Association between intake of artificially sweetened and sugar-sweetened beverages and preterm delivery: a large prospective cohort study[1–3]

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ABSTRACT

Background: Artificially sweetened (AS) and sugar-sweetened (SS) beverages are commonly consumed during pregnancy. A recent Danish study reported that the daily intake of an AS beverage was associated with an increased risk of preterm delivery.

Objective: We examined the intake of AS and SS beverages in pregnant women to replicate the Danish study and observe whether AS intake is indeed associated with preterm delivery.

Design: This was a prospective study of 60,761 pregnant women in the Norwegian Mother and Child Cohort Study. Intakes of carbonated and noncarbonated AS and SS beverages and use of artificial sweeteners in hot drinks were assessed by a self-reported food-frequency questionnaire in midpregnancy. Preterm delivery was the primary outcome, and data were obtained from the Norwegian Medical Birth Registry.

Results: Intakes of both AS and SS beverages increased with increasing BMI and energy intake and were higher in women with less education, in daily smokers, and in single women. A high intake of AS beverages was associated with preterm delivery; the adjusted OR for those drinking >1 serving/d was 1.11 (95% CI: 1.00, 1.24). Drinking >1 serving of SS beverages per day was also associated with an increased risk of preterm delivery (adjusted OR: 1.25; 95% CI: 1.08, 1.45). The trend tests were positive for both beverage types.

Conclusion: This study suggests that a high intake of both AS and SS beverages is associated with an increased risk of preterm delivery. *Am J Clin Nutr* 2012;96:552–9.

Or ... maybe it was the food dye? The sodium benzoate? the caffeine? The combination?

INTRODUCTION

Preterm delivery, defined as delivery before 37 completed gestational weeks, is a major public health problem associated with both perinatal mortality and long-term morbidity (1–3). Preterm-born infants, especially if born before 32 wk of gestation, incur substantially high costs for society (4, 5). This is not only a major medical problem but a considerable trauma for affected families as well.

There is growing interest in the issue of whether dietary factors can affect the risk of preterm delivery, and several nutritional factors have been investigated with both inconclusive and conflicting results, including the Mediterranean diet, fish consumption, vitamin and mineral supplements (eg, folic acid and vitamins C and E), caffeine, and probiotic food (6–14).

Artificial sweeteners are widely used. The most commonly used substance is aspartame, which has several beneficial effects. It does not increase blood sugar concentrations and it is almost free of calories, which makes its use popular in both food and beverages. The main sources of artificial sweeteners are carbonated and noncarbonated soft beverages (15). Despite the assumption that artificial sweeteners lead to weight loss, several studies have reported the opposite effect (16–18). Increased weight also increases the risk of type 2 diabetes (19). Animal studies have confirmed these findings. Rats fed artificial sweeteners have greater food intake, body weight, and body fat than do rats fed sugar, possibly because energy regulation is related to the sweet taste rather than to energy intake (17). However, the causality of this association has not been confirmed. On the other hand, sugar-sweetened (SS)[4] beverages have been linked to obesity and to many adverse health outcomes (20, 21). Both obesity (22) and high plasma glucose concentrations (23), even in nondiabetic

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[4] Abbreviations used: aOR, adjusted OR; AS, artificially sweetened; FFQ, food-frequency questionnaire; MBRN, Medical Birth Registry of Norway; MoBa, the Norwegian Mother and Child Cohort Study; SS, sugar-sweetened.

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subjects, are correlated with inflammatory response and preterm delivery.

A recent study from the Danish National Birth Cohort found no association between SS soft beverages and preterm delivery but did report a significantly increased risk of preterm delivery related to daily intake of artificially sweetened (AS) soft beverages (24). The use of artificial sweeteners during pregnancy has not been fully investigated, and the authors of the Danish study encouraged replication of their findings (25).

Therefore, we hypothesized that the association between intake of AS beverages and preterm delivery also was evident in a similar cohort of Norwegian women. Hence, the primary aim of this study was to further investigate the suggested connection between intake of AS beverages and preterm delivery. In a secondary analysis, we also examined possible associations between SS beverages and the risk of preterm delivery. Furthermore, we looked at the association between AS and SS beverages and outcome subgroups (BMI, gestational age, and spontaneous compared with iatrogenic delivery).

