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Intake of artificially sweetened soft drinks and risk of preterm delivery: a prospective cohort study of 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* doi: 10.3945/ajcn.2009.28968.

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

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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

	Servings of soft drinks						
	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 socioоccupational 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 (18.5 < BMI)			
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 socioccupational 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 servings/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 socioccupational 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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The authors' responsibilities were as follows—TIH and SFO: study conception and design; TIH, MS, SBP, and SFO: analyses and interpretation of data; TIH: draft of the manuscript, statistical analyses, and responsibility for the integrity of the data and accuracy of data analyses; SFO: funding; TIH, MS, SBP, and SFO: critical revision of the manuscript; and TIH and SFO: acquisition of data and responsibility for the entire contents of the manuscript. All authors had full access to study data. None of the authors had a conflict of interest.

REFERENCES

1. Block G. Foods contributing to energy intake in the US: data from NHANES III and NHANES 1999–2000. J Food Compost Anal 2004;17: 439–47.
2. Schulze MB, Manson JE, Ludwig DS, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA 2004;292:927–34.
3. Dhingra R, Sullivan L, Jacques PF, et al. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. Circulation 2007;116: 480–8.
4. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. Circulation 2008;117:754–61.
5. Winkelmayer WC, Stampfer MJ, Willett WC, Curhan GC. Habitual caffeine intake and the risk of hypertension in women. JAMA 2005;294: 2330–5.
6. Lean ME, Hankey CR. Aspartame and its effects on health. BMJ 2004; 329:755–6.
7. Whitehouse CR, Boullata J, McCauley LA. The potential toxicity of artificial sweeteners. AAOHN J 2008;56:251–9.
8. Soffritti M, Belpoggi F, Degli ED, Lambertini L, Tibaldi E, Rigano A. First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. Environ Health Perspect 2006;114:379–85.
9. Soffritti M, Belpoggi F, Tibaldi E, Esposti DD, Lauriola M. Life-span exposure to low doses of aspartame beginning during prenatal life increases cancer effects in rats. Environ Health Perspect 2007;115:1293–7.
10. Jacob SE, Stechschulte S. Formaldehyde, aspartame, and migraines: a possible connection. Dermatitis 2008;19:E10–1.
11. Lipton RB, Newman LC, Cohen JS, Solomon S. Aspartame as a dietary trigger of headache. Headache 1989;29:90–2.
12. Newman LC, Lipton RB. Migraine MLT-down: an unusual presentation of migraine in patients with aspartame-triggered headaches. Headache 2001;41:899–901.
13. Van den Eeden SK, Koepsell TD, Longstreth WT Jr, van Belle G, Daling JR, McKnight B. Aspartame ingestion and headaches: a randomized crossover trial. Neurology 1994;44:1787–93.
14. London RS. Saccharin and aspartame. Are they safe to consume during pregnancy? J Reprod Med 1988;33:17–21.
