**ONLINE SUPPLEMENT**

**1. Search Strategies**

All databases searched May 2, 2019, updated on April 9, 2020.

MEDLINE

1. (Aspartame or acesulfame-K or Acesulfame potassium or Ace-K or sucralose or neotame or advantame or Steviol glycosides or stevia or Rebaudioside A or reb a or Stevioside or Rebaudioside D or newtame or sunnett or sweet one or sugar twin or nutrasweet or necta sweet or sweet and low or sweet’n low or Luo Han Guo or monk fruit or Siraitia grosvenorii Swingle fruit extract or SGFE or saccharin or sugar substitute or artificial sweeteners or non-nutritive sweetener or sucrose or splenda or cyclamate\*).ti,ab.
2. aspartame/ or sucrose/ or non-nutritive sweeteners/ or stevia/ or saccharin or cyclamates/
3. 1 or 2
4. Pregnancy/ or Pregnant women/ or pregnan\*.ti,hw,kf. or exp Pregnancy Trimesters/ or Peripartum Period/ or Postpartum Period/ or (antenatal or prenatal or perinatal or postnatal or prepartum or antepartum or postpartum or pre partum or ante partum or post partum or puerper\* or primigravid\* or primiparous or multiparous or nulliparous or multigravid\* or trimester\* or obstetric\*).ti,kf.
5. 3 and 4
6. exp Diabetes Mellitus, Type 1/ or pregnancy in diabetics.sh. or ((type 1 or type one) adj diabet\*).ti,ab,kf.
7. Gastrointestinal Microbiome/ or Exp hyperglycemia/ or hyperinsulism/ or exp insulin resistance/ or Body mass index/ or Exp body weight/ or Exp asthma/ or Exp hypersensitivity/ or Exp immunity/ or Immune system.sh. Or Exp Oxidative stress/ or exp weight gain/ or Exp adipose tissue/
8. Birth weight/ or fetal weight/
9. exp abortion, spontaneous/ or (spontaneous abortion or miscarr\*).ti,ab,kf.
10. exp Diabetes Mellitus, Type 1/ or pregnancy in diabetics.sh. or ((type 1 or type one) adj diabet\*).ti,ab,kf.
11. exp Obstetric Labor, Premature/ or Exp Cesarean Section/ ((premature or preterm or pre-term) adj2 (labo?r or birth)).ti,ab,kf.
12. glucose intolerance/ or hypertension/ or hypertension, pregnancy-induced/
13. (cesarean section or fecal microbiome or gestational hypertension or large for gestational age or LGA or bmi-z or hypertensi\* or pre-eclampsia or preeclampsia).ti,ab,kf.
14. (f?etal or f?etus or intrauterine) adj2 (growth)).ti,ab,kf.
15. or/6-14
16. 15 and 5
17. animals/ not (animals/ and humans/)
18. 16 NOT 17

