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Author contributions

KSL, GP and AMNA designed the study. GP and KSL analysed data and drafted the paper. All authors contributed to the analysis plan and data interpretation and critically revised the paper. Authors participated in two workshops during spring 2012 at which the analysis plan and data interpretation were discussed.

Abstract

Women who drink light-to-moderately during pregnancy have been observed to have lower risk of unfavourable pregnancy outcomes than abstainers. This has been suggested to be a result of bias. In a pooled sample, including 193 747 live-born singletons from nine European cohorts, we examined the associations between light-to-moderate drinking and preterm birth, birth weight, and small-for-gestational age in term born children (term SGA). To address potential sources of bias, we compared the associations from the total sample with a sub-sample restricted to first-time pregnant women who conceived within six months of trying, and examined whether the associations varied across calendar time. In the total sample, drinking up to around six drinks per week as compared to abstaining was associated with lower risk of preterm birth, whereas no significant associations were found for birth weight or term SGA. Drinking six or more drinks per week was associated with lower birth weight and higher risk of term SGA, but no increased risk of preterm birth. The analyses restricted to women without reproductive experience revealed similar results. Before 2000 approximately half of pregnant women drank alcohol. This decreased to 39% in 2000-2004, and 14% in 2005-2011. Before 2000, every additional drink was associated with reduced mean birth weight, whereas in 2005-2011, the mean birth weight increased with increasing intake. The period-specific associations between low-to-moderate drinking and birth weight, which also were observed for term SGA, are indicative of bias. It is impossible to distinguish if the bias is attributable to unmeasured confounding, which change over time or cohort heterogeneity.

Key words: Alcohol, birth weight, cohort study, confounding, preterm birth, small for gestational age

Key Messages

- Intake of maximum three alcoholic drinks/week during pregnancy reduced the risk of preterm birth, while no association was found with birth weight or term SGA.
- Slightly lower birth weight and higher risk of term SGA were observed for drinking above this level, though not statistically significant before a minimum around six drinks/week. No increased risk was observed for preterm birth.
- The proportion of women drinking alcohol during pregnancy decreased dramatically over time from around 50% in the period 1984-1999 to 14% in 2005-2011.
- Bias seems to play a crucial role as associations between light-to-moderate drinking and birth weight and term SGA changed from indicating harmful effects in children born before 2000, to no or even beneficial effects in 2000-2004 and 2005-11.
- It was impossible to separate bias attributable to changes in unmeasured characteristics of the drinkers across time and cohort heterogeneity.

Introduction

It remains unsettled whether there is a safe level for alcohol drinking during pregnancy (1). A substantial part of the literature suggests that - compared to abstainers - light-to-moderate drinkers, i.e. women consuming less than 7 drinks per week, have lower risk of low birth weight, small for gestational age, and preterm birth (1-3). Possible explanations for this may be that light-to-moderate drinking during pregnancy is genuinely beneficial. No strong evidence, even from animal settings, support a beneficial effect and it seems more plausible that these apparently beneficial effects of light-to-moderate drinking are artefacts caused by characteristics of the drinkers (4). Women who drink light-to-moderately during pregnancy have been shown to be more socially advantaged and healthier than women who abstain or drink heavily during pregnancy (5-7). Higher social position and being healthier are linked to more favourable pregnancy outcomes, and thus a 'healthy-drinker' effect may explain the observed beneficial effects of light-to-moderate drinking. Characteristics of the 'pregnancy drinkers' presumably change over time and varies between populations, e.g. countries; thus the associations with pregnancy outcomes might also change accordingly. For instances a country effect has been shown in a systematic review of the relation between maternal alcohol consumption and spontaneous abortion (8).