15. Khashu M, Narayanan M, Bhargava S, Osiovich H. Perinatal outcomes associated with preterm birth at 33 to 36 weeks' gestation: a population-based cohort study. Pediatrics 2009;123:109–13.
16. Lindstrom K, Winbladh B, Haglund B, Hjern A. Preterm infants as young adults: a Swedish national cohort study. Pediatrics 2007;120:70–7.
17. Siega-Riz AM, Promislow JH, Savitz DA, Thorp JM Jr, McDonald T. Vitamin C intake and the risk of preterm delivery. Am J Obstet Gynecol 2003;189:519–25.
18. Olsen SF, Secher NJ. Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study. BMJ 2002; 324:447.
19. Berkowitz GS, Blackmore-Prince C, Lapinski RH, Savitz DA. Risk factors for preterm birth subtypes. Epidemiology 1998;9:279–85.
20. Scholl TO, Sowers M, Chen X, Lenders C. Maternal glucose concentration influences fetal growth, gestation, and pregnancy complications. Am J Epidemiol 2001;154:514–20.
21. Burbacher TM, Grant KS, Shen DD, et al. Chronic maternal methanol inhalation in nonhuman primates (*Macaca fascicularis*): reproductive performance and birth outcome. Neurotoxicol Teratol 2004;26:639–50.
22. Trocho C, Pardo R, Rafecas I, et al. Formaldehyde derived from dietary aspartame binds to tissue components in vivo. Life Sci 1998;63:337–49.
23. Olsen J, Melbye M, Olsen SF, et al. The Danish National Birth Cohort–its background, structure and aim. Scand J Public Health 2001;29:300–7.
24. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? Epidemiology 2006;17:413–8.
25. Olsen SF, Mikkelsen TB, Knudsen VK, et al. Data collected on maternal dietary exposures in the Danish National Birth Cohort. Paediatr Perinat Epidemiol 2007;21:76–86.
26. National Food Institute–Technical University of Denmark (DTU). Danish Food Composition Databank–edition 6.02. Search food data. Available from: http://www.foodcomp.dk/v6/fcdb_search.asp (cited 20 August 2009).
27. Mikkelsen TB, Osler M, Olsen SF. Validity of protein, retinol, folic acid and n−3 fatty acid intakes estimated from the food-frequency questionnaire used in the Danish National Birth Cohort. Public Health Nutr 2006;9:771–8.
28. Nohr EA, Vaeth M, Bech BH, Henriksen TB, Cnattingius S, Olsen J. Maternal obesity and neonatal mortality according to subtypes of preterm birth. Obstet Gynecol 2007;110:1083–90.
29. Willett W. Chapter 11. In: Nutritional epidemiology. New York, NY: Oxford University Press, 1990:273–307.
30. Leth T, Jensen U, Fagt S, Andersen R. Estimated intake of intense sweeteners from non-alcoholic beverages in Denmark, 2005. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2008;25:662–8.
31. Bergsten C. Inntak av kunstige søtstoffer acesulfam K, aspartam, cyklamat og sakkarin. In: Statens næringsmiddeltilsyn. [Intake of artificial sweeteners. Acesulfame-K, aspartame, cyclamate and saccharin.] Available from: http://www.mattilsynet.no/mattilsynet/multimedia/archive/00017/Inntak_av_kunstige_s_17359a.pdf. Oslo, Norway; Norwegian Food Safety Authority, 1998:12–64 (in Norwegian).
32. Magnuson BA, Burdock GA, Doull J, et al. Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. Crit Rev Toxicol 2007;37:629–727.
33. Sperber EF, Moshe SL, Dowedwards DL. Prenatal exposure to aspartame and seizure susceptibility. J Epilepsy 1995;8:51–6.
34. Butchko HH, Stargel WW, Comer CP, et al. Aspartame: review of safety. Regul Toxicol Pharmacol 2002;35:S1–93.
35. Magnuson B, Williams GM. Carcinogenicity of aspartame in rats not proven. Environ Health Perspect 2008;116:A239–40.