= 91

CINAHL

1. TI ( Aspartame or acesulfame-K or Acesulfame potassium or Ace-K or sucralose or neotame or advantame or Steviol glycosides or stevia or Rebaudioside A or reb a or Stevioside or Rebaudioside D or newtame or sunnett or sweet one or sugar twin or nutrasweet or or necta sweet or sweet and low or sweet’n low or Luo Han Guo or monk fruit or Siraitia grosvenorii Swingle fruit extract or SGFE or saccharin or sugar substitute or artificial sweeteners or non-nutritive sweetener or sucrose or splenda or cyclamate\* ) OR AB ( Aspartame or acesulfame-K or Acesulfame potassium or Ace-K or sucralose or neotame or advantame or Steviol glycosides or stevia or Rebaudioside A or reb a or Stevioside or Rebaudioside D or newtame or sunnett or sweet one or sugar twin or nutrasweet or or necta sweet or sweet and low or sweet’n low or Luo Han Guo or monk fruit or Siraitia grosvenorii Swingle fruit extract or SGFE or saccharin or sugar substitute or artificial sweeteners or non-nutritive sweetener or sucrose or splenda or cyclamate\* )
2. MH aspartame or sucrose or non-nutritive sweeteners or stevia or saccharin or cyclamates
3. 1 or 2
4. MH Pregnancy Trimesters or Peripartum Period or Postpartum Period
5. MH pregnancy or pregnancy women
6. TI ( pregnan\* or antenatal or prenatal or perinatal or postnatal or prepartum or antepartum or postpartum or pre partum or ante partum or post partum or puerper\* or primigravid\* or primiparous or multiparous or nulliparous or multigravid\* or trimester\* or obstetric\* ) OR AB ( pregnan\* or antenatal or prenatal or perinatal or postnatal or prepartum or antepartum or postpartum or pre partum or ante partum or post partum or puerper\* or primigravid\* or primiparous or multiparous or nulliparous or multigravid\* or trimester\* or obstetric\* ) OR MW ( pregnan\* or antenatal or prenatal or perinatal or postnatal or prepartum or antepartum or postpartum or pre partum or ante partum or post partum or puerper\* or primigravid\* or primiparous or multiparous or nulliparous or multigravid\* or trimester\* or obstetric\* )
7. S4 OR S5 OR S6
8. S3 AND S7
9. MH ( Diabetes Mellitus, Type 1 or pregnancy in diabetics ) OR TI ( (type 1 or type one) n3 diabet\* ) OR AB ( (type 1 or type one) n3 diabet\* ) OR MW ( (type 1 or type one) n3 diabet\* )
10. MH Gastrointestinal Microbiome or hyperglycemia or hyperinsulism or insulin resistance or Body mass index or body weight or asthma or hypersensitivity or immunity or Immune system Or Oxidative stress or weight gain or adipose tissue
11. MH birth weight or fetal weight
12. TI ( fat mass or body fat or Gastrointestinal Microbiome or hyperglycemi\* or hyperinsulin\* or insulin resistance or Body mass index or BMI or body weight or asthma or hypersensitivity or immunity or Immune system or Oxidative stress or weight gain or adipose tissue or Birth weight or fetal weight ) OR AB ( fat mass or body fat or Gastrointestinal Microbiome or hyperglycemi\* or hyperinsulin\* or insulin resistance or Body mass index or BMI or body weight or asthma or hypersensitivity or immunity or Immune system or Oxidative stress or weight gain or adipose tissue or Birth weight or fetal weight )
13. MH abortion, spontaneous OR TI ( spontaneous and (abortion or miscarr\*) ) OR AB ( spontaneous and (abortion or miscarr\*) )
14. MH Diabetes Mellitus, Type 1 or pregnancy in diabetics
15. MH ( obstetric Labor, Premature or Cesarean Section ) OR TI ( (premature or preterm or pre-term) n2 (labor or labour or birth) ) OR AB ( (premature or preterm or pre-term) n2 (labor or labour or birth) )
16. MH glucose intolerance or hypertension or hypertension, pregnancy-induced/
17. TI ( cesarean section or fecal microbiome or gestational hypertension or large for gestational age or LGA or bmi-z or hypertensi\* or pre-eclampsia or preeclampsia ) OR AB ( cesarean section or fecal microbiome or gestational hypertension or large for gestational age or LGA or bmi-z or hypertensi\* or pre-eclampsia or preeclampsia ) OR SU ( cesarean section or fecal microbiome or gestational hypertension or large for gestational age or LGA or bmi-z or hypertensi\* or pre-eclampsia or preeclampsia )
18. TI ( (fetal or foetal or fetus or foetus) and grow\* ) OR AB ( (fetal or foetal or fetus or foetus) and grow\* )
19. S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18
20. (S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18) AND (S8 AND S19)
21. ( (S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18) AND (S8 AND S19) ) NOT TI ( mice or cats or rats or rodent\* or animal\* ) NOT AB ( mice or cats or rats or rodent\* or animal\* ) NOT MW ( mice or cats or rats or rodent\* or animal\* )

= 92

EMBASE

1. (Aspartame or acesulfame-K or Acesulfame potassium or Ace-K or sucralose or neotame or advantame or Steviol glycosides or stevia or Rebaudioside A or reb a or Stevioside or Rebaudioside D or newtame or sunnett or sweet one or sugar twin or nutrasweet or necta sweet or sweet and low or sweet n low or Luo Han Guo or monk fruit or Siraitia grosvenorii Swingle fruit extract or SGFE or saccharin or sugar substitute or artificial sweeteners or non-nutritive sweetener or sucrose or splenda or cyclamate\*).ti,ab.
2. aspartame/ or sucrose/ or non-nutritive sweeteners/ or stevia/ or saccharin or cyclamates/
3. 1 or 2
4. Pregnancy/ or Pregnant women/ or pregnan\*.ti,hw,kf. or exp Pregnancy Trimesters/ or Peripartum Period/ or Postpartum Period/ or (antenatal or prenatal or perinatal or postnatal or prepartum or antepartum or postpartum or pre partum or ante partum or post partum or puerper\* or primigravid\* or primiparous or multiparous or nulliparous or multigravid\* or trimester\* or obstetric\*).ti,ab.
5. 3 and 4
6. exp Diabetes Mellitus, Type 1/ or pregnancy in diabetics.sh. or ((type 1 or type one) adj diabet\*).ti,ab.
7. Gastrointestinal Microbiome/ or Exp hyperglycemia/ or hyperinsulism/ or exp insulin resistance/ or Body mass index/ or Exp body weight/ or Exp asthma/ or Exp hypersensitivity/ or Exp immunity/ or Immune system.sh. Or Exp Oxidative stress/ or exp weight gain/ or Exp adipose tissue/
8. Birth weight/ or fetal weight/
9. exp abortion, spontaneous/ or (spontaneous abortion or miscarr\*).ti,ab.
10. exp Obstetric Labor, Premature/ or Exp Cesarean Section/ or ((premature or preterm or pre-term) adj2 (labo?r or birth)).ti,ab.
11. glucose intolerance/ or hypertension/ or hypertension, pregnancy-induced/
12. (cesarean section or fecal microbiome or gestational hypertension or large for gestational age or LGA or bmi-z or hypertensi\* or pre-eclampsia or preeclampsia).ti,ab.
13. (f?etal or f?etus or intrauterine) adj2 (growth).ti,ab.
14. or/6-13
15. 14 and 5
16. animals/ not (animals/ and humans/)
17. 15 NOT 16
18. mice or cats or rats or rodent\* or animal\* or guinea pig\*
19. 17 NOT 18