SUBJECTS AND METHODS

Population and study design

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective, population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (26, 27). Participants were recruited from throughout Norway from 1999 to 2008, and 38.5% of invited women consented to participate. The cohort now includes 108,000 children, 90,700 mothers, and 71,500 fathers. Women were recruited to the study by postal invitation in connection with their first routine ultrasound examination at gestational weeks 17–18. Follow-up is conducted by questionnaires at regular intervals and by linkage to national health registries. In this study, we used data from 3 follow-up questionnaires answered at gestational weeks 15 (questionnaire 1), 22 (questionnaire 2), and 30 (questionnaire 3). In questionnaires 1 and 3, the women were asked to provide information about lifestyle, background, illness, and health-related factors. Questionnaire 2 was a semiquantitative food-frequency questionnaire (FFQ), in which women reported their eating habits during the current pregnancy. Pregnancy and birth records from the Medical Birth Registry of Norway (MBRN) are linked to the MoBa database (28). Informed consent was obtained from each participant before participation, and the study was approved by the Regional Committee for Ethics in Medical Research and the Data Inspectorate in Norway.

This study is based on version 5 of the quality-assured MoBa data files released for research in 2010. At the time of this analysis, 99,229 women had completed singleton pregnancies and answered questionnaire 1; 86,307 of them had also answered the FFQ and had an energy intake within the accepted MoBa range (>4.5 and <20 MJ), described in detail elsewhere (29). We excluded women with missing information on the covariates (n = 6630), which left 79,677 women. Furthermore, we included only women who gave birth to a live baby between gestational weeks 22+0 and 41+6, which left 68,563 women. To avoid the use of multiple dependent observations, our analyses were restricted to the first enrollment in the study during the respective pregnancy, which resulted in 61,692 women. Furthermore, we excluded women with any diagnosis of preexisting or gestational diabetes, which resulted in a final study sample of 60,761 women.

Dietary information

The MoBa FFQ (downloadable at http://www.fhi.no/dokumenter/011fbd699d.pdf) has been used from February 2002 onward. This semiquantitative FFQ is designed to provide information on dietary habits and intake of dietary supplements during the first 4–5 mo of pregnancy (29). For each food and beverage item, the frequency of consumption was reported by selecting 1 of 8 to 10 frequencies, ranging from several times daily, weekly, or monthly, to never. The FFQ was read optically, and energy intake was calculated by using FoodCalc and the Norwegian Food Composition Table. The FFQ included 6 questions for reporting intake of AS and SS beverages: carbonated cola (AS and/or SS, respectively), other carbonated soft beverages (AS and/or SS, respectively), and noncarbonated beverages (AS and/or SS, respectively). The alternative frequencies were given as servings per day (between 1 and 8), servings per week (between 1–2 and 5–6), or servings per month (between 0 and 2–3). A serving was defined as 250 mL for all beverages. We combined the intakes of carbonated AS soft beverages (cola and others) and noncarbonated AS beverages into a group called AS beverages. We likewise combined the intakes of SS carbonated soft beverages (cola and others) and noncarbonated SS beverages into a group called SS beverages. These 2 groups were then divided into 6 intake categories (never, <1 serving/wk, 1–6 servings/wk, 1 serving/d, 2–3 servings/d, and ≥4 servings/d). The 6 intake categories were used to examine a possible dose-response correlation with preterm delivery. For the analyses of secondary outcomes related to preterm delivery, we reduced the frequency alternatives to <1 serving/wk, 1–6 servings/wk, and ≥1 serving/d.

Preterm delivery

The primary outcome—preterm delivery—was defined as birth before gestational week 37+0. Gestational age was determined by ultrasonography at gestational weeks 17–18 and was obtained from the MBRN (28) for all 60,761 women in this study. Secondary outcomes were studied according to the subgroups late preterm delivery (34+0 to 36+6 wk), moderately preterm delivery (32+0 to 33+6 wk), and early preterm delivery (<32+0 wk). We also examined different BMI (in kg/m^2) groups (<18.5, 18.5−25, and >25) in relation to preterm delivery and examined whether there was an association with spontaneous compared with iatrogenic preterm delivery.

Covariates

Eight covariates were selected for their known association with preterm delivery. Maternal history of previous preterm delivery and maternal age at delivery were obtained from the MBRN. Previous preterm delivery was used as dichotomous data, and maternal age was used as a continuous variable. BMI was calculated from self-reported prepregnancy weight and height, as reported in questionnaire 1. Only women who reported weight in the range 35–180 kg and height >1.40 m were included. BMI was used as a continuous variable, except in stratified analyses, in which it was divided into BMI categories (<18.5, 18.5–25,

and >25). Marital status was obtained from questionnaire 1 and was categorized as either living alone or cohabiting (regardless of legal marriage). Parity was used as a dichotomous variable denoting either nulli- or multiparity, based on information from questionnaire 1. Women were defined as smokers during pregnancy if they reported either occasional or daily smoking in questionnaire 1 or questionnaire 3. Information about education was taken from questionnaire 1, and the reported categories were combined into a dichotomous variable denoting ≤12 y or >12 y of school, regardless of the kind of education. Besides the above covariates, total energy intake was used as continuous data. We also adjusted for the alternative beverage (AS or SS) in the respective analysis.

