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# Intake of sucrose-sweetened soft beverages during pregnancy and risk of congenital heart defects (CHD) in offspring: a Norwegian pregnancy cohort study

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## Abstract

Studies report increased risk of congenital heart defects (CHD) in the offspring of mothers with diabetes, where high blood glucose levels might confer the risk. We explored the association between intake of sucrose-sweetened soft beverages during pregnancy and risk of CHD. Prospective cohort data with 88,514 pregnant women participating in the Norwegian Mother and Child Cohort Study was linked with information on infant CHD diagnoses from national health registers and the Cardiovascular Diseases in Norway Project. Risk ratios were estimated by fitting generalized linear models and generalized additive models. The prevalence of children with CHD was 12/1000 in this cohort (1049/88,514). Among these, 201 had severe and 848 had non-severe CHD (patent ductus arteriosus; valvular pulmonary stenosis; ventricular septal defect; atrial septal defect). Only non-severe CHD was associated with sucrose-sweetened soft beverages. The adjusted risk ratios (aRR) for non-severe CHD was 1.30 (95% CI 1.07–1.58) for women who consumed 25–70 ml/day and 1.27 (95% CI 1.06–1.52) for women who consumed ≥ 70 ml/day when compared to those drinking ≤ 25 ml/day. Dose–response analyses revealed an association between the risk of non-severe CHD and the increasing exposure to sucrose-sweetened soft beverages, especially for septal defects with aRR = 1.26 (95% CI 1.07–1.47) per tenfold increase in daily intake dose. The findings persisted after adjustment for maternal diabetes or after excluding mothers with diabetes (n = 19). Fruit juices, cordial beverages and artificial sweeteners showed no associations with CHD. The findings suggest that sucrose-sweetened soft beverages may affect the CHD risk in offspring.

**Keywords** Cohort study · Sugar consumption · Pregnancy · Congenital heart defect

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## Introduction

Congenital heart defects (CHD) are the most common type of serious birth defects, with a birth prevalence of 10/1000 live births [1, 2]. Both environmental and genetic factors have a role in the causal pathway, and it has been suggested that modifiable factors cause nearly 30% of CHDs [3–5]. CHD prevention has been hampered by limited understanding of modifiable factors [4, 6]. Risk factors such as rubella, retinoic acid, thalidomide, or high alcohol intake have been identified [6–8], but are relatively uncommon exposures in many populations.

Maternal diabetes, a common chronic disease increasing in numbers and significance [9, 10], is the best documented risk factor for CHD [11–17]. The teratogenic mechanism is debated. It has been suggested that hyperglycemia and diabetic ketoacidosis, a severe complication occurring frequently among persons with type 1 diabetes, affect embryonic heart development [18, 19], especially for defects arising before the 7th week of gestation during cardiac looping and conotruncal septation [9, 16]. However, current studies indicate that women with less severe conditions than diabetes mellitus, such as lesser degrees of hyperglycemia, also are at risk of adverse pregnancy outcomes [20]. Priest et al. [21] report that subclinical abnormalities of glucose and insulin metabolism among nondiabetic mothers confer the CHD risk. Øyen et al. [14], support the view that glucose plays a role in the causal pathway for CHD risk. They found an eightfold increase in CHD risk among mothers with a pre-pregnancy history of acute diabetes complications. However, the CHD risk conferred by maternal pregestational diabetes mellitus has not changed over the last decades, and the CHD risk for offspring of mothers with type 1 and type 2 diabetes mellitus did not differ, despite different etiologies. High glucose levels in early pregnancy may be responsible for the association between CHD and maternal diabetes mellitus. The exact mechanism is unknown, but one suggestion is that abnormal glucose levels disrupt the expression of regulatory genes in the embryo, resulting in cell death [22]. An alternative hypothesis is that abnormal glucose levels increase the rate of significant DNA mutations [23].

The intake of sucrose, known as table sugar, increased significantly in many parts of the world in the decades before the year 2000. In Norway the annual intake was 29 kg per person in 2012 [24], where sucrose-sweetened soft beverages contribute on average 40% of all added sucrose among children and adolescents [25]. The consumption of sucrose-sweetened soft beverages has increased from 9 l per capita per year in 1950 (whole population) to 100 l at the turn of the century (Norway Brewery and the Softdrinks Union, Oslo, Norway, 2007), but by 2014 consumption had declined to 55 l [25]. High consumption of sucrose-sweetened soft beverages is associated with maternal risk of obesity, cardiometabolic disease [26–28] and having neonates large-for-gestational-age (LGA) [29]. Maternal obesity is a risk factor for offspring CHDs [30, 31], and neonates with LGA have higher CHD risk than neonates with normal birth weight, independent of maternal diagnosis of diabetes [32]. Taken together, high sucrose intake can be a risk factor for infant CHD, as previous studies report an association between nondiabetic mothers dietary glycemic intake and different birth defects in offspring [33].

As less severe degrees of maternal hyperglycemia, with slightly higher-than-normal blood glucose levels during early pregnancy, was a risk factor for a range of pregnancy and delivery-related complications [21, 34], we hypothesized that maternal intake of sucrose-sweetened soft beverages during the first trimester would be a risk factor for CHD. We also explored if maternal daily intake of artificially sweetened soft beverages or juice and cordial beverages could be a risk factor. As the heart forms early in embryogenesis and is largely complete by the second trimester, the periconceptional period and the first trimester are the most sensitive periods for modifiable risk factors. Our aim is therefore to examine the association between maternal intake of sucrose-sweetened soft beverages in the first trimester and risk of CHD in offspring, and explore a potential dose–response relationship between increased consumption levels and CHD risk.

## Materials and methods

### Study population and data sources

This study is a sub-project within the Norwegian Mother and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health [35]. MoBa is a pregnancy cohort which invited pregnant women in Norway attending routine ultrasound examinations at gestational weeks 16–18 from 1999 through 2008. 41% of the invited women consented to participate. A total of 88,743 births were eligible for this study [36].

Questionnaires in MoBa were administered from early pregnancy at regular intervals during childhood and can be found online at http://www.fhi.no/moba-en. For the purpose of this study, we used questionnaire data from gestational week 15 (questionnaire 1, Q1) and weeks 17–22 (questionnaire 2, Q2). Q1 contains information on maternal lifestyle, background variables, and health-related matters while Q2 is a semi-quantitative food frequency questionnaire with information on maternal drinking and eating habits during early

pregnancy. The present study used version 8 of the quality-assured data files made available in 2014.

Information on the pregnancy and delivery from the Medical Birth Registry of Norway (MBRN) is included in the MoBa database. The MBRN is based on antenatal forms and data that are mandatorily recorded at the maternity departments after delivery and during the hospital stay [37].