Letters to the Editor

Intake of artificially sweetened soft drinks and risk of preterm delivery

Dear Sir:

We are writing to comment on the article by Haldorsson et al (1). First, we wish to laud the authors for their clear writing. The prospective design and the very large sample size are study strengths. Although some of our concerns were expressed as potential weaknesses by the authors in their discussion, we wish to elaborate on several points that may compromise the study findings.

In the multivariate analysis, only pregravid body mass index was entered, but not weight gain during pregnancy nor presence of diabetes, which are potential confounders. It is entirely plausible that those women who had excessive weight gain during pregnancy may have been more predisposed to drinking noncaloric soda. Since only late preterm delivery, especially medically induced delivery, was associated with noncaloric soda intake, is it possible that those women who gained excessive weight and whose babies had macrosomia might have been more likely to be candidates for medically induced late preterm delivery? This possibility cannot be ruled out.

Only soda beverages with noncaloric sweeteners were considered in this study. Yet, noncaloric sweeteners are also used extensively in tea, coffee, and other foods and beverages. Thus, the data limited to soda drinking are incomplete and potentially introduce bias.

The gestational period was examined as a categorical rather than a continuous variable. The latter approach would have led to a more robust statistical analysis. Greater error could have been introduced by misclassification.

The design of this study is cohort. Yet, the results are presented as odds ratios rather than relative risk, which is a standard measure of risk in cohort studies. It appears that this choice was made to estimate relative risk because the outcomes in this study were infrequent. The use of odds ratios in this very large-scale cohort study reinforces the fact that the overall association between diet soda intake and preterm delivery was based on small outcome number and thus, the associations were relatively weak although statistically significant.

In observational studies such as this, applying the Hill criteria for assessing disease causation can help gain further insight into the nature of the relation found (2).

For sake of brevity, only salient points are outlined below:

1) Strength of the association: the observed associations in this study were all quite weak (ie, odds ratios <2.0). The extremely large sample size in the study would render many very weak associations and trends as highly statistically significant due to the sheer numbers of subjects. The real question here is whether the very weak component associations are biologically meaningful. Strength of an association refers to the magnitude of an association rather than to its statistical significance. The stronger an observed association, the more likely it is to be valid, and the associations reported in this paper are quite weak. Weak associations are usually viewed with caution, as they are likely to be due to chance, bias, misclassification, or confounding.

2) Dose-response relation: with such a large sample size, if there had been a clear dose-response relation with an incremental increase in the soda intake, the merging of the "higher" exposure categories would not have been necessary.

3) Temporality: although the putative causal factor preceded the delivery, the information on noncaloric sweetener use was obtained at only one point in time during pregnancy (ie, 20–24 wk). It is entirely possible that those who answered "yes" may have stopped soda consumption during the latter half of pregnancy or vice-versa (ie, taken up soda drinking during the latter part of pregnancy). Nevertheless, as this was a prospective study, the information was collected antecedent to the outcome of interest.

4) Plausibility: at this point, it is unclear what the underlying mechanism for late preterm delivery is. It is difficult to imagine one single mechanism because the data on noncaloric sweeteners were aggregate information on different sweeteners and they are all very different compounds with different metabolisms and different metabolic breakdown products. Given the potential heterogeneity of the sweeteners included in the data set, it would be difficult to envision a common biological mechanism for the observed late preterm delivery.

Although the authors speculate about the potential role of methanol, a temporary breakdown product of aspartame metabolism, it is well known that the amount of methanol produced from the aspartame used to sweeten a 12-oz soda is less than that from a banana or a comparable amount of orange juice. Ounce for ounce, tomato juice produces 6 times the methanol as aspartame-sweetened soda. Clearly, a dietary methanol-based mechanism does not appear plausible.

5) Consistency: to the best of our knowledge there has been no prior report of an association between noncaloric sweetener use and preterm delivery. Thus, this single report of an association remains in question until further studies confirm this finding and causality can be established. The authors themselves cautioned that this observation needs to be confirmed by other studies before any further casual inferences on aspartame and preterm delivery can be made. The consistency of observed associations is one of the most important criteria in scientific methodology and has been a mainstay long before the Hill criteria were formulated. Scientific methodology requires the testing and retesting of hy-

potheses to confirm the first study's results. It is only after the confirmatory process has been completed that a hypothesis can be considered valid. So this paper and its findings can only be considered as hypothesis-generating and require further retesting to assess validity. This is extremely important in light of the very weak associations observed.

In conclusion, we wish to reiterate that aspartame is a time-tested product, which was first approved by the US Food and Drug Administration in 1981 (for use in foods) (3) and 1983 (for beverages) (4). It has been extensively and safely used for more than a quarter of a century. Preference for sweet taste is a universal trait among humans and noncaloric sweeteners are an important aid for many people who want to control their energy intake without sacrificing taste. As we are facing a global epidemic of obesity and its associated morbidity, one needs to be especially cautious in drawing conclusions which could compromise the utility of an important tool used for weight control.