Statistical methods

Statistical analyses were performed with predictive analytic software (PASW) statistics version 19 for Windows (SPSS Inc). All *P* values were 2-sided, and values <0.05 were considered statistically significant. Continuous variables were described as means ± SDs, whereas categorical variables were described as relative frequencies. Chi-square tests were used to assess associations between categorical variables. Simple linear regression analyses were used to test for trend in means (ie, *P*-trend).

We used binary logistic regression analyses to examine the associations of AS and SS beverages with preterm delivery. All regression analyses were performed crudely and with adjustment for maternal age, prepregnancy BMI, height, and total energy intake as continuous variables and for marital status, parity, smoking, education, previous preterm delivery, and alternative beverage as categorical data. *P*-trend was obtained by incorporating the categorical variables as linear terms into the regression models.

RESULTS

Of the 60,761 women in the study, consumption of both AS and SS beverages was positively associated with increasing BMI and energy intake (**Table 1**). The percentage of single women and daily smokers increased with increasing consumption, and the percentage of women with >12 y of education decreased with increasing consumption of both AS and SS beverages. Intake of additional added sugar (ie, added sugar from sources other than beverages) did not differ with increased frequency of AS beverage intake. However, a positive association between intake of additional added sugar and SS beverage intake was found.

Our primary outcome was preterm delivery, which accounted for 5.4% (n = 3281) of all deliveries. Of the 3281 preterm deliveries, 3.9% were late preterm deliveries (*see* definition above), 0.8% were moderately preterm deliveries, and 0.7% were early preterm deliveries (data not shown in tables).

In univariate analyses, frequent AS beverage drinkers (≥4 servings/d) had an OR for preterm delivery of 1.22 (95% CI: 1.00, 1.47), relative to never-drinkers of AS beverages (**Table 2**). The association was not statistically significant after adjustment

TABLE 1
Maternal characteristics in relation to intake of artificially and sugar-sweetened beverages in 60,761 women from the Norwegian Mother and Child Cohort study[1]

Servings	Never	<1/wk	1–6/wk	1/d	2–3/d	≥4/d	*P*
AS beverages (*n*)	22,229	14,919	13,204	4309	3998	2102	
Maternal age (y)	30.3 ± 4.7[2]	30.0 ± 4.6	29.8 ± 4.4	29.9 ± 4.4	30.0 ± 4.4	30.2 ± 4.6	<0.001[3]
BMI (kg/m^2)[4]	23.3 ± 3.8	23.6 ± 3.9	24.3 ± 4.2	24.8 ± 4.5	25.5 ± 4.9	26.3 ± 5.4	<0.001[3]
Energy intake (MJ/d)	9.8 ± 2.6	9.6 ± 2.5	9.6 ± 2.2	9.9 ± 2.7	9.8 ± 2.7	10.0 ± 2.9	0.516[3]
Added sugar intake (g/d)	64 ± 42	59 ± 36	60 ± 34	66 ± 38	65 ± 42	66 ± 47	0.116[3]
Nulliparous (%)	50.8	43.4	42.4	46.3	48.2	52.7	<0.001[5]
Single (%)	3.5	3.6	3.0	2.7	3.3	4.6	<0.001[5]
Daily smoker (%)[6]	8.8	6.6	7.3	9.1	12.3	19.2	<0.001[5]
Education level (%)[7]	66.6	71.7	71.1	69.8	64.0	53.4	<0.001[5]
Previous preterm delivery (%)	4.0	3.3	3.0	3.7	3.8	5.2	<0.001[5]
SS beverages (*n*)	6155	18,082	24,906	5832	4148	1638	
Maternal age (y)	31.2 ± 4.5	30.5 ± 4.4	29.7 ± 4.5	29.6 ± 4.6	29.1 ± 4.8	28.0 ± 5.0	<0.001[3]
BMI (kg/m^2)	24.3 ± 4.7	23.8 ± 4.1	23.8 ± 4.0	23.9 ± 4.2	24.3 ± 4.5	24.8 ± 4.9	0.003[3]
Energy intake (MJ/d)	8.9 ± 2.4	9.1 ± 2.3	9.8 ± 2.5	10.5 ± 2.6	11.1 ± 2.8	12.5 ± 3.1	0.001[3]
Added sugar from SS beverages (g/d)	0 ± 0	3 ± 1	11 ± 6	30 ± 7	56 ± 11	130 ± 45	<0.001[3]
Added sugar from other sources (g/d)	39 ± 24	42 ± 23	48 ± 25	53 ± 28	54 ± 30	55 ± 33	<0.001[3]
Nulliparous (%)	47.9	41.6	46.4	55.3	54.7	53.4	<0.001[5]
Single (%)	3.0	3.3	3.1	3.5	4.6	7.0	<0.001[5]
Daily smoker (%)[6]	7.4	5.5	7.6	11.6	16.8	29.1	<0.001[5]
Education level (%)[7]	69.9	75.6	69.1	61.4	53.4	36.4	<0.001[5]
Previous preterm delivery (%)[8]	3.6	3.1	3.5	4.6	5.1	4.5	<0.001[5]