Women with an unfavourable reproductive history have more reasons to abstain from drinking alcohol during pregnancy than first-time pregnant women or women who already have a healthy child. This may result in behaviour-modification bias (9), as unfavourable reproductive experience is an indicator of future higher-risk pregnancies (10, 11) and abstainers might thereby have a higher a priori risk of adverse pregnancy outcomes. One way to make abstainers and light-to-moderate drinkers more comparable in terms of their underlying obstetric risk is to only include first-time pregnancies (9), ideally with no or short time to pregnancy. An approximation of this approach was used in a study based on the Danish National Birth Cohort (DNBC) examining the association between light-to-moderate drinking and preterm birth (12). In contrast to results of the main

analysis, no reduced risk of preterm birth was observed among light drinkers as compared to abstainers in the sub-set of nulliparous women. Restriction to first-time pregnancies conceived within a short period of trying requires very large sample size, as for instances approximately one quarter of the pregnancies in the DNBC was a first-time pregnancy conceived within six months of trying (13). In this study, we have pooled data from nine European birth cohorts to examine the associations between light-to-moderate drinking and preterm birth, birth weight, and small-for-gestational-age in term born children (term SGA), both in the full sample and in a subsample of first-time pregnant women who have conceived within six months of trying. Moreover, we exploit that the birth year of the children included in the cohorts spans more than 20 years to explore whether the associations vary over calendar time.

Methods

Eligibility of cohorts and restriction of the study population:

Eligible European birth cohorts were identified through the online birth cohort inventories (www.birthcohorts.net and www.enrieco.dk), accessed in August 2011. We additionally supplemented with information from the cohorts' websites and published profiles. Principal investigators for the birth cohort studies were invited to contribute if participants were enrolled during pregnancy, and if information on average number of alcohol drinks during pregnancy, gravidity, time-to-pregnancy, birth weight, and gestational age at birth had been collected. Out of 66 identified European birth cohorts, 15 cohorts fulfilled the above inclusion criteria; of these, three cohorts did not reply to the invitation, one declined participation, and two were excluded as it turned out that the required information was not available. This left us with the following nine cohorts: Aarhus Birth Cohort (ABC) (14), The Danish National Birth Cohort (DNBC) (15), Generation R (GenR) (16), Healthy Habits for two (HHf2) (17), Environment and Childhood Project

(INMA) (18), The Norwegian Mother and Child Cohort (MoBa) (19), Nascita e INFanzia: gli Effetti dell'Ambiente (NINFEA) (20), Endocrine disruptors: longitudinal study on pathologies of pregnancy, infertility and childhood (PELAGIE) (21), and Mother Child Cohort in Crete (RHEA) (22).

Data sets without personal identifiers from each cohort were transferred to the University of Copenhagen. Each data set was checked for inconsistencies and completeness, and the pooled data included 248 254 live born singletons with non-missing data on birth weight and gestational age. This study population was restricted to observations with birth weight between 500 and 6500 g, gestational age between 22 and 43 completed weeks, and plausible birth weight for gestational age combinations defined by the conservative approach given by Alexander et al (23). There was an overlap of individuals between the DNBC and ABC (n=5551 participants) for these observations data from DNBC was used. We furthermore restricted the study population to women with complete information on alcohol drinking during pregnancy, time-to-pregnancy, number of previous pregnancies, and a number of a priori defined potential confounders, leaving 193 747 observations eligible for the analyses of birth weight. For the analyses of term SGA, this population was furthermore restricted to deliveries after 37 completed weeks of gestation (n= 184 960). Finally, in the analyses of preterm birth, the study population was restricted to women recruited before 37 completed weeks of gestation and did not include the HHf2 cohort where 54% of women were recruited after 36 completed weeks (n=183 900), see Figure 1.

