 (3.1)	1.00
<1 serving/wk	7323	237 (3.2)	1.04 (0.90, 1.20)
1–6 servings/wk	9506	309 (3.3)	1.05 (0.93, 1.20)
≥1 serving/d	2235	81 (3.6)	1.20 (0.95, 1.51)
P for trend	—	—	0.14
Only medically induced preterm deliveries (<37 wk)[3]			
Never	38,722	566 (1.5)	1.00
<1 serving/wk	7200	114 (1.6)	1.06 (0.89, 1.34)
1–6 servings/wk	9369	172 (1.8)	1.26 (1.06, 1.50)
≥1 serving/d	2213	59 (2.7)	1.75 (1.34, 2.30)
P for trend	—	—	<0.0001

[1] OR, odds ratio. P values were determined by using the chi-square test.
[2] Adjusted for maternal age, height, prepregnancy BMI (continuous variable), total energy intake, cohabitant status, parity, smoking during pregnancy, and familial sociooccupational status.
[3] Induction or cesarean section before the onset of labor.

Although sugar-sweetened and artificially sweetened carbonated soft drinks differ with regard to the types of sweetener used and energy contents, they should be similar with respect to the types and amounts of other additives and aromatic compounds. The same associations can be concluded for noncarbonated soft drinks. The covariate structure observed in our study was also relatively comparable between different types of soft drinks with respect to social factors such as occupational and cohabitant status and maternal smoking. Furthermore, monitoring surveys from both Denmark and Norway identified soft drink consumption as the predominant route of intake for artificial sweeteners (30, 31). Therefore, it is reasonable to suspect that the content of artificial sweeteners might be the causal factor for the increased risk of preterm delivery observed in our study.

However, it is difficult to make inferences on which sweeteners might be at fault because most artificially sweetened soft drinks include mixtures of different sweeteners. A monitoring survey from 2005 quantified artificial sweeteners in 76 soft drinks from the Danish market (30). For carbonated soft drinks, aspartame and acesulfame-K were primarily used in products from the major international brands, and the average concentration of these 2 sweeteners was around 2–3-fold higher in carbonated than in noncarbonated soft drinks (30). With the assumption that either aspartame or acesulfame-K might have affected preterm delivery in our study, the more modest effect size observed for noncarbonated soft drinks might be due to lower concentration of these artificial sweeteners in noncarbonated compared with carbonated soft drinks. Lower concentrations of these sweeteners in noncarbonated soft drinks were primarily compensated by cyclamate, saccharine, or both.

To our knowledge, relatively few studies in humans have investigated the potential toxicity of artificial sweeteners. Most animal studies that looked at the safety of aspartame intake during pregnancy have focused on neurologic and behavioral disturbances (32). The small litter sizes and high doses used in many of these studies make it difficult to draw any conclusion on potential effects on outcomes such as preterm delivery or birth weight. In many cases such results were often not even reported or presented (33).

After ingestion, aspartame is broken down into aspartic acid, phenylalanine, and methanol. Methanol is oxidized into formaldehyde and then to formic acid, which is considered responsible for the toxic effects of methanol. Despite arguments that aspartame intake should not affect blood methanol concentrations (34), animal studies have reported the accumulation of formaldehyde adducts derived from aspartame in tissue components (22). This might be one explaining factor for reports on headaches linked to the intake of aspartame (10). More relevant to our findings, a study in low dose methanol exposure through inhalation in nonhuman primates observed a significant decrease in the length of gestation in exposed animals compared with control animals (21). A shortening of gestation was even observed at methanol vapor concentrations that barely affected blood methanol concentrations in these animals (200 ppm; 2.5 h/d). Furthermore, 5 out of 28 exposed animals needed medical intervention and were delivered by cesarean delivery either because of vaginal bleeding (n = 4) or unproductive labor (n = 1). None of the 9 control animals required cesarean delivery. The authors suggested that the observed shortening of gestation could either be related to the effects of methanol on the fetal neuroendocrine system (hypothalamic–pituitary–adrenal axis) or an indirect action of methanol on the maternal uterine environment. The latter explanation would be more compatible with our findings of an increased risk of medically induced preterm deliveries.

The main strengths of our study are its prospective design with a large number of pregnant women. Furthermore, a previous

validation study from this cohort suggested that exposure risk associations for preterm delivery should not be biased because of nonparticipation (24). As with all observational studies, we cannot exclude that our findings may be a result of unidentified and unadjusted confounders. The different association observed for sugar-sweetened and artificially sweetened soft drinks with preterm delivery implies that such confounders would have to be specific for women who drank artificially sweetened soft drinks. Despite careful covariate adjustment, residual confounding cannot be excluded either. Given that a mixture of artificial sweeteners are used in the production of soft drinks, the lack of studies with respect to pregnancy complications, and the controversy surrounding the health effects for some of those sweeteners (9, 35), the replication or rejection of our findings in other independent data are warranted.

In conclusion, our findings suggest that the daily intake of artificially sweetened soft drinks may be associated with an increased risk of preterm delivery. The relative consistency of our findings for carbonated and noncarbonated soft drinks and the absence of an association for sugar-sweetened soft drinks suggest that the content of artificial sweeteners might be the causal factor. However, the replication of our findings in another experimental setting is warranted.

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