[1] AS, artificially sweetened; SS, sugar-sweetened.
[2] Mean ± SD (all such values).
[3] Determined by using a test for linear trend.
[4] Prepregnancy BMI.
[5] Determined by chi-square test.
[6] Daily or occasional smoking in pregnancy week 17 and/or week 30.
[7] Education level refers to >12 y in school.
[8] Percentage of women giving birth before 37 gestational weeks in previous pregnancies.

TABLE 2
Associations between intake of AS and SS beverages during pregnancy and PTD, <37 completed gestational weeks, in 60,761 women from the Norwegian Mother and Child Cohort Study[1]

	All	PTD	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	Adjusted OR[3] (95% CI)
	n	%			
AS beverages					
Never	22,229	5.0 ± 0.15[4]	1	1	1
<1 serving/wk	14,919	5.1 ± 0.18	1.01 (0.92, 1.11)	1.01 (0.92, 1.11)	1.01 (0.92, 1.12)
1–6 servings/wk	13,204	5.4 ± 0.20	1.08 (0.98, 1.19)	1.07 (0.97, 1.18)	1.09 (0.99, 1.20)
1 serving/d	4309	6.0 ± 0.36	1.21 (1.05, 1.39)	1.19 (1.03, 1.37)	1.20 (1.04, 1.39)
2–3 servings/d	3998	5.2 ± 0.35	1.04 (0.90, 1.21)	0.99 (0.85, 1.16)	1.01 (0.87, 1.18)
≥4 servings/d	2102	6.0 ± 0.52	1.22 (1.00, 1.47)	1.08 (0.89, 1.32)	1.12 (0.92, 1.36)
P-trend[5]			0.007	0.127	0.053
SS beverages					
Never	6155	4.7 ± 0.27	1	1	1
<1 serving/wk	18,082	5.2 ± 0.17	1.13 (0.98, 1.29)	1.14 (0.99, 1.31)	1.15 (1.00, 1.32)
1–6 servings/wk	24,906	5.2 ± 0.14	1.11 (0.97, 1.26)	1.14 (1.00, 1.30)	1.15 (1.01, 1.32)
1 serving/d	5832	5.6 ± 0.30	1.21 (1.03, 1.42)	1.23 (1.04, 1.46)	1.25 (1.05, 1.48)
2–3 servings/d	4148	5.5 ± 0.35	1.19 (0.99, 1.42)	1.16 (0.97, 1.40)	1.19 (0.99, 1.43)
≥4 servings/d	1638	6.8 ± 0.62	1.48 (1.18, 1.86)	1.37 (1.08, 1.74)	1.41 (1.11, 1.79)
P-trend[5]			0.003	0.017	0.008

[1] ORs were calculated by using logistic regression models. AS, artificially sweetened; PTD, preterm delivery; SS, sugar-sweetened.
[2] Adjusted for previous preterm delivery, maternal age, prepregnancy BMI, height, total energy intake, marital status, parity, smoking during pregnancy, and education.
[3] Additional adjustments for the other type of beverage.
[4] Percentage ± SE (all such values).
[5] *P* values for linear trend were obtained by incorporating the variable as a linear term in logistic regression models.

for potential confounders and the alternative beverage. However, when consumption categories entailing at least one serving per day were analyzed together, the adjusted association was statistically significant for AS beverages (*see* Table 3). The highest frequency (≥4 servings/d) of SS beverages (Table 2) was associated with preterm delivery in both crude and adjusted analyses. Frequent drinkers had a significantly higher risk than did never-drinkers [adjusted OR (aOR): 1.37; 95% CI: 1.08, 1.74]. The linear trend over SS beverage frequency groups was statistically significant in both the univariate analyses and the adjusted analyses. However, after adjustment for the AS beverages, the linear trend for SS beverages was stronger, and all SS beverage consumption frequency groups were significantly associated with the outcome. As indicated by the aOR, the dose-response relation was not significant for AS beverages but the trend test was significant between SS beverages and preterm delivery, although not significant for 2–3 servings/d. If not adjusted for previous preterm delivery, the aOR for the highest frequency group of AS beverages (≥4 servings/d) was 1.15 (95% CI: 0.94, 1.42) and for the SS beverages was 1.34 (95% CI: 1.04, 1.73).