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REFERENCES

1. Halldorsson TI, Strøm M, Petersen SB, Olsen SF. Intake of artificially sweetened soft drinks and risk of preterm delivery: a prospective cohort study of 59,334 Danish pregnant women. Am J Clin Nutr 2010; 92:626–33.
2. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295–300.
3. US Food and Drug Administration. Aspartame: Commissioner's final decision. Final Rule. Federal Register 1981;46:38285–307.
4. US Food and Drug Administration. Aspartame use in carbonated beverages and syrups. Federal Register 1983;48:31376–96.

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Intake of artificially sweetened soft drinks and risk of preterm delivery

Dear Sir:

The study by Halldorsson et al (1) found some association between regular use (≥1 drinks/d) of artificially sweetened carbonated soft drinks and preterm delivery, with a multivariate odds ratio (OR) of 1.38 (95% CI: 1.15–1.65), on the basis of 140 cases of regular drinkers of soft drinks. The multivariate OR is close to the crude OR (1.40; 95% CI: 1.16–1.68). There were, moreover, 415 cases of regular drinkers of noncarbonated soft drinks, corresponding to a crude OR of 1.23 (95% CI: 1.10–1.38) compared with never drinkers, computed from data presented in Table 3 in their original article (1). From this analysis, and from Table 3, it is clear that the association is stronger and more consistently linear for carbonated than for noncarbonated drinks.

Given the much larger number of regular users of noncarbonated than of carbonated drinks (415 compared with 140), there is no justification for presenting stratified analyses in Tables 4, 5, and 6 for carbonated drinks only. The authors state at the end of Results that the associations were similar for noncarbonated drinks, but no data are provided.

More important, if the key issue of this report is artificially sweetened soft drinks (or artificial sweeteners), the most powerful way to address it is by combining noncarbonated plus carbonated artificially sweetened soft drinks. The authors do not present this analysis. Thus, the key point to understanding any possible role of artificial sweeteners should be addressed by combining carbonated plus noncarbonated artificially sweetened soft drinks and presenting this as the main analysis. An additional point is to present stratified analyses (Tables 4, 5, and 6) for the combination of carbonated plus noncarbonated drinks and (given the larger numbers of cases) for noncarbonated drinks only.

In the absence of these analyses, the data do not allow inference on all artificially sweetened soft drinks (carbonated and noncarbonated) combined and hence on any potential role of artificial sweeteners on preterm delivery.

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REFERENCE

1. Halldorsson TI, Strøm M, Petersen SB, Olsen SF. Intake of artificially sweetened soft drinks and risk of preterm delivery: a prospective cohort study in 59,334 Danish pregnant women. Am J Clin Nutr 2010;92: 626–33.

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Reply to RG Bursey and ML Watson

Dear Sir:

We thank Bursey and Watson for their interest in our article, because they raise important issues that cannot always be addressed appropriately in a short scientific paper.

First, they suggest that women who gained excessive weight might be more predisposed to drink noncaloric soda and those subjects might be more likely to have medically induced preterm delivery due to macrosomic infants. Gestational weight gain was not entered in our final analyses due to high number of missing values (31%). Gestational weight gain in our data are based on self-reported measures from telephone interviews conducted around gestation weeks 12 and 30 divided by the time between the 2 telephone interviews. Failure to participate in both interviews is the main explanation for the number of missing values. By restricting our analyses to subjects where this information was available ($n = 41{,}069$), some inferences can be made:

- The effect estimate for those consuming artificially sweetened carbonated soft drinks $\geq$1 serving/d compared with those with zero intake was now 1.32 (95% CI: 1.04, 1.67) compared with 1.38 (95% CI: 1.15, 1.65) for the full data ($n = 59{,}334$). Adjusting for gestational weight gain (categorical, in quintiles) in the restricted sample resulted in an essentially unchanged effect estimate 1.32 (1.04, 1.67).
- Nonsignificant correlation was observed between artificially sweetened carbonated soft drinks and maternal weight gain. Furthermore, in our full data ($n = 59{,}334$), adjustment for macrosomia (dichotomized either as $\geq$4.0 or $\geq$ 4.5 kg) had minor effect on the association between artificially sweetened soft drinks and preterm delivery.