Clinical information on CHD diagnoses was retrieved from the nationwide research project "Congenital Heart Defects in Norway" [38], and includes medical data from four data sources: (1) the MBRN, which contains information about all live births and stillbirths in Norway since 1967 [37]; (2) the Cardiovascular Disease project in Norway (CVDNOR, http://www.cvdnor.no) with information on all patients hospitalised for cardiovascular diseases and associated malformations in Norway from 1994 to 2009 [12]; (3) the National Hospital's clinical database for children with heart disease (Berte) contains information on all children with a heart condition who have been examined by a pediatric cardiologist or have received surgery or intervention at the National Hospital since 1992 [39]. The National Hospital conducted about 80% of congenital heart surgeries in Norway before 2004 and nearly all thereafter [38]; (4) and the Cause of Death Register containing death certificate information, including date and cause of death.

Offspring with CHD in MoBa were identified by linkage, using the personal identification number from the Norwegian Population Register. Statistics Norway performed data linkage and de-identification.

## Classification of congenital heart defects

Senior paediatric cardiologists (EL, HH, and Gottfried Greve, Haukeland University Hospital, Bergen, Norway) and a clinical geneticist (NØ) classified the cardiac defects and ensured the quality of the cardiac registry data. As previously described in detail by Leirgul et al. [38], individuals with a heart defect have been identified by diagnostic CHD codes (ICD codes and van Mierop codes), and classified into embryologically related heart defect phenotypes using a modified version of a classification proposed by Botto et al. (2007), and recently used in large population-based cohorts in Denmark and Canada [3, 4, 14]. In the present study we assigned the cardiac defects into severe CHD (heterotaxias, conotruncal defects, atrioventricular septal defects, anomalous pulmonary venous return, left ventricle outflow tract obstruction, right ventricle outflow tract obstruction) or non-severe CHD (patent ductus arteriosus, valvular pulmonary stenosis, ventricular septal defect, atrial septum defects, unspecified septal defects, isolated valve defects, other specified heart defects, unspecified heart defects) (Table 1) [40]. Additional information on co-morbidity such as chromosome aberrations and extracardiac defects was also retrieved by ICD-10 codes and van Mierop codes (see Leirgul et al. [38]).

In the MoBa cohort of 88,743 infants, we identified a total number of 1278 infants with CHD. Preterm patent ductus arteriosus (n = 155) was not considered as a CHD and infants with chromosome aberrations (n = 74) were excluded from the data file, leaving us with a study cohort of 88,514 births, among them 1049 offspring with CHD (Fig. 1). There were no cases of stillbirths in the CHD group. See Table 1 and Fig. 1 for more information.

## Beverages measures

In the MoBa Q2, the mothers reported their intake of fruit juice, cordial beverages and soft drink beverages since the

**Table 1** Heart defect phenotype in 1049 children among 88,514 individuals in the Norwegian Mother and Child Cohort Study, 2000–2009

| Severe CHD | n | Non-severe CHD | n |
|---|---|---|---|
| Heterotaxia | 11 | Patent ductus arteriosus, PDA | 89 |
| Conotruncal defect | 79 | Valvular pulmonary stenosis, vPS | 18 |
| Atrioventricular septal defect, AVSD | 22 | Ventricular septal defect, VSD | 500 |
| Anomalous pulmonary venous return, APVR | 10 | Atrial septal defect, ASD | 135 |
| Left ventricle outflow tract obstruction, LVOTO | 64 | Unspecified septal defect | 6 |
| Right ventricle outflow tract obstruction, RVOTO[b] | 15 | Isolated valve defect | 50 |
| | | Other specified heart defect[c] | 27 |
| | | Unspecified heart defect[d] | 23 |
| Total[a] | 201 | | 848 |

*CHD* congenital heart defect

[a]After excluding preterm PDA (n = 155) and chromosome aberrations (n = 74) the final CHD-sample consisted of 1049 children

[b]Except valvular pulmonary stenosis, vPS

[c]For example isolated valvular malformations not classified as LVOTO, RVOTO, or venous malformations

[d]Not registered with lethal conditions

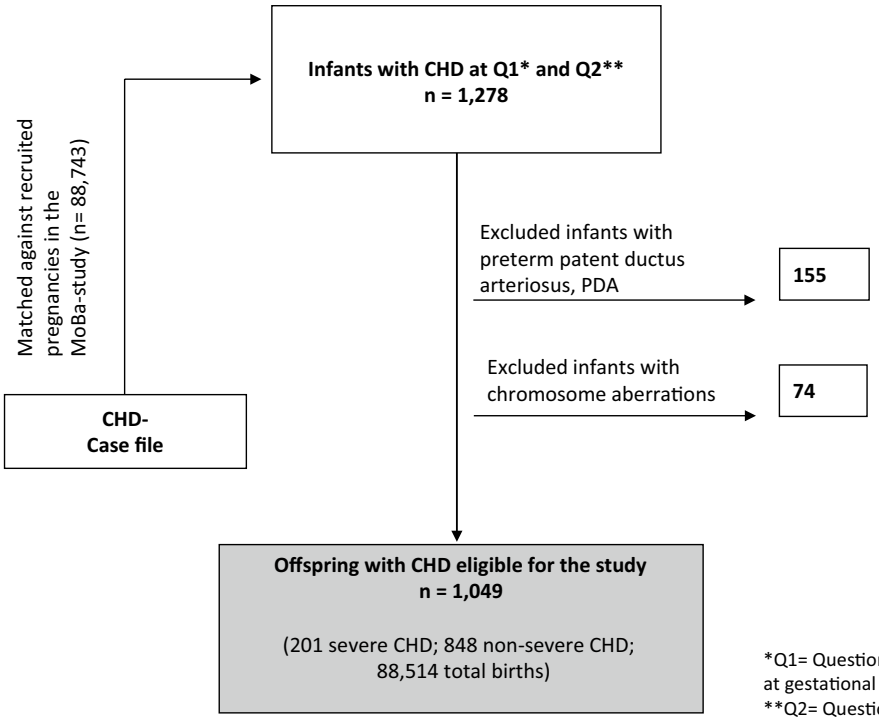


**Fig. 1** Flow-chart displaying participant disposition of the CHD case group

start of pregnancy. For each beverage item, the respondents reported how many glasses they had been drinking, per day, week or month. Beverages were categorized as sucrose-sweetened soft beverages (Coca-Cola, Pepsi and other soft beverages with sucrose), artificially-sweetened soft beverages (Diet Coke, Diet Pepsi, and other light or diet soft beverages), fruit juice (apple and orange) and cordial beverages (concentrated fruit-based syrup mixed with water). We defined a glass as 250 ml for all beverages, and we grouped the daily consumption into three categories: low ($\leq$25 ml), moderate (25–70 ml) and high ($\geq$70 ml) per day. In the analysis, the lowest intake group was used as the reference category.