Furthermore, to evaluate whether the observed association could be explained by a correlation of SS beverages with other sources of empty calories, we included the calculated intake of added sugar from sources other than SS beverages to the confounding variables. The results still showed an independent association between SS beverage intake and preterm delivery (aOR: 1.41; 95% CI: 1.11, 1.79) for ≥4 servings/d, compared with no SS intake.

We also analyzed carbonated and noncarbonated AS beverages separately. For the carbonated AS beverages, the crude OR for the highest frequency group (≥4 servings/d) was 1.11 (95% CI: 0.87, 1.41), and the aOR was 0.99 (95% CI: 0.77, 1.26). The crude OR for the noncarbonated AS beverages was 1.21 (95% CI: 0.88, 1.65), and the aOR was 1.08 (95% CI: 0.79, 1.49). None of these figures were significant.

Statistically significant associations were found between intake of both AS and SS beverages and the all preterm delivery subgroup (**Table 3**). For daily intake of AS beverages, the aOR was 1.11 (95% CI: 1.00, 1.24); for daily intake of SS beverages, the aOR was 1.25 (95% CI: 1.08, 1.45). A positive dose-response effect for preterm delivery was found for both AS and SS beverages. After stratification by time of delivery, AS beverage intake was associated only with late preterm delivery [aOR: 1.14; 95% CI: 1.00, 1.29 (for daily intake compared with no intake); *P*-trend = 0.022]. SS beverage intake was significantly associated only with early preterm delivery [aOR: 1.75; 95% CI: 1.13, 2.73 (daily intake compared with no intake); *P*-trend = 0.081].

We also examined exposure-outcome associations within the strata of 3 BMI groups (**Table 4**). An increased risk of preterm delivery was observed for daily intake compared with no intake of AS in the normal-weight group. Women in the overweight group had significantly increased risks in all consumption categories of SS, compared with no intake. We found a positive trend test toward increased risk of preterm delivery with increasing intake of AS beverages in the normal-weight group and for increasing SS beverage intake in the overweight group (*P*-trend = 0.024). Interaction terms between BMI groups and intake of AS and SS beverages were not significant.

One of the primary aims of this study was to examine whether daily intake of AS beverages increased the risk of spontaneous preterm delivery. After mutual adjustment for AS and SS

TABLE 3
Associations between intake of AS and SS beverages during pregnancy and PTD subgroups in the Norwegian Mother and Child Cohort Study[1]

	AS beverages			SS beverages		
	All	PTD	Adjusted OR[2] (95% CI)	All	PTD	Adjusted OR[2] (95% CI)
All preterm delivery (<37 wk)	*n*	%		*n*	%	
Never	22,229	5.0 ± 0.15[3]	1	6155	4.7 ± 0.27	1
<1 serving/wk	14,919	5.1 ± 0.18	1.01 (0.92, 1.12)	18,082	5.2 ± 0.17	1.15 (1.00, 1.32)
1–6 servings/wk	13,204	5.4 ± 0.20	1.09 (0.98, 1.20)	24,906	5.2 ± 0.14	1.16 (1.01, 1.32)
≥1 serving/d	10,409	5.7 ± 0.23	1.11 (1.00, 1.24)	11,618	5.7 ± 0.22	1.25 (1.08, 1.45)
P-trend[4]			0.025			0.009
Late preterm delivery (34 to <37 wk)						
Never	21,929	3.7 ± 0.13	1	6090	3.7 ± 0.24	1
<1 serving/wk	14,733	3.9 ± 0.16	1.05 (0.94, 1.18)	17,818	3.8 ± 0.14	1.07 (0.91, 1.25)
1–6 servings/wk	13,017	4.1 ± 0.17	1.11 (0.99, 1.24)	24,590	3.9 ± 0.12	1.12 (0.96, 1.30)
≥1 serving/d	10,255	4.3 ± 0.20	1.14 (1.00,1.29)	11,436	4.2 ± 0.19	1.17 (0.99, 1.39)
P-trend[4]			0.022			0.046
Moderately preterm delivery (32 to <34 wk)						
Never	21,276	0.8 ± 0.06	1	5904	0.6 ± 0.10	1
<1 serving/wk	14,261	0.7 ± 0.07	0.89 (0.69, 1.14)	17,275	0.8 ± 0.07	1.34 (0.93, 1.94)
1–6 servings/wk	12,580	0.7 ± 0.08	0.92 (0.71, 1.20)	23,789	0.7 ± 0.05	1.22 (0.84, 1.75)
≥1 serving/d	9897	0.8 ± 0.09	1.03 (0.78, 1.35)	11,046	0.8 ± 0.09	1.41 (0.95, 2.11)
P-trend[4]			0.997			0.282
Early preterm delivery (<32 wk)						
Never	21,248	0.6 ± 0.06	1	5895	0.5 ± 0.09	1
<1 serving/wk	14,247	0.6 ± 0.07	0.94 (0.71, 1.23)	17,259	0.7 ± 0.06	1.56 (1.03, 2.36)
1–6 servings/wk	12,585	0.8 ± 0.08	1.17 (0.90, 1.53)	23,769	0.6 ± 0.05	1.37 (0.91, 2.07)
≥1 serving/d	9885	0.7 ± 0.09	1.06 (0.79, 1.42)	11,042	0.8 ± 0.09	1.75 (1.13, 2.73)
P-trend[4]			0.396			0.081