= 271

Cochrane Library

= 111

ClinicalTrials.gov=37

SCOPUS

( ( ( TITLE-ABS-KEY ( "type 1 diabet\*" OR "type one diabet\*" OR "Gastrointestinal Microbiome" OR hyperglycemia OR hyperinsulism OR "insulin resistance" OR "Body mass index" OR "body weight" OR asthma OR hypersensitivity OR immunity OR "Immune system" ) ) OR ( ( TITLE-ABS-KEY ( "Oxidative stress" OR "weight gain" OR "adipose tissue" OR "Birth weight" OR "fetal weight" OR miscarr\* OR "spontaneous abortion" ) OR TITLE-ABS-KEY ( "glucose intolerance" OR hypertension OR "pregnancy induced hypertension" ) OR TITLE-ABS-KEY ( "cesarean section" OR "fecal microbiome" OR "gestational hypertension" OR "large for gestational age" OR lga OR bmi-z OR hypertensi\* OR pre-eclampsia OR preeclampsia ) OR TITLE-ABS-KEY ( "premature birth" OR "pre-mature birth" OR "preterm birth" OR "pre-term birth" OR "premature labor" OR "pre term labor" OR "pre-term labor" OR "premature labour" OR "pre term labour" OR "pre-term labour" ) ) ) ) AND ( ( TITLE-ABS-KEY ( aspartame OR "Acesulfame potassium" OR sucralose OR neotame OR advantame OR "Steviol glycosides" OR stevia OR rebaudioside-a OR stevioside OR rebaudioside-d OR newtame OR sunnett OR "sweet one" OR "sugar twin" OR nutrasweet ) OR TITLE-ABS-KEY ( "sweet n low" OR "Luo Han Guo" OR "monk fruit" OR "Siraitia grosvenorii Swingle fruit extract" OR sgfe OR saccharin OR "sugar substitute" OR "artificial sweetener\*" OR "non-nutritive sweetener" OR sucrose OR splenda OR cyclamate ) OR TITLE-ABS-KEY ( "necta sweet" OR "sweet and low" ) ) ) AND ( ( TITLE-ABS-KEY ( antenatal OR prenatal OR perinatal OR postnatal OR prepartum OR antepartum OR postpartum OR "pre partum" OR "ante partum" OR "post partum" OR puerper\* OR primigravid\* OR primiparous OR multiparous OR nulliparous OR multigravid\* OR trimester\* OR obstetric\* ) OR TITLE-ABS-KEY ( pregnan\* ) ) ) ) AND NOT ( TITLE-ABS-KEY ( mice OR cats OR rats OR rodent\* OR animal\* OR "guinea pig\*" ) )

= 267

FSTA - the food resource database (via Web of Science)

= 32; after removal of animal studies, = 18

References from search: 874 +37

Duplicates: 297+37

Final references: 577+37=614

Updated on April 9,2020:

UPDATED SEARCH

MEDLINE = 3

CINAHL = 7

EMBASE = 32

COCHRANE = 14

Scopus = 39

FSTA = 1  
Clinicaltrials.gov = 30

Subtotal: 127

Duplicates: 28

FINAL UPDATE TOTAL: 99

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, Year published** | **Location** | **Study Period** | **Study Design** | **Sample size** | **Exposures Defined** | **Method of Exposure Assessment** | **Outcomes included in the analysis** | **Outcome Definition** | **Method of Outcome Measurement** | **Adjusted or unadjusted risk ratio used in the analysis** |
| Azad 2016 | Canada  (CHILD study) | 2009-2012 | Prospective cohort | 3033 | Diet soft drinks or pop, AS added to tea or coffee | FFQ | Infant BMI z score and risk of overweight at 1-year-old , GA, BW | BMI- z scores: 2006 WHO standards. Overweight: infants with BMI- z scores exceeding the 97th percentile | Objective anthropometric measurements | BW and GA: unadjusted; BMI- z scores and overweight: adjusted for maternal BMI, maternal total energy intake, Healthy Eating Index score, maternal postsecondary education, maternal smoking and diabetes during pregnancy, breastfeeding duration, infant sex, and introduction of solid foods before 4 months, beverage types. |
| Azad 2020 | Canada  (CHILD study) | 2008-2012 | Prospective cohort | 2298 | Diet soft drinks or pop, AS added to tea or coffee | FFQ | Infant BMI z score at 3-year-old | BMI- z scores : according to the 2006 World Health Organization standards. | Objective anthropometric measurements | Adjusted for maternal BMI, maternal and child consumption of both beverage types and pregnancy and early life covariates, three-year covariates, and child sweetened beverage consumption |
| Englund-Ögge 2012 | Norway  ( MoBa Study) | 1999-2008 | Prospective cohort | 60761 | Carbonated and noncarbonated drinks (AS) | FFQ | Preterm delivery | Birth before 37 week | Norwegian Medical Birth Registry | More than 1/d :Unadjusted  subgroup analysis: adjusted |
| Gillman 2017 | USA  (Project Viva) | 1999-2002 | Prospective cohort | 1078 | Low calorie sugar free carbonated beverages | FFQ | Child BMI-z at 7-year-old | BMI- z scores : using US national reference | Objective anthropometric measurements | Adjusted for maternal age, race and/or ethnicity, education, smoking, parity, and prepregnancy BMI; household income; and child age and sex. |
| Plows 2020 | USA  (Project Viva) | 1999-2002 | Prospective cohort | 1683 | Diet soda + NutraSweet  (aspartame packets) | FFQ | Child BMI-z at 6 months,3 years, 7 years and 12 years | BMI- z scores (no mention) | no mention | Adjusted for maternal pre-pregnancy BMI, age, race/ethnicity, education, parity, and pregnancy smoking status. |
| Halldorsson 2010 | Denmark  (DNBC study) | 1996-2002 | Prospective cohort | 59334 | Carbonated and noncarbonated soft drinks (AS) | FFQ | Preterm delivery | Birth before 37 week | Danish Civil Registration System | more than 1/d :Unadjusted  subgroup analysis: adjusted |
| Maslova 2013 | Denmark  (DNBC study)) | 1996-2003 | Prospective cohort | 60466 | Carbonated soft drinks (AS) | FFQ | Child allergic disease outcomes; BW; GA; gestational weight gain | Asthma at 18 months: doctor asthma diagnosis; Asthma at 7 years: a doctor diagnosed asthma and wheezing symptoms; Allergic rhinitis at 7 years: a reported doctor-diagnosis of hay fever. | Self-report doctor diagnosis, medical record | BW,GA and gestational weight gain: unadjusted; Child allergic disease outcomes: adjusted for maternal age, smoking, parity, prepregnancy BMI, physical activity, breastfeeding, socioeconomic position, child sex, maternal history of asthma, maternal history of allergies, paternal history of asthma, paternal history of allergies, and energy |
| Zhu 2017 | Denmark  (DNBC study) | 1996-2002 | Prospective cohort | 918 | AS soft drinks | FFQ | Child BMI-z scores and overweight /obesity status at 1-years-old and 7-year-old; BW; GA; LGA | BMI-z scores: WHO Child Growth Standards Reference; Childhood overweight/obesity : WHO cut offs; LGA: a BW greater than the 90th percentile. | Danish Medical Birth Registry and questionnaire | BW, GA and LGA: unadjusted; BMI-z scores and overweight: adjusted for maternal pre-pregnancy BMI, maternal age, socioeconomic status, smoking during pregnancy, intakes of total energy, desserts and sweets, oil/margarine/butter, potato, processed meat, refined grains, and whole grains during pregnancy, and physical activity during pregnancy, offspring sex, breastfeeding duration, consumption of AS or SS beverages and physical activity at 7 years, and maternal intake of SS beverages during pregnancy. |
| Petherick 2014 | UK  (BiB study) | 2007-2010 | Prospective cohort | 8914 | Daily AS cola | Questionnaire | Preterm delivery | < 37 completed gestational weeks | Birth record | more than 1/d :Unadjusted  subgroup analysis: adjusted |
| Hinkle 2019 | USA(NICHD Fetal  Growth Studies) | 2009-2013 | Prospective cohort | 2808 | Artificially sweetened beverages | FFQ | GDM | N/A | Medical records | Adjusted for relevant confounders including diet quality |
| Renault 2015 | Denmark | 2009-2011 | RCT (Obese women),used cohort data only | 342 | AS soft drinks | FFQ | Excessive weight gain (>9kg) | Difference between self-reported pre-pregnancy weight recorded at baseline and weight measured at end point | Measured by an electronic scale | Adjusted for energy intake, maternal age, smoking during pregnancy, parity, pre-pregnancy BMI and intervention group |