## Background variables

Tables 2 and 3 shows the distribution of variables from MBRN and Q1. Gestational age is determined by predictions from ultrasound measures, or if this is missing, from the date of the last menstrual period. This information, as well as information on parity, maternal age at childbirth (categorized: <20 years, 20–24, 25–29, 30–34, 35+), the child's sex (girl or boy) and birth weight (measured in grams), is taken from the MBRN.

From Q1, with assessment point at gestation week 15, we have information on maternal smoking before and during pregnancy (response categories: nonsmoker, occasional smoker, daily smoker, dichotomized as "Nonsmokers" and "Smokers"), pre-pregnancy height and weight and maternal educational attainment (<12 years, 12 years, 13–16 years, 17 years or more). Pre-pregnancy height and body weight were used to calculate body mass index (BMI = kg/m$^2$) which was categorized as: <20, 20–24, 25–29, 30+. Further, maternal distress was measured by the SCL-5 from Q1, a shortened version of the Hopkins Symptom Checklist shown to correlate strongly with the SCL-25 index [41]. SCL-5 has five items, with four response categories from 1 = not bothered to 4 = very bothered; an item was: 'Worrying too much about things.' The index was scored as the mean of the item scores, where a mean score less than two is considered within the normal range on the SCL-5. The mothers were asked if they exercised once a week or more before pregnancy, and the responses were dichotomized as 'no' and 'yes.' Previous treatment for infertility was dichotomized as 'no' and 'yes.' Paternal smoking during the last 6 months before pregnancy and during pregnancy was included and the responses were dichotomized as 'Nonsmokers' and 'Smokers.' Maternal diabetes mellitus is reported in MBRN and Q1 and was categorized as pregestational diabetes treated with insulin (type 1) and insulin-independent diabetes (type 2). However, the total cases were so few among the mothers with CHD (n = 19) that all women with pregestational diabetes were merged into one group in the analyses. We did not consider maternal gestational diabetes as a risk factor for offspring CHD, since gestational diabetes develops later in pregnancy and after the fetal heart development.

**Table 2** Characteristics of individuals without CHD, with non-severe CHD, and severe CHD among 88,514 births in the Norwegian Mother and Child Cohort Study, 2000–2009

| | Without CHD (n = 87,465) | Non-severe CHD (n = 848) | Severe CHD (n = 201) | $\chi^2$/F | $p^{\ddagger}$ |
|---|---|---|---|---|---|
| Mother | | | | | |
| Gestational week (mean ± SD) | 39.4 ± 2.1 | 38.6 ± 2.8* | 38.3 ± 3.2* | 97.9 | < .001 |
| Age at child birth, years (mean ± SD) | 30.2 ± 4.6 | 30.2 ± 4.6 | 29.6 ± 5.0 | 2.2 | .115 |
| Education > 12 years (%) | 80.8 | 80.6 | 76.5 | 2.7 | .265 |
| Smoking during pregnancy, yes (%) | 8.5 | 8.7 | 12.0 | 3.8 | .150 |
| Smoking before pregnancy, yes (%) | 28.8 | 31.5 | 28.4 | 3.6 | .166 |
| Pre-pregnancy BMI (mean ± SD) | 22.2 ± 7.7 | 22.4 ± 7.5 | 21.7 ± 7.6 | 1.1 | .340 |
| Infertility, yes (%) | 9.5 | 8.9 | 10.1 | 0.5 | .784 |
| Exercise before pregnancy ≥ once a week (%) | 78.5 | 77.2 | 73.7 | 3.4 | .187 |
| Psychological distress gestation week 18, raw score from 1 to 4 (mean ± SD) | 1.3 ± 0.4 | 1.3 ± 0.4 | 1.3 ± 0.4 | 1.3 | .272 |
| Diabetes (type 1 or 2), yes (%) | 0.8 | 1.2 | 4.5* | 14.46 | < .001 |
| Child | | | | | |
| Boys (%) | 51.3 | 47.9* | 61.1* | 14.1 | < .001 |
| Birth weight, g (mean ± SD) | 3559 ± 610 | 3431 ± 805 * | 3233 ± 825* | 55.7 | < .001 |
| Year of birth (prevalence)[a] | | | | | |
| 1999 | | 0.0 | 0.0 | – | – |
| 2000 | | 7.8 | 1.4 | – | – |
| 2001 | | 10.2 | 1.9 | – | – |
| 2002 | | 9.9 | 2.3 | – | – |
| 2003 | | 10.4 | 2.7 | – | – |
| 2004 | | 11.1 | 2.1 | – | – |
| 2005 | | 9.2 | 2.5 | – | – |
| 2006 | | 9.4 | 1.9 | – | – |
| 2007 | | 10.6 | 2.4 | – | – |
| 2008 | | 7.3 | 2.1 | – | – |
| 2009 | | 6.8 | 2.3 | – | – |
| Father | | | | | |
| Smoking during pregnancy, yes (%) | 20.6 | 18.9 | 24.2 | 3.6 | .164 |
| Smoking before pregnancy, yes (%) | 27.3 | 26.2 | 29.3 | 1.1 | .579 |

[a]Prevalence per 1.000 births per year of birth

*Differs significantly from control group

$^{\ddagger}p$ values were calculated using ANOVA for continuous variables and $\chi^2$ test for categorical variables

## Covariates

We decided a priori the following covariates that could potentially influence the association between maternal soft drink consumption and CHD; year of birth, parity, maternal age at delivery, years of education, diabetes, pre-pregnancy body mass index, and smoking before pregnancy. These covariates were included in the main analyses.