[1] ORs were calculated by using logistic regression models. AS, artificially sweetened; PTD, preterm delivery; SS, sugar-sweetened.
[2] Adjusted for previous preterm delivery, maternal age, prepregnancy BMI, height, total energy intake, marital status, parity, smoking during pregnancy, education, and the other type of beverage.
[3] Percentage ± SE (all such values).
[4] *P* values for linear trend were obtained by incorporating the variable as a linear term in logistic regression models.

beverage consumption, a small but significant association between daily intake of AS beverages and spontaneous preterm delivery was found (aOR: 1.15; 95% CI: 1.01, 1.32; *P*-trend = 0.07). No association was observed between SS beverage intake and spontaneous preterm delivery (**Table 5**).

In questionnaire 1, answered at gestational week 15, the women were asked about their intake of AS and SS beverages before pregnancy. In questionnaire 3, they reported intake of AS and SS beverages in the third trimester. The mean (±SD) intake of AS beverages before pregnancy was 1.05 ± 2.77 glasses/d for the women consuming AS beverages; the corresponding figure in the third trimester was 0.78 ± 2.56 glasses/d. The respective values for SS beverages were 1.15 ± 3.37 glasses/d before pregnancy and 0.97 ± 2.84 glasses/d in the third trimester. Reanalysis of the data with AS and SS beverage intakes before pregnancy did not change the results (data not shown). No association was found between high intake of artificial sweeteners in hot beverages and preterm delivery (aOR: 1.03; 95% CI: 0.86, 1.24; data not shown in tables).

DISCUSSION

The primary aim of this study was to investigate possible associations between intake of AS and SS beverages and preterm delivery. We found a slightly increased risk of preterm delivery for women consuming at least one serving of AS beverages daily after adjusting for SS beverage intake. However, an even greater risk of preterm delivery, especially for early preterm, was suggested in women reporting at least one serving of SS beverages daily. This association remained even after adjustment for added sugar, which indicated an independent risk between high intake of SS beverages and preterm delivery.

Halldorsson et al (24) found in a comparable Danish cohort study that daily intake of AS beverages significantly increased the risk of preterm delivery. The hypothesis was that methanol formed by the metabolism of aspartame might lead to preterm delivery, because methanol has been shown to decrease gestational length in primates (30, 31).

However, the association between intake of SS beverages and preterm delivery could be explained by elevated glucose concentrations after consumption. Scholl et al (23) reported an increased risk of preterm delivery in nondiabetic women with elevated plasma glucose concentrations. Higher glucose concentrations, associated with chorioamnionitis, increased the risk of preterm delivery by 12-fold. Interleukins (eg, IL-1, IL-6, and IL-8) are known to be part of the inflammatory reaction and are associated with both preterm delivery and chorioamnionitis (32, 33). Pregnancy itself is a condition with reduced sensitivity to insulin in peripheral tissues (34). We found that women in the overweight group had a stronger association between SS beverages and preterm delivery. Decreased insulin sensitivity might be a plausible explanation for this. Decreased insulin sensitivity is also a known risk factor for preterm delivery (35, 36), and high plasma glucose concentrations are associated with elevated

TABLE 4
Intake of AS and SS beverages in relation to PTD, stratified by prepregnancy BMI (in kg/m^2) in the Norwegian Mother and Child Cohort Study (n = 60,761)[1]