**Online Supplement Table 1.** Study Characteristics

**Abbreviations**: AS: artificially sweetened; BMI: body mass index; BW: birth weight; GA: gestational age; GDM: gestational diabetes mellitus; PTD: preterm delivery; LGA: large-for-gestational age; WHO: World Health Organization; SS: sugar-sweetened

Table S2: Risk of bias assessment for included studies.

**Excluded articles with reasons**

**No outcome of interest**

1. Brantsaeter AL, Haugen M, Samuelsen SO, Torjusen H, Trogstad L, Alexander J, et al. A dietary pattern characterized by high intake of vegetables, fruits, and vegetable oils is associated with reduced risk of preeclampsia in nulliparous pregnant Norwegian women. Journal of Nutrition. 2009;139(6):1162-8.

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15. Morales-Arroyo E, Rivera-Berrios N. Sweeteners...Are they really sweetening our life? effects in preterm delivery, asthma, and allergic rhinitis. Journal of the American Pharmacists Association. 2016;56 (3):e81-e2.

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17. Sausenthaler S, Koletzko S, Schaaf B, Lehmann I, Borte M, Herbarth O, et al. Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. American Journal of Clinical Nutrition. 2007;85(2):530-7.

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No original data

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**List of authors who were sent letters requesting additional information:**

* Dr. Rifas-Shiman,

Gillman MW, Rifas-Shiman SL, Fernandez-BarresS, et al. Beverage Intake During Pregnancy and Childhood Adiposity. Pediatrics. 2017;140(2):e20170031

* Dr. Zhu

Zhu, Y., Olsen, S.F., Mendola, P., Halldorsson, T.I., Rawal, S., Hinkle, S.N., Yeung, E.H., Chavarro, J.E., Grunnet, L.G., Granström, C. and Bjerregaard, A.A., 2017. Maternal consumption of artificially sweetened beverages during pregnancy, and offspring growth through 7 years of age: a prospective cohort study. International journal of epidemiology, 46(5), pp.1499-1508.

* Dr. Englund-O¨gge,

Englund-Ögge, L., Brantsæter, A.L., Haugen, M., Sengpiel, V., Khatibi, A., Myhre, R., Myking, S., Meltzer, H.M., Kacerovsky, M., Nilsen, R.M. and Jacobsson, B., 2012. Association between intake of artificially sweetened and sugar-sweetened beverages and preterm delivery: a large prospective cohort study. The American journal of clinical nutrition, 96(3), pp.552-559.

* Dr. Petherick,

Petherick, E.S., Goran, M.I. and Wright, J., 2014. Relationship between artificially sweetened and sugar-sweetened cola beverage consumption during pregnancy and preterm delivery in a multi-ethnic cohort: analysis of the Born in Bradford cohort study. European journal of clinical nutrition, 68(3), p.404.

* Dr. Maslova,

Maslova, E., Strøm, M., Olsen, S.F. and Halldorsson, T.I., 2013. Consumption of artificially-sweetened soft drinks in pregnancy and risk of child asthma and allergic rhinitis. PloS one, 8(2), p.e57261.

**List of authors who responded to the request for additional information:**

* Dr. Rifas-Shiman

Gillman MW, Rifas-Shiman SL, Fernandez-BarresS, et al. Beverage Intake During Pregnancy and Childhood Adiposity. Pediatrics. 2017;140(2):e20170031

Online Supplement Table 2**.** Results of quality assessment of the includes studies.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **References** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **Quality** |
| Azad 2016 | Y | Y | Y | Y | NR | Y | Y | Y | Y | N | Y | Y | Y | Y | Good |
| Azad 2020 | Y | Y | Y | Y | NR | Y | Y | Y | Y | N | Y | Y | Y | Y | Good |
| Englund-Ögge 2012 | Y | Y | N | Y | NR | Y | Y | Y | Y | Y | Y | Y | N | Y | Good |
| Gillman 2017 | Y | Y | Y | Y | NR | Y | Y | Y | Y | Y | Y | NR | N | Y | Good |
| Plows 2020 | Y | N | NR | NR | NR | Y | Y | N | NR | Y | NR | NR | NR | Y | Poor |
| Halldorsson 2010 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Good |
| Maslova 2013 | Y | Y | Y | Y | NR | Y | Y | Y | Y | Y | Y | NR | N | Y | Good |
| Zhu 2017 | Y | Y | NR | Y | NR | Y | Y | Y | Y | N | Y | Y | N | Y | Fair |
| Petherick 2014 | Y | Y | NR | Y | NR | Y | Y | Y | Y | N | Y | NR | NR | Y | Fair |
| Hinkle 2019 | Y | N | NR | NR | NR | Y | Y | N | N | Y | Y | Y | NR | Y | Poor |
| Renault 2015 | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | N | N | Fair |

Abbreviations: Y, yes; N, no; NR, not reported.