## Analytic strategy

The association between maternal soft drink consumption and offspring risk of CHD was calculated as relative risks (RR) comparing offspring risk of CHD among high-level or medium-level soft drink intake with offspring risk of CHD among low-level intake as the reference. The RRs were estimated with 95% confidence intervals (CI) using log-link binominal regression models, and also with adjustment for the a priori confounders. The distribution of sucrose-sweetened soft beverages intake was skewed to the right, with a small subgroup of mothers with a large intake. Therefore, consumption of sucrose-sweetened soft beverages was transformed to a log scale continuous variable to obtain (1) dose–response curves for adjusted RRs of offspring CHD risk plotted against the maternal consumption of sucrose-sweetened soft beverages, and (2) trend analyses, i.e. the change in RRs for each tenfold risk increase in soft drink intake. Log-transforming the intake values stabilizes the

**Table 3** Characteristics of pregnant women by their reported daily intake of sucrose-sweetened soft beverages before gestational week 18 for 88,514 births in the Norwegian Mother and Child Cohort Study, 2000–2009

| | ≤ 25 ml (n = 45,281) | 25–70 ml (n = 18,604) | ≥ 70 ml (n = 24,629) | $\chi^2$/F | $p^{\ddagger}$ |
|---|---|---|---|---|---|
| Gestational week (mean ± SD) | 39.3 ± 2.1 | 39.4 ± 2.1 | 39.3 ± 2.0 | .130 | .878 |
| Age at child birth (mean ± SD) | 30.2 ± 4.6 | 30.1 ± 4.6 | 30.2 ± 4.7 | .775 | .461 |
| Education > 12 years (%) | 80.6 | 81.0 | 81.0 | 2.53 | .283 |
| Smoking during pregnancy, yes (%) | 8.6 | 8.6 | 8.3 | 3.80 | .150 |
| Smoking before pregnancy, yes (%) | 28.7 | 28.8 | 28.9 | .155 | .925 |
| Pre-pregnancy BMI (mean ± SD) | 22.2 ± 7.6 | 22.1 ± 7.7 | 22.2 ± 7.8 | .695 | .499 |
| Infertility, yes (%) | 9.6 | 9.3 | 9.4 | 1.89 | .388 |
| Exercise before pregnancy ≥ once a week (%) | 78.3 | 78.8 | 78.6 | 2.00 | .367 |
| Psychological distress gestation week 18, raw score from 1 to 4 (mean ± SD) | 1.3 ± 0.4 | 1.3 ± 0.4 | 1.3 ± 0.4 | .055 | .946 |
| Diabetes (type 1 and 2), yes (%) | 1.6 | 1.5 | 1.6 | 1.26 | .533 |

$^{\ddagger}p$ values were calculated using ANOVA for continuous variables and $\chi^2$ test for categorical variables

analyses and enables more precise confidence intervals for RRs at the large intake values. The log-transformation reduces undue influence by the highest values on the dose–response analyses. For the dose–response analyses we used a generalized additive model (GAM) for binomial outcomes with log link, a flexible procedure that allows for nonlinear predictor effects using function smoothers such as splines, i.e. piecewise polynomial functions [42].

### Sensitivity analysis

In this study, maternal diabetes is a covariate that can act as a confounder or an intermediate factor. We conducted a sensitivity analysis to explore the potential effects of maternal diabetes on CHD-risk. To capture uncontrolled confounding by maternal diabetes or systematic change of behavior due to having diabetes, we did adjust for maternal diabetes as a factor that potentially could influence both maternal sucrose consumption and the infant CHD risk in the main analysis (Table 4). In the sensitivity analysis we excluded all diabetic mothers in the case group (n = 19) and in the cohort-controls (n = 705) to see if that influenced our risk estimates. Further, we explored the association between sucrose-sweetened soft beverages during pregnancy and offspring whose mothers had maternal diabetes mellitus in the second analysis compared to the controls (see Table 6).

Foetuses with CHD could have been undiagnosed due to early foetal loss. If high beverage intake increases the risk of early losses, CHD cases caused by the high intake may be lost early and thus go undetected. Then our estimated relative risks would most likely be attenuated. We therefore performed sensitivity analysis to check for associations with sugar exposure, diabetes and risk of stillbirths. In our datafile we have 512 cases classified as stillborns (365 died before delivery, 37 died during delivery and 110 had unknown time code of death). This case group was our dependent variable in the sensitivity analysis.

## Results

### Characteristics of the study population

In the study population of 88,514 births, the overall daily mean maternal intake of sucrose-sweetened soft beverages was 86.50 ml (CI 85.10–87.91) while the median daily intake was 24.66 ml. The birth prevalence of CHDs was 12/1000 live births (1049/88,514) after exclusion of preterm PDA and chromosomal aberrations. Table 2 compares mothers of children with and without CHD. Mothers of children with severe and non-severe CHD did not differ from mothers of children without CHD with regard to age, education, smoking, having a partner who smokes, pre-pregnancy BMI, infertility treatment, exercise, or psychological distress before pregnancy. Boys were overrepresented among children with severe CHD and underrepresented among children with non-severe CHD, and children with severe and non-severe CHD had lower birth weight and shorter gestational age than controls. Diabetic women were overrepresented among mothers of children with severe CHD. We further explored the characteristics of women according to their daily intake of sucrose-sweetened soft beverages before pregnancy week 18, and found no differences on the background variables (Table 3).

### Sucrose-sweetened soft beverages and infant CHD

We observed that consumption of sucrose-sweetened soft beverages was associated with CHD (moderate: 25–70 ml, aRR = 1.29, 95% CI 1.08–1.53 and high: ≥ 70 ml,

**Table 4** The association between maternal daily intake of sucrose-sweetened soft beverages during pregnancy and risk of CHD in offspring for 88,514 births in the Norwegian Mother and Child Cohort Study, 2000–2009

| Sucrose-sweetened soft beverages (ml/day) | Total no. of births | CHDs (n) | Prevalence CHDs[a] | RR (95% CI) | aRR (95% CI)[b] |
|---|---|---|---|---|---|
| | | All CHDs | | | |
| ≤25 ml | 45,281 | 497 | 11.0 | 1 | 1 |
| 25–70 ml | 18,604 | 243 | 13.1 | 1.19 (1.02, 1.39) | 1.29 (1.08, 1.53) |
| ≥70 ml | 24,629 | 309 | 12.5 | 1.14 (0.08, 1.23) | 1.22 (1.04, 1.44) |
| Trend[c] | | | | | 1.18 (1.04, 1.34) |
| | | Severe | | | |
| ≤25 ml | 45,281 | 103 | 2.3 | 1 | 1 |
| 25–70 ml | 18,604 | 42 | 2.3 | 0.99 (0.69, 1.42) | 1.26 (0.85, 1.88) |
| ≥70 ml | 24,629 | 56 | 2.3 | 1.00 (0.72, 1.38) | 1.06 (0.72, 1.55) |
| Trend[c] | | | | | 1.19 (0.89, 1.60) |
| | | Non-severe | | | |
| ≤25 ml | 45,281 | 394 | 8.7 | 1 | 1 |
| 25–70 ml | 18,604 | 201 | 10.8 | 1.24 (1.05, 1.47) | 1.30 (1.07, 1.58) |
| ≥70 ml | 24,629 | 253 | 10.3 | 1.18 (1.01, 1.38) | 1.27 (1.06, 1.52) |
| Trend[c] | | | | | 1.18 (1.02, 1.36) |
| | | All septal | | | |
| ≤25 ml | 45,281 | 290 | 6.4 | 1 | 1 |
| 25–70 ml | 18,604 | 152 | 8.2 | 1.26 (1.05, 1.51) | 1.29 (1.03, 1.62) |
| ≥70 ml | 24,629 | 199 | 8.1 | 1.28 (1.05, 1.55) | 1.36 (1.11, 1.67) |
| Trend[c] | | | | | 1.26 (1.07, 1.47) |
| | | ASD | | | |
| ≤25 ml | 45,281 | 56 | 1.2 | 1 | 1 |
| 25–70 ml | 18,604 | 37 | 2.0 | 1.61 (1.06, 2.44) | 1.39 (0.84, 2.29) |
| ≥70 ml | 24,629 | 42 | 1.7 | 1.38 (0.93, 2.06) | 1.31 (0.82, 2.09) |
| Trend[c] | | | | | 1.30 (0.91, 1.86) |
| | | VSD | | | |
| ≤25 ml | 45,281 | 230 | 5.1 | 1 | 1 |
| 25–70 ml | 18,604 | 113 | 6.1 | 1.20 (0.96, 1.50) | 1.26 (0.98, 1.64) |
| ≥70 ml | 24,629 | 157 | 6.4 | 1.26 (1.03, 1.53) | 1.40 (1.11, 1.76) |
| Trend[c] | | | | | 1.27 (1.06, 1.52) |