Based on the above, it is our conclusion that there is no strong signal suggesting that our data are confounded by gestational weight gain, macrosomia, or combination of both.

Another concern raised is that the lack of information on total consumption of noncaloric sweeteners might bias our findings. Intuitively one would expect that use of other artificially sweetened products might be positively correlated with intake of artificially sweetened soft drinks. In that case we underestimate the overall intake, but it is not clear how this could bias our findings.

Concerning our use of categorical outcome measure we also observe a significant decrease in length of gestation when that variable was entered as a continuous outcome.

With respect to our presentation of results, we agree that using relative risks might have been appropriate, but using odds ratios is also conventional for cohort studies. For the association between artificially sweetened soft drinks and preterm delivery, the adjusted odds ratios for $\geq$ 1 servings/d and for $\geq$ 4 servings/d, using those with zero intake as a referent, were 1.38 and 1.78, respectively. The corresponding relative risk ratios were 1.35 and 1.72. Although these relative risk numbers reflect modest strengths, they are still relevant from a public health point of view given the number of exposed women.

Concerning the application of some of Hill's (1) points of view regarding causality in our findings, we have the following comments:

Regarding the *strength of association*, studies in nutritional epidemiology are often bound to observe weak associations—even in cases when there may be a true, relatively strong, underlying association—because of imprecise intake estimates.

Regarding *dose response*, it is important to note that preterm delivery is a rare outcome in our population and relatively few women reported frequent consumption of artificially sweetened beverages. Despite large numbers of subjects and a relatively clear dose response, implying stratifications in the high intake groups quickly reaches its limitations. Therefore, merging exposure groups was necessary in our opinion and the secondary analyses give an important insight into the observed association. The effect measure for daily intake can also be considered as more balanced compared with those reported at more extreme intakes.

With respect to *temporality*, we agree that this point is met due to clear temporal separation between the intake assessment in gestation week 25 and the outcome (preterm birth), typically many weeks later.

Concerning the issue of *plausibility*, our exposure variable describes low to high intake of artificially sweetened soft drinks. High intake of artificially sweetened soft drinks in a large group of people is a marker for relatively high average intake of the most dominant sweeteners used on the market (2). Despite differences in biological activity and inability to distinguish between different sweeteners, it cannot be fully excluded that one particular sweetener might be responsible for the observed association. Plausibility is a function of available information and lack of studies is no argument for not making interferences on the subject.

Different conclusions have been reached concerning the relevance of methanol derived from aspartame (3, 4) so the plausibility of a methanol-based mechanism can certainly be debated. It cannot be discarded, however, by quoting the methanol content in certain fruits. Methanol content in freshly squeezed grapes and oranges can be as low as 1 mg/L (5–7), although concentrations vary depending on the amount of fermentation. In comparison, a content of 56 mg/L methanol is often reported for diet soft drinks (5). Furthermore, the mean total dietary intake of methanol from foods (not aspartame-derived) has been estimated around 11 mg/d (8). Estimates do, however, vary and in an expert review on reproductive and developmental toxicity of methanol, the 90th percentile for methanol intake from fruit juices and wines was reported as high as 48 mg/d (5). Adding 1 L of aspartame-sweetened soda to that diet would still lead to $\approx$2-fold increase in exposure. Median intakes from fruits and wines should, however, be much lower particularly since pregnant women rarely consume alcoholic beverages. In the absence of robust data on dietary methanol exposures (5) and potential adverse effects during pregnancy (9), we think our speculation on a methanol-based mechanism was justifiable.