1. Was the research question or objective in this paper clearly stated? 2. Was the study population clearly specified and defined? 3. Was the participation rate of eligible persons at least 50%? 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? 5. Was a sample size justification, power description, or variance and effect estimates provided? 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 10. Was the exposure(s) assessed more than once over time? 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 12. Were the outcome assessors blinded to the exposure status of participants? 13. Was loss to follow-up after baseline 20% or less? 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Online Supplement Table 3**.** The association between prenatal artificial sweetener consumption (≥1 serving per day) and health outcomes.

| **Certainty assessment** | | | | | | | **Effect** | Certainty | Importance |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Relative (95% CI)** |
| **Association between prenatal artificial sweetener consumption (≥1 serving per day) and preterm delivery** | | | | | | | | | |
| 3 | observational studies | not serious | not serious | not serious | not serious | none | **RR 1.18** (1.09 to 1.28) | ⨁⨁◯◯  LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (=1 serving per day) and preterm delivery** | | | | | | | | | |
| 3 | observational studies | not serious | not serious | not serious | not serious | none | **RR 1.21** (1.07 to 1.37) | ⨁⨁◯◯  LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (2-3 serving per day) and preterm delivery** | | | | | | | | | |
| 3 | observational studies | not serious | not serious | not serious | serious b | none | **RR 1.11** (0.88 to 1.39) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (≥4 serving per day) and preterm delivery** | | | | | | | | | |
| 3 | observational studies | not serious | serious a | not serious | serious b | none | **RR 1.34** (0.95 to 1.89) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (≥1 serving per day) and gestational age** | | | | | | | | | |
| 3 | observational studies | not serious | not serious | not serious | not serious | none | **MD -0.11 weeks** (-0.19 to -0.03) | ⨁⨁◯◯  LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (≥1 serving per day) and excessive weight gain (>9kg)** | | | | | | | | | |
| 1 | observational studies | not serious | serious c | not serious | not serious d | none | **RR 1.43** (1.10 to 1.86) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (≥1 serving per day) and gestational weight gain** | | | | | | | | | |
| 1 | observational studies | not serious | serious c | not serious | not serious d | none | **MD -8 g/week**  ( -17.9 to 1.9) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (≥1 serving per day) and gestational diabetes** | | | | | | | | | |
| 1 | observational studies | seriouse | serious c | not serious | not serious d | none | **RR 0.53** (0.16 to 1.80) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (≥1 serving per day) and birth weight** | | | | | | | | | |
| 3 | observational studies | not serious | not serious | not serious | not serious | none | **MD 23.74g**  ( 0.89 to 46.58) | ⨁⨁◯◯  LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (≥1 serving per day) and large-for-gestational age** | | | | | | | | | |
| 1 | observational studies | not serious | serious c | not serious | not serious d | none | **RR 1.57** (1.05 to 2.35) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (≥1 serving per day) and overweight** **of one-year-old children** | | | | | | | | | |
| 2 | observational studies | not serious | serious a | not serious | serious b | none | **RR 1.54** (0.84 to 2.85) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (≥1 serving per day) and overweight of seven-year-old children** | | | | | | | | | |
| 1 | observational studies | not serious | serious c | not serious | not serious d | none | **RR 1.93** (1.24 to 3.01) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (≥1 serving per day) and BMI-z scores of one-year-old children** | | | | | | | | | |
| 2 | observational studies | not serious | serious a | not serious | serious b | none | **CC 0.025** (-0.325 to 0.369) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (≥1 serving per day) and BMI-z scores of seven-year-old children** | | | | | | | | | |
| 1 | observational studies | not serious | serious c | not serious | not serious d | none | **β 0.59** (0.23 to 0.96) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal artificial sweetener consumption (≥1 serving per day) and BMI-z scores of three-year-old children** | | | | | | | | | |
| 1 | observational studies | not serious | serious c | not serious | not serious d | none | **β 0.17** (-0.05 to 0.39) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal additional serving per day of artificial sweetener and BMI-z scores of 6-months-old children** | | | | | | | | | |
| 1 | observational studies | not serious | serious c | not serious | not serious d | none | **β 0.17** (0.06 to 0.28) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal additional serving per day of artificial sweetener and BMI-z scores of 3-years-old children** | | | | | | | | | |
| 1 | observational studies | seriousf | serious c | not serious | not serious d | none | **β 0.13** (0.03 to 0.24) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal additional serving per day of artificial sweetener and BMI-z scores of 7-years-old children** | | | | | | | | | |
| 1 | observational studies | seriousf | serious c | not serious | not serious d | none | **β 0.16** (0.04 to 0.29) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal additional serving per day of artificial sweetener and BMI-z scores of 12-years-old children** | | | | | | | | | |
| 1 | observational studies | seriousf | serious c | not serious | not serious d | none | **β 0.16** (0.01 to 0.31) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal additional serving per day of artificial sweetener and asthma diagnosis in 18 months old** | | | | | | | | | |
| 1 | observational studies | not serious | serious c | not serious | not serious d | none | **RR 1.57** (1.05 to 2.35) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal additional serving per day of artificial sweetener and asthma diagnosis in seven years old** | | | | | | | | | |
| 1 | observational studies | not serious | serious c | not serious | not serious d | none | **RR 1.30** (1.01 to 1.66) | ⨁◯◯◯  VERY LOW | CRITICAL |
| **Association between prenatal additional serving per day of artificial sweetener and allergic rhinitis in seven years old** | | | | | | | | | |
| 1 | observational studies | not serious | serious c | not serious | not serious d | none | **RR 1.31** (0.98 to 1.74) | ⨁◯◯◯  VERY LOW | CRITICAL |