*CI* confidence interval, *CHD* congenital heart defect, *ASD* atrial septal defect, *VSD* ventricular septal defect

[a]Birth prevalence per 1000 births (preterm PDA and chromosomal aberrations excluded)

[b]Relative risks compared CHD birth prevalences for medium- or high-level intake of beverages with CHD birth prevalence for low-level intake of beverages (reference) with adjustment for year of birth, smoking before pregnancy, mother's age, education, parity, diabetes mellitus, and pre-pregnancy BMI

[c]Trend is estimated as a linear trend on log-transformed daily intake dose; the stated RRs measure the relative risk increase corresponding to a tenfold increase in daily intake dose

aRR = 1.22, 95% CI 1.04–1.44). We found a positive association between consumption of sucrose-sweetened soft beverages and non-severe CHD, when compared to mothers of children without CHD (moderate: 25–70 ml, aRR = 1.30, 95% CI 1.07–1.58, high: ≥ 70 ml, aRR = 1.27, 95% CI 1.06–1.52). Moreover, Table 4 shows a significant association between sucrose-sweetened soft beverages and septal defects (moderate: 25–70 ml, aRR = 1.29, 95% CI 1.03–1.62, high: ≥ 70 ml, aRR = 1.36, 95% CI 1.1–1.67). A similar association was found for VSD but was only significant when women reported drinking ≥ 70 ml/day (aRR = 1.40 (95% CI 1.11–1.76). Intake of sucrose-sweetened soft beverages was not associated with risk of severe CHD (moderate: 25–70 ml, aRR = 1.26, 95% CI 0.85–1.88, high: ≥ 70 ml, aRR = 1.06, 95% CI 0.72–1.55).

Figure 2 displays dose–response curves obtained from the log-binomial GAMs with adjusted RRs. When we conducted a dose–response analysis for the trend estimation, there was no clear trend for severe CHD. The CHD-risk in severe CHD showed no significant increase when the average frequency of daily consumption of sucrose-sweetened soft beverages increased. For septal defects and VSDs the

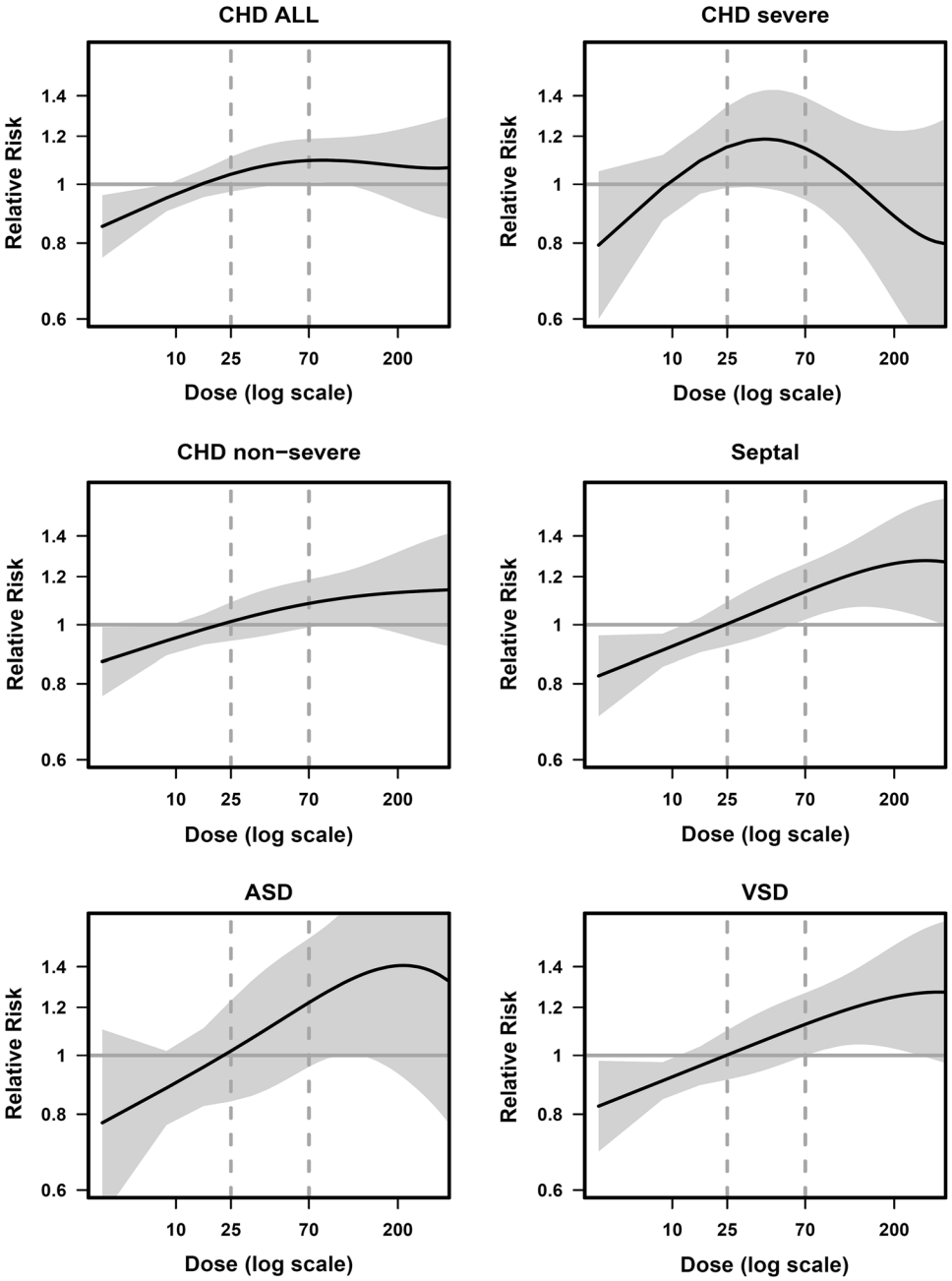


**Fig. 2** Dose–response curves with adjusted relative risk (95% confidence intervals) among different CHD groups for 88,514 births in the Norwegian Mother and Child Cohort Study, 2000–2009. Dose is measured as average daily intake of sucrose-sweetened soft beverages in milliliters. The horizontal reference line at RR = 1, indicates the average population risk level [42]. *CHD* congenital heart effects, *ASD* atrial septal defect, *VSD* ventricular septal defect. Prepared with R [43]