	AS beverages			SS beverages		
	All	PTD	Adjusted OR[2] (95% CI)	All	PTD	Adjusted OR[2] (95% CI)
	n	%		*n*	%	
Underweight (BMI <18.5)						
Never	919	7.6 ± 0.88[3]	1	186	7.0 ± 1.88	1
<1 serving/wk	467	6.2 ± 1.12	0.80 (0.51, 1.27)	506	7.9 ± 1.20	1.27 (0.65, 2.46)
1–6 servings/wk	293	8.9 ± 1.66	1.25 (0.77, 2.01)	744	7.0 ± 0.94	1.18 (0.61, 2.29)
≥1 serving/d	222	10.8 ± 2.09	1.48 (0.89, 2.46)	465	9.5 ± 1.36	1.60 (0.80, 3.20)
P-trend[4]			0.118			0.224
Normal weight (BMI 18.5−25)						
Never	15,834	4.6 ± 0.17	1	3921	4.5 ± 0.33	1
<1 serving/wk	10,470	4.7 ± 0.21	1.02 (0.90, 1.15)	12,275	4.8 ± 0.19	1.07 (0.90, 1.27)
1–6 servings/wk	8400	5.0 ± 0.24	1.11 (0.98, 1.25)	16,821	4.7 ± 0.16	1.08 (0.91, 1.28)
≥1 serving/d	5621	5.4 ± 0.30	1.16 (1.01, 1.36)	7308	5.2 ± 0.26	1.15 (0.95, 1.39)
P-trend[4]			0.020			0.176
Overweight (BMI >25)						
Never	5476	5.8 ± 0.32	1	2048	4.9 ± 0.48	1
<1 serving/wk	3982	6.0 ± 0.38	1.06 (0.89, 1.26)	5301	6.1 ± 0.33	1.30 (1.03, 1.65)
1–6 servings/wk	4511	6.0 ± 0.35	1.07 (0.90, 1.27)	7341	5.9 ± 0.28	1.31 (1.04, 1.65)
≥1 serving/d	4566	5.9 ± 0.35	1.07 (0.90, 1.27)	3845	6.3 ± 0.39	1.41 (1.10, 1.82)
P-trend[4]			0.415			0.024

[1] ORs were calculated by using logistic regression models. AS, artificially sweetened; PTD, preterm delivery; SS, sugar-sweetened.
[2] Adjusted for previous preterm delivery, maternal age, prepregnancy BMI, total energy intake, height, marital status, parity, smoking during pregnancy, education, and the other type of beverage.
[3] Percentage ± SE (all such values).
[4] *P* values for linear trend were obtained by incorporating the variable as a linear term in logistic regression models.

interleukin concentrations (37). Consumption of SS beverages was more strongly associated with early preterm delivery (Table 3), possibly because the more immature the fetus, the more sensitive it is to increased concentrations of interleukins associated with preterm delivery and amniotic infections (38). On the other hand, consumption of AS beverages was more strongly associated with late preterm delivery.

Because this is an observational study, it is not clear whether the increased risk is an effect of the beverages or whether there are other, unaccounted for associations. Intakes of both AS and SS beverages are strongly associated with educational level and marital status, which indicates a strong influence of socioeconomic factors, and other dietary factors may play a role. The association between high intake of soft drinks and a generally

TABLE 5
Intake of AS and SS beverages (servings/wk or servings/d) in relation to spontaneous or iatrogenic delivery (PTD; n = 54,832 deliveries) in the Norwegian Mother and Child Cohort Study[1]

	AS beverages			SS beverages		
	All	PTD	Adjusted OR[2] (95% CI)	All	PTD	Adjusted OR[2] (95% CI)
	n	%		*n*	%	
Spontaneous preterm deliveries (<37 wk)						
Never	18,167	3.6 ± 0.14[3]	1	4769	3.5 ± 0.27	1
<1 serving/wk	11,954	3.7 ± 0.17	1.00 (0.88, 1.13)	14,267	3.8 ± 0.16	1.10 (0.92, 1.31)
1–6 servings/wk	10,476	3.7 ± 0.19	1.02 (0.90, 1.17)	20,237	3.7 ± 0.13	1.09 (0.91, 1.30)
≥1 serving/d	8072	4.2 ± 0.22	1.15 (1.01, 1.32)	9396	3.9 ± 0.20	1.13 (0.93, 1.37)
P-trend[4]			0.068			0.332
Iatrogenic preterm deliveries (<37 wk)						
Never	2042	8.4 ± 0.61	1	674	7.4 ± 1.01	1
<1 serving/wk	1513	9.2 ± 0.74	1.15 (0.91, 1.46)	1865	7.6 ± 0.61	1.00 (0.71, 1.40)
1–6 servings/wk	1366	8.8 ± 0.77	1.10 (0.85, 1.41)	2416	8.9 ± 0.58	1.16 (0.83, 1.62)
≥1 serving/d	1242	7.7 ± 0.76	0.93 (0.71, 1.21)	1208	9.9 ± 0.86	1.24 (0.86, 1.78)
P-trend[4]			0.700			0.093

[1] ORs were calculated by using logistic regression models. AS, artificially sweetened; PTD, preterm delivery; SS, sugar-sweetened.
[2] Adjusted for previous preterm delivery, maternal age, prepregnancy BMI, total energy intake, height, marital status, parity, smoking during pregnancy, education, and the other type of beverage.
[3] Percentage ± SE (all such values).
[4] *P* values for linear trend were obtained by incorporating the variable as a linear term in logistic regression models.