**CC:** Correlation coefficients **; CI:** Confidence interval; **RR:** Risk ratio; β: Standardized beta coefficients

#### **Explanations**

a. Serious in inconsistency because the heterogeneity was high (I^2≥50%). Serious imprecision.

b. The 95% CI crosses the line of no effect, such that our recommendation would be different if the true effect were at one end of the CI or the other.

c. Serious inconsistency because only one study.

d. No serious imprecision; only one study but already downgraded for serious inconsistency for this reason.

e. Serious risk of bias because study did not report eligibility criteria, loss to follow-up, or sample size estimation; and did not examine different levels of the exposure as related to the outcome.

f. Serious risk of bias because study did not report eligibility criteria, loss to follow-up, sample size estimation, or clear outcome measurement method; and did not examine different levels of the exposure as related to the outcome.

Secondary outcomes

Gestational weight gain

Two studies reported the association between prenatal AS consumption and gestational weight gain but could not be included in a pooled estimate because the outcomes were reported in different forms (e.g., weekly weight gain versus >9kg). Renault et al.,(2015) indicated that prenatal AS consumption (≥1 serving per day) was associated with a 43% increase in the risks of excessive weight gain (>9kg) compared with no AS consumption (RR=1.43, 95% CI: 1.10 to 1.86; “very low” certainty evidence) (1) while the other study found that prenatal AS consumption (≥1 serving per day) was not associated with weekly gestational weight gain compared with no AS consumption (2) (MD=-8 g/week,95% CI: -17.9 to 1.9; “very low” certainty evidence).

Gestational diabetes

Only one study (n=2808) reported the association between prenatal AS consumption and gestational diabetes, and indicated that prenatal AS consumption (≥1 serving per day) was not associated with risk of gestational diabetes compared with no AS consumption (RR=0.53, 95% CI: 0.16 to 1.80; “very low” certainty evidence)(3).

LGA

Only one study (n=918) reported the association between prenatal AS consumption and large-for-gestational age (LGA), and indicated that prenatal AS consumption (≥1 serving per day) was associated with a 57% increase in the risks of LGA compared with no AS consumption (RR=1.57, 95% CI: 1.05 to 2.35; “very low” certainty evidence)(4).

*Child outcomes*

Categorization as overweight in childhood

Evidence from two studies (n=3,951) demonstrated that prenatal AS consumption (≥1 serving per day) was not associated with overweight of one-year-old children compared with no AS consumption (RR=1.54, 95% CI: 0.84 to 2.85, I2=59%; “very low” certainty, downgraded because of inconsistency; see *online supplement figure 8*)(4, 5). One study (N=918) reported that prenatal AS consumption (≥1 serving per day) was associated with a 93% increase in the risks of overweight of seven-year-old children compared with no AS consumption (95% CI: 1.24 to 3.01, “very low” certainty)(4).