CHD-risk increased approximately linearly when the average frequency of daily consumption of sucrose-sweetened soft beverages increased. For non-severe CHD and ASD there was also an apparent increase, although less pronounced. For non-severe CHD, increased consumption during pregnancy did not display any threshold effects; i.e. there was no specific amount of exposure of sucrose-sweetened soft beverages that led to a marked increase in CHD-risk. Instead, the curve gradually increased at the lowest doses and continued to increase steadily. There are some CHD categories where the trend is not obvious; for instance, for non-severe CHD the RRs in Table 4 are 1.30 (95% CI 1.07–1.58) and 1.27(95% CI 1.06–1.52) for medium and high doses, respectively. This is also seen in the corresponding plot for non-severe CHD in Fig. 2, where the effect seems to level off at around 70 ml/day. This indicate that medium doses are enough to trigger the risk increase, but additional increase in dose does not result in a further increase in risk. Still, the corresponding trend estimates are positive, since the trend is estimated as an overall dose–response, going from the lowest levels to the highest.

## Other sweetened beverages and infant CHD

Table 5 shows the association of artificially sweetened soft beverages, apple- and orange juice, cordial beverages with each CHD, including adjusted relative risks and 95% confidence intervals for each consumption level. In contrast to the finding for sucrose-sweetened soft beverages, we found no significant associations with beverages containing less or no sucrose and offspring CHD.

**Table 5** The association between maternal daily intake of artificially-sweetened beverages, juice, or cordial beverages during pregnancy and risk of CHD in offspring for 88,514 births in the Norwegian Mother and Child Cohort Study, 2000 to 2009

| Exposure (ml/day) | Total no. of births | CHDs (n) | Prevalence CHDs[a] | RR (95% CI) | aRR (95% CI)[b] |
|---|---|---|---|---|---|
| Artificially-sweetened soft beverages | | All CHDs | | | |
| ≤25 ml | 46,374 | 552 | 11.9 | 1 | 1 |
| 25–70 ml | 12,324 | 143 | 11.6 | 0.98 (0.81, 1.17) | 0.95 (0.77, 1.18) |
| ≥70 ml | 29,816 | 354 | 11.9 | 1.00 (0.87, 1.14) | 0.96 (0.83, 1.12) |
| | | Severe | | | |
| ≤25 ml | 46,374 | 103 | 2.2 | 1 | 1 |
| 25–70 ml | 12,324 | 32 | 2.6 | 1.17 (0.79, 1.74) | 0.82 (0.57, 1.19) |
| ≥70 ml | 29,816 | 66 | 2.2 | 1.00 (0.84, 1.18) | 1.05 (0.66, 1.67) |
| | | Non-severe | | | |
| ≤25 ml | 46,374 | 449 | 9.7 | 1 | 1 |
| 25–70 ml | 12,324 | 111 | 9.0 | 0.93 (0.76, 1.14) | 0.93 (0.73, 1.18) |
| ≥70 ml | 29,816 | 288 | 9.7 | 1.00 (0.86, 1.16) | 1.00 (0.84, 1.18) |
| Apple/orange juice | | All CHDs | | | |
| ≤25 ml | 19,438 | 245 | 12.6 | 1 | 1 |
| 25–70 ml | 13,221 | 165 | 12.5 | 0.91 (0.78, 1.05) | 0.97 (0.77, 1.22) |
| ≥70 ml | 55,855 | 639 | 11.4 | 0.99 (0.81, 1.21) | 0.94 (0.79, 1.11) |
| | | Severe | | | |
| ≤25 ml | 19,438 | 39 | 2.0 | 1 | 1 |
| 25–70 ml | 13,221 | 38 | 2.9 | 1.43 (0.92, 2.24) | 1.12 (0.66, 1.90) |
| ≥ 70 ml | 55,855 | 124 | 2.2 | 1.11 (0.77, 1.58) | 1.03 (0.69, 1.53) |
| | | Non-severe | | | |
| ≤25 ml | 19,438 | 206 | 10.6 | 1 | 1 |
| 25–70 ml | 13,221 | 127 | 9.6 | 0.90 (0.73, 1.13) | 0.94 (0.72, 1.21) |
| ≥70 ml | 55,855 | 515 | 9.2 | 0.87 (0.74, 1.02) | 0.92 (0.76, 1.11) |
| Cordial | | All CHDs | | | |
| ≤25 ml | 55,791 | 643 | 11.5 | 1 | 1 |
| 25–70 ml | 13,099 | 166 | 12.6 | 1.10 (0.93, 1.03) | 1.11 (0.91, 1.35) |
| ≥70 ml | 19,624 | 240 | 12.2 | 1.06 (0.92, 1.23) | 1.13 (0.95, 1.33) |
| | | Severe | | | |
| ≤25 ml | 55,791 | 129 | 2.3 | 1 | 1 |
| 25–70 ml | 13,099 | 28 | 2.1 | 0.93 (0.62, 1.39) | 1.18 (0.76, 1.83) |
| ≥70 ml | 19,624 | 44 | 2.2 | 0.97 (0.69, 1.37) | 1.03 (0.69, 1.53) |
| | | Non-severe | | | |
| ≤25 ml | 55,791 | 514 | 9.2 | 1 | 1 |
| 25–70 ml | 13,099 | 138 | 10.5 | 1.14 (0.95, 1.38) | 1.09 (0.88, 1.37) |
| ≥70 ml | 19,624 | 196 | 10.0 | 1.08 (0.92, 1.28) | 1.15 (0.95, 1.39) |

*CI* confidence interval, CHD congenital heart defect, *ASD* atrial septal defect, *VSD* ventricular septal defect

[a]Birth prevalence per 1000 births (excluding preterm PDA and chromosomal aberrations)