More importantly, we appear to agree on how our results should be interpreted (*consistency*), and we urge cautious interpretation until

further studies have been conducted. Indeed, as with any other observational study, we cannot exclude the role of bias or unadjusted confounding. This is why we encourage replication of our findings.

Finally we would like to thank Bursey and Watson for relevant comments on our article.

The author had no conflicts of interest to declare.

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REFERENCES

1. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295–300.
2. Leth T, Jensen U, Fagt S, Andersen R. Estimated intake of intense sweeteners from non-alcoholic beverages in Denmark, 2005. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2008; 25:662–8.
3. Butchko HH, Stargel WW, Comer CP, et al. Aspartame: review of safety. Regul Toxicol Pharmacol 2002;35:S1–93.
4. Monte WC. Aspartame: Methanol and the public health. J Appl Nutr 1984;36:42–54.
5. Shelby M, Portier C, Goldman L, et al. NTP-CERHR expert panel report on the reproductive and developmental toxicity of methanol. Reprod Toxicol 2004;18:303–90.
6. Kirchner JG, Miller JM. Canning and Storage Effects, Volatile Water-Soluble and Oil Constituents of Valencia Orange Juice. J Agric Food Chem 1957;5:283–91.
7. Kirchner JG, Miller JM, Rice RG, Keller J, Fox MM. Volatile Water Soluble Constituents of Grapefruit Juice. J Agric Food Chem 1953; 1:510–2.
8. Magnuson BA, Burdock GA, Doull J, et al. Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. Crit Rev Toxicol 2007;37:629–727.
9. Burbacher TM, Grant KS, Shen DD, et al. Chronic maternal methanol inhalation in nonhuman primates (Macaca fascicularis): reproductive performance and birth outcome. Neurotoxicol Teratol 2004;26: 639–50.

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Intake of artificially sweetened soft drinks and risk of preterm delivery

Dear Sir:

The study by Halldorsson et al (1) found some association between regular use (≥1 drinks/d) of artificially sweetened carbonated soft drinks and preterm delivery, with a multivariate odds ratio (OR) of 1.38 (95% CI: 1.15–1.65), on the basis of 140 cases of regular drinkers of soft drinks. The multivariate OR is close to the crude OR (1.40; 95% CI: 1.16–1.68). There were, moreover, 415 cases of regular drinkers of noncarbonated soft drinks, corresponding to a crude OR of 1.23 (95% CI: 1.10–1.38) compared with never drinkers, computed from data presented in Table 3 in their original article (1). From this analysis, and from Table 3, it is clear that the association is stronger and more consistently linear for carbonated than for noncarbonated drinks.

Given the much larger number of regular users of noncarbonated than of carbonated drinks (415 compared with 140), there is no justification for presenting stratified analyses in Tables 4, 5, and 6 for carbonated drinks only. The authors state at the end of Results that the associations were similar for noncarbonated drinks, but no data are provided.

More important, if the key issue of this report is artificially sweetened soft drinks (or artificial sweeteners), the most powerful way to address it is by combining noncarbonated plus carbonated artificially sweetened soft drinks. The authors do not present this analysis. Thus, the key point to understanding any possible role of artificial sweeteners should be addressed by combining carbonated plus noncarbonated artificially sweetened soft drinks and presenting this as the main analysis. An additional point is to present stratified analyses (Tables 4, 5, and 6) for the combination of carbonated plus noncarbonated drinks and (given the larger numbers of cases) for noncarbonated drinks only.

In the absence of these analyses, the data do not allow inference on all artificially sweetened soft drinks (carbonated and noncarbonated) combined and hence on any potential role of artificial sweeteners on preterm delivery.

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REFERENCE

1. Halldorsson TI, Strøm M, Petersen SB, Olsen SF. Intake of artificially sweetened soft drinks and risk of preterm delivery: a prospective cohort study in 59,334 Danish pregnant women. Am J Clin Nutr 2010;92: 626–33.

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