BMI-z scores

Overall, there was “very low” certainty evidence from two observational studies (n= 3,951) regarding the association between prenatal AS consumption (≥1 serving per day) and BMI-z scores of one-year-old children(4, 5). The certainty of evidence was downgraded from ‘low’ to ‘very low’ because of inconsistency and imprecision. Prenatal AS consumption (≥1 serving per day) showed no significant associations with BMI-z scores of one-year-old children (Correlation coefficient =0.025, 95% CI: -0.325 to 0.369, I2=98%; see *Appendix 10*). Three studies reported the association between prenatal AS consumption and BMI-z scores of older children but were not included in a pooled estimate because data were reported in different forms. Zhu et al., (2017) (n=918) reported that prenatal AS consumption (≥1 serving per day) was associated with was associated with higher BMI-z scores at 7 years (β= 0.59, 95% CI, 0.23 to 0.96; ‘very low’ certainty evidence)(4). However, Azad et al., (2020)(n=2298) reported prenatal AS consumption (≥1 serving per day) was no association with BMI-z scores of three-year-old children after adjusting for potential confounders (6). The other study (n=1683) demonstrated additional serving per day of AS were NNS was associated with higher BMI-z scores at 6 months (β=0.17; 95% CI, 0.06, 0.28), 3 years (β=0.13; 95% CI, 0.03, 0.24), 7 years (β=0.16; 95% CI, 0.04, 0.29) and 12 years (β=0.16; 95% CI, 0.01, 0.31)(7).

Asthma

Only one study (n=60,466)(2) reported the association between prenatal AS consumption and child asthma, and indicated that prenatal AS consumption (≥1 serving per day) was associated with the increased risks of asthma diagnosis in 18 months old (RR=1.57, 95% CI: 1.05 to 2.35; “very low” certainty evidence) and seven years old (RR=1.30, 95% CI: 1.01, 1.66; “very low” certainty evidence) compared with no AS consumption. It was also associated with the increased risks of allergic rhinitis in seven years old (RR=1.31, 95% CI: 0.98,1.74; “very low” certainty evidence).

No study reported on inadequate gestational weight gain, SGA, C-section, miscarriage, stillbirth, gestational hypertension, preeclampsia, and glucose intolerance.

**Reference**

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2. Maslova E, Strom M, Olsen SF *et al.* (2013) Consumption of artificially-sweetened soft drinks in pregnancy and risk of child asthma and allergic rhinitis. *PLoS One* 8, e57261.

3. Hinkle S, Li M, Grewal J *et al.* (2019) Beverage Intake in US Women Across Pregnancy and Gestational Diabetes Risk (P11-010-19). 3, nzz048. P011-010-019.

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6. Azad MB, Archibald A, Tomczyk MM *et al.* (2019) Non-nutritive sweetener consumption during pregnancy affects adiposity in mouse and human offspring. *bioRxiv*, 713974.

7. Plows J, Aris I, Rifas-Shiman S *et al.* (2020) Associations of Maternal Non-Nutritive Sweetener Intake During Pregnancy with Childhood BMI Trajectory. 4, 1058-1058.



Online Supplement Figure 1: Effects of prenatal artificial sweetener consumption (≥1 serving per day) on risks of preterm delivery. Subgroup analyses were conducted with studies in UK, Denmark and Norway. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel method.



Online Supplement Figure 2: Effects of prenatal artificial sweetener consumption (≥1 serving per day) on risks of preterm delivery. Subgroup analyses were conducted with studies in good quality and fair quality. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel method.



Online Supplement Figure 3: Effects of prenatal artificial sweetener consumption (≥1 serving per day) on gestational age. Subgroup analyses were conducted with studies in Canada and Denmark. CI, confidence interval; df, degrees of freedom; IV, inverse-variance method.



Online Supplement Figure 4: Effects of prenatal artificial sweetener consumption (≥1 serving per day) on gestational age. Subgroup analyses were conducted with studies in good quality and fair quality. CI, confidence interval; df, degrees of freedom; IV, inverse-variance method.



Online Supplement Figure 5: Effects of prenatal artificial sweetener consumption (≥1 serving per day) on birth weight. Subgroup analyses were conducted with studies in Canada and Denmark. CI, confidence interval; df, degrees of freedom; IV, inverse-variance method.



Online Supplement Figure 6: Effects of prenatal artificial sweetener consumption (≥1 serving per day) on birth weight. Subgroup analyses were conducted with studies in good quality and fair quality. CI, confidence interval; df, degrees of freedom; IV, inverse-variance method.

A picture containing bird

Description automatically generated Online Supplement Figure 7.Effects of prenatal artificial sweetener consumption (≥1 serving per day) on risk of overweight of one-year-old children. CI, confidence interval; df, degrees of freedom; IV, inverse-variance method.

A screenshot of a cell phone

Description automatically generated

Online Supplement Figure 8.Effects of prenatal artificial sweetener intake (≥1 serving per day) on BMI-z score of one-year-old children. Confidence intervals (95%) are calculated using sample size and correlation coefficients.