[b]Relative risks compared CHD birth prevalences for medium- or high-level intake of beverages with CHD birth prevalence for low-level intake of beverages (reference) with adjustment for year of birth, smoking before pregnancy, mother's age, education, parity, diabetes mellitus, and pre-pregnancy BMI

## The potential confounding effect of maternal pregestational diabetes

In this cohort, the prevalence of mothers with diabetes mellitus type 1 and 2 was 8/1000 (724/88,514). We identified altogether 19 offspring with CHD whose mother had pregestational diabetes (type 1 and 2). Among mothers with diabetes, nine offspring had severe CHD and 10 had non-severe CHD. Maternal diabetes had no significant associations with non-severe CHD (RR = 1.55, 95% CI 0.89–2.69), however it had a strong positive association with severe CHD risk in the offspring (RR = 4.66, 95% CI 2.37–9.10). In this sense, maternal diabetes could be an important confounder associated with both sucrose-sweetened soft beverages consumption and CHD-risk. In the sensitivity analysis, we excluded all diabetic mothers to see if that influenced our risk estimates. Table 6 shows it had no influence on the observed associations. When we excluded all diabetic mothers from the main analysis, we found that the risk ratios for CHD in offspring remained unchanged compared to our risk estimates from our main analysis (in Table 4) where mothers with diabetes were included. Further, we did not find any significant associations between consumption of sucrose-sweetened soft beverages during pregnancy and risk of maternal diabetes mellitus (see Table 6).

Although we did not have information on spontaneous abortions, we investigated whether maternal diabetes or consumption of sucrose-sweetened soft beverages were associated with stillbirths. The RRs of stillbirths for maternal diabetes compared to no diabetes was 1.42 (95% CI 0.63–3.18).

**Table 6** The association between of sucrose-sweetened soft beverages during pregnancy and infant CHD risk by excluding a total number of 724 mothers with diabetes in the first analysis (A), and the association between sucrose-sweetened soft beverages during pregnancy and maternal diabetes mellitus as outcome in the second analysis (B)

| Sucrose-sweetened soft beverages (ml/day) | Total no. of births | Case group (n) | RR (95% CI)[a] |
|---|---|---|---|
| (A) Excluding offspring whose mothers had diabetes mellitus | | | |
| | | All CHDs | |
| ≤ 25 ml | 44,904 | 486 | 1 |
| 25–70 ml | 18,463 | 238 | 1.19 (1.02, 1.40) |
| ≥ 70 ml | 24,423 | 306 | 1.16 (1.00, 1.34) |
| | | Severe CHDs | |
| ≤ 25 ml | 44,904 | 97 | 1 |
| 25–70 ml | 18,463 | 39 | 0.98 (0.67, 1.42) |
| ≥ 70 ml | 24,423 | 56 | 1.06 (0.77, 1.48) |
| | | Non-severe CHDs | |
| ≤ 25 ml | 44,904 | 389 | 1 |
| 25–70 ml | 18,463 | 199 | 1.25 (1.05, 1.48) |
| ≥ 70 ml | 24,423 | 250 | 1.18 (1.01, 1.40) |
| | | All septal CHDs | |
| ≤ 25 ml | 44,904 | 285 | 1 |
| 25–70 ml | 18,463 | 152 | 1.30 (1.07, 1.58) |
| ≥ 70 ml | 24,423 | 197 | 1.27 (1.06, 1.53) |
| | | ASD | |
| ≤ 25 ml | 44,904 | 55 | 1 |
| 25–70 ml | 18,463 | 37 | 1.64 (1.08, 2.49) |
| ≥ 70 ml | 24,423 | 42 | 1.41 (0.94, 2.10) |
| | | VSD | |
| ≤ 25 ml | 44,904 | 226 | 1 |
| 25–70 ml | 18,463 | 113 | 1.22 (0.97, 1.53) |
| ≥ 70 ml | 24,423 | 155 | 1.25 (1.03, 1.55) |
| (B) Consumption of sucrose-sweetened soft beverages and risk of diabetes mellitus | | | |
| | | Diabetes | |
| ≤ 25 ml | 45,281 | 377 | 1 |
| 25–70 ml | 18,604 | 141 | 0.91 (0.75, 1.11) |
| ≥ 70 ml | 24,629 | 206 | 1.00 (0.85, 1.19) |

*CI* confidence interval, *CHD* congenital heart defect, *ASD* atrial septal defect, *VSD* ventricular septal defect

[a]Relative risks compared CHD birth prevalences for medium- or high-level intake of beverages with CHD birth prevalence and diabetes prevalence for low-level intake of beverages (reference)

And, The RRs of stillbirths for maternal high-level (≥ 70 ml/day) and medium-level (25–70 ml/day) consumption compared to low-level (≤ 25 ml/day) consumption were 0.88 (95% CI 0.70–1.11) and 0.98 (95% CI 0.78–1.26), respectively. These null findings persisted after adjustment.

## Discussion

To our knowledge, this is the first population-based exploration of the association between intake of sucrose-sweetened soft beverages during the first trimester and the risk of CHD in offspring.

We found a slightly increased risk of non-severe CHD among offspring of mothers consuming more than 70 ml sucrose-sweetened soft beverages per day compared to mothers consuming less than 25 ml/day. Dose–response analysis identified a tendency of increased risk for septal defects when the average daily consumption increased. Further, the findings persisted after adjustment for potential confounders such as maternal age, year of birth, diabetes mellitus, parity, education, smoking and pre-pregnancy BMI. Our results remained unchanged in a sensitivity analysis excluding diabetic mothers, supporting a significant positive association between maternal consumption of sucrose-sweetened soft beverages and infant risk of non-severe CHD.

Interestingly, we did not find significant associations between CHD-risk and other beverages such as fruit juice, cordial beverages and artificially sweetened soft beverages. Artificial sweeteners are widely used, and some studies have explored if additives like caramels for coloring, caffeine or phosphoric acid could cause adverse effects [28]. However, we did not find any associations between CHD risk and beverages containing no sucrose (artificial sweeteners) or for cordial beverages containing less sucrose.