"unhealthier" diet is well known (39). According to the "Barker theory," the fetus is sensitive to changes in maternal diet. Nutritional factors can cause changes to genes, altering activation. Effects of diet can therefore be passed on to the offspring and may influence the risk of diseases later in life (40, 41) and pregnancy outcome (42).

In the Danish study, Halldorsson et al (24) showed that AS intake, but not SS intake, was correlated with preterm delivery. The questions about the various beverages were identical in the 2 cohorts. However, the time of assessment and the time period covered by the FFQ differed. Women in the MoBa filled out the FFQ at gestational weeks 17–22 and were asked to report their average intake since the beginning of pregnancy (29), whereas the women in the Danish study filled out the FFQ at gestational week 25 and were asked to report their average intake over the past 4 wk (24). Because 2 different time periods were studied, it is possible that women with an "unhealthy" lifestyle, high-risk pregnancies, or early pregnancy complications might have shifted from SS to AS beverages before answering the FFQ in the Danish study. To test this, we performed an analysis comparing intake of carbonated soft drinks before pregnancy with intake in the third trimester. These results did not indicate a shift in consumption of SS to AS beverages with progressing pregnancy duration. However, dietary recall during early pregnancy can be challenging because many women suffer from nausea, with resulting changes in appetite and eating patterns. The Danish study did not adjust for previous preterm delivery. We therefore also performed an analysis without adjustment for previous preterm delivery, but this did not change our results. Halldorsson et al (24) concluded in their report that further studies of these subjects are warranted. The Danish study has been criticized for not combining carbonated and noncarbonated AS beverages (21) and for including diabetic subjects, which we considered in our study. The Danish study also raised some debate regarding the safety of AS beverages, issues that this study does not completely resolve. Observational studies such as the MoBa and the Danish National Birth Cohort are not suitable to establish causal diet-disease relations but are nonetheless important for discovering relations that warrant further investigations.

This study has both strengths and limitations. One strength is the large sample size, representing pregnant women from all parts of Norway and all socioeconomic groups. Furthermore, dietary intake was assessed before delivery. We also have information about previous preterm delivery—the strongest risk factor for preterm delivery in subsequent pregnancies. However, our study also has limitations. First, all dietary assessments are susceptible to measurement error, and the food-frequency method challenges respondents with complex tasks: the possibility of misreporting can thus not be ruled out. A study of Icelandic pregnant women showed that food items perceived as unhealthy, such as SS beverages, were underreported to a larger degree than were more healthy items (43). The MoBa FFQ has been validated against a 4-d weighed food diary and several biomarkers and was shown to be a useful instrument for detecting high and low intakes of energy, nutrients, and foods (44). The participation rate was 38.5%, and demographic differences between the cohort and the remaining pregnant population must be considered. Women participating in the MoBa study are generally healthier and better educated than the general population of pregnant Norwegian women (26, 27). Evaluation of a potential bias resulting from self-selection in the MoBa showed that, despite differences in prevalence estimates between the cohort participants and the total pregnant population, no statistically significant differences were found regarding 8 evaluated exposure outcomes, including the association with preterm delivery (45). Furthermore, we cannot rule out the possibility that the results, as in all observational studies, may be influenced by residual and unmeasured confounding. Confounding variables in the current study were chosen to parallel the Danish study as closely as possible. In both studies, AS and SS beverage intakes were strongly associated with socioeconomic factors, and frequent consumers were more likely to consist of more single women and more daily smokers and to have higher BMIs, greater energy intakes, and less education than those with lower intakes. However, adjustment of AS beverage intake for SS beverage intake and vice versa changed the results for AS beverage intake. In a recent study that included 3 prospective cohorts in the United States, both SS and AS beverages were independently associated with an increased risk of hypertension. Parallel to the findings in our study, the associations could not be explained by sugar but were likely to be mediated by factors common to both SS and AS drinks (46).

In conclusion, our findings in this Norwegian cohort of pregnant women suggest that daily intake of AS beverages and SS beverages may be associated with an increased risk of preterm delivery. The association was more consistent for SS beverages than for AS beverages, but whether this risk is caused by effects of the beverages, other dietary factors, or socioeconomic factors remains to be investigated.

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