The overall total content of carbohydrates in both juice and sucrose-sweetened soft beverages are similar. However, consumption of fruit juice during pregnancy showed no associations with offspring CHD. This is in line with previous studies, where it was difficult to provide consistent associations between adverse birth effects and fruit juice intake [28, 44]. An essential difference is that fruit juice provides vitamins, minerals, fiber and various phenolic compounds [44]. Moreover, juice contains fructose naturally, while the added sucrose in the soft beverages is composed of 50:50 glucose and fructose. An explanation can be that glucose and fructose have different effects on the glucose homeostasis [45], where absorbed glucose gives acute spikes in blood glucose level [45], while fructose is more gradually converted to glucose, lactate and glycogen in the liver [46]. Moreover, there might be a difference in the glycemic load of the diet. Juice is often consumed as part of a meal, while sucrose-sweetened soft beverages often are consumed in larger amounts and between meals [47], leading to higher glycemic load with greater expected elevation in blood glucose and insulin concentration. Also of relevance, is that juice and sucrose-sweetened soft beverages seem to have different associations with different surrogate markers on insulin resistance among healthy adults [44]. Compared to fruit juice consumption, adverse effect was only found for sucrose-sweetened soft beverages, with a positive association with fasting insulin, which is a marker of insulin resistance and a risk factor for diabetes type 2. The authors speculate that the absence of adverse metabolic effects of fruit juice was due to confounding by lifestyle factors [44].

In accordance with previous studies [6, 7, 11–14, 16–19], we identified a significant association between maternal diabetes mellitus (type 1 and 2) and CHD in offspring. Interestingly, there is a tendency in our results that maternal diabetes, as compared to consumption of sucrose-sweetened soft beverages, has different associations to particular CHD phenotypes: Diabetes was associated with increased risk of severe CHD subtypes, whereas sucrose-sweetened soft beverages consumption was slightly associated with non-severe CHD subtypes. Further, the associations between sucrose-sweetened soft beverages and non-severe CHD tended to be weaker than the associations between maternal diabetes and severe CHD. The explanation of the different effects on the CHD subtypes might be that diabetes mellitus is present before conception and consequently is more commonly associated with defects of early cardiogenesis such as atrioventricular septal defects, heterotaxy and outflow tract anomalies, which are defined as severe CHDs in our study [9, 16]. Priest et al. [21] finds a strong association between mid-trimester maternal glucose levels and offspring risk of ToF (Tetralogy of Fallot) but not TGA (Transposition of the Great Arteries), both severe conotruncal defects. This indicates specific CHD vulnerabilities due to serum glucose levels among nondiabetic women. Concurrently, a possible fluctuation in glucose levels due to consumption of sucrose-sweetened soft beverages in our study appeared to influence later cardiac development, such as ventricular septal defects (VSDs), occurring around pregnancy week 8. Taken together, these findings need more investigation, as there may seem to be complex mechanisms and different pathways between different CHD-malformations and high glucose-levels when caused by a chronic disease such as diabetes mellitus, observed subclinical abnormalities of glucose levels or by intake of sucrose-sweetened soft beverages.

If confirmed in other samples, preferably conducted earlier in pregnancy, these observations could have important public health implications for identifying women at risk for carrying offspring with CHD. Strict glycaemic control in diabetic women before conception and during pregnancy has been reported to reduce the risk of erroneous embryonic development [20, 49], in the same way; it is conceivable to

reduce the intake of sucrose-sweetened soft beverages to improve glucose homeostasis even as early as when women are planning a pregnancy, or often more effective; by reducing sugar consumption in the whole population.

### Strengths and limitations of study

Our study has unique features that buttress our findings. It builds on prospective cohort data linked to clinical data, ascertained through national health registers with a comprehensive systematic classification of CHDs suited for etiologic studies. The sizable cohort permitted adjustment for relevant confounders. However, the study has limitations that might have affected the validity of our findings.

First, mothers' responses were self-report measures and may be influenced by social desirability, underreporting, recall bias and other response biases. A study from Iceland showed that food items such as sucrose-sweetened soft beverages and other food items perceived as unhealthy were underreported [48]. Considering that the annual consumption of sucrose-sweetened soft beverages was about 55 l/capita in 2014 (i.e. approximately 150 ml/day) [25], one could speculate if some of the mothers in our study may have underreported their intake. This can be a potential source of misclassification error toward inclusion of heavy drinkers in the lower drinking categories. This should lead to a bias toward the null value in the estimate of the effects of intake of sucrose-sweetened soft beverages during pregnancy on infant CHD risk. However, the MoBa semi-quantitative food frequency questionnaire has been validated against a 4-day weighed food diet combined with several biomarkers and was shown suitable to detect high and low intakes of energy, nutrients, and foods [49]. The lower mean consumption among mothers in MoBa (86.5 ml/day) could also reflect that the MoBa cohort is a more healthy selection of the Norwegian population [36].

Second, higher intake of sucrose-sweetened soft beverages could be a marker of an overall undesirable diet because it tends to cluster with other unhealthy dietary and lifestyle habits such as higher intake of saturated and trans fats and food with a high glycemic load [27, 50]. We did adjust for various lifestyle factors, and the consistency of our results reduces the likelihood that residual confounding by lifestyle is causing the findings. However, residual confounding cannot be ruled out. Third, small sample sizes influence statistical power; in particular, small numbers within each cardiac phenotype reduce the power to identify associations. We find no evidence of effect of sucrose intake on the risk of severe CHD; however, an association cannot entirely be ruled out since the corresponding confidence intervals in Table 4 are wide. Fourth, birth prevalence of CHD might be underestimated during the last period of the MoBa-study if not all cases were ascertained. However, about 94% of most CHDs have been diagnosed within 6 months of age, especially for severe CHD and VSD [38, 40]. We acknowledge that ASD could have been underestimated the last period with a median age of diagnosis of 323 days [38]. However, the analyses are adjusted for year of birth. This corrects for a possible association between changing beverage intake through the MoBa period and a possible reduction in case ascertainment at the end of the period. Finally, to better understand the possible link between sucrose-sweetened soft beverages and CHD development, data on maternal pregestational glucose levels would have been helpful, and our findings should inspire more detailed clinical and experimental studies to explore the possible underlying mechanisms between sucrose-sweetened soft beverages and offspring CHD-risk.

## Conclusion and clinical implications

In conclusion, we found a modest positive association between maternal consumption of sucrose-sweetened soft beverages during the first weeks of pregnancy and non-severe CHD in offspring. Since the embryological development of the heart is largely completed by the first trimester, there is a "time window" where fetuses exposed to modifiable risk factors in utero may be at higher risk for CHD. This large cohort study, suited for exploring environmental risk factors, provides the basis for larger studies and population-based molecular epidemiological studies on the process underlying erroneous embryonic development and prevention of CHDs. Our findings suggest that sucrose-sweetened soft beverages may affect the CHD risk in offspring. Further studies are needed to investigate whether the association is causal.

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**Author contributions** MTGD, NØ and PM designed the study. MTGD and HG analyzed the data and MTGD drafted the paper. Authors participated in project meetings at which the analysis plan and data interpretation were discussed. All authors were responsible for interpretation of data and critically revised the article for important intellectual content.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest

**Ethical approval** Written informed consent was obtained from all participating women, and the study has been approved by the Regional Committee for Ethics in Medical Research and the Data Inspectorate.

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