Figure 1

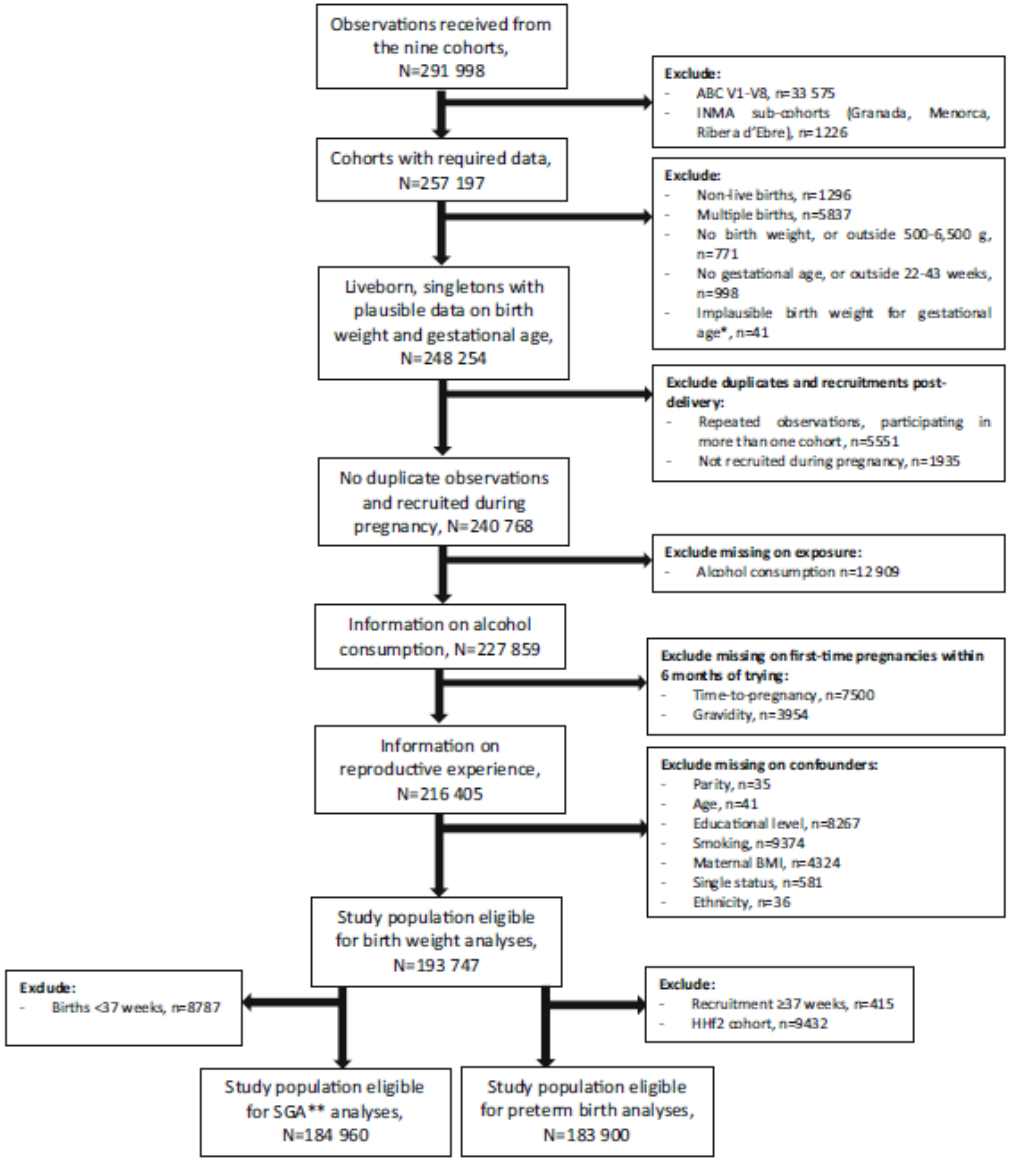


Fig. 1 Flow-chart from delivered data to the study population. *Defined by the conservative approach, described in Alexander et al. ** Small-for-Gestational age (SGA).

Alcohol intake:

In all cohorts, information on alcohol intake was collected during pregnancy. We used the earliest collected information on alcohol intake in the four cohorts where we received more than one measure of alcohol intake during pregnancy. Different types of questionnaires for assessing alcohol intake were used in the cohorts, see Table 1. Furthermore, the questionnaires concerned different time periods of pregnancy, making it impossible to harmonize data on different exposure windows. For the DNBC cohort and the latest inclusion years of the ABC and the NINFEA cohorts, uncategorised alcohol intake in drinks per week was available. In the MoBa and RHEA cohorts, food-frequency questionnaires were used to assess alcohol intake and we categorised into drinks per week directly. In the rest of the cohorts, average alcohol intake was assessed in categories (e.g. 2-4 drink per week). For alcohol intake in categories (14% of observations), we imputed the average number of drinks per week within each interval based on the uncategorised data from the DNBC, ABC and NINFEA cohorts instead of using interval midpoints. Ten sets of imputations were made, assuming equal distribution of alcohol intake within each interval between the cohorts. For cohorts that asked about the beverage-specific type of alcohol in categories, the alcohol intake was imputed by drinks of beer, wine and spirits and then added together. In the PELAGIE cohort, women were asked about daily alcohol intake, and the categories were converted from drinks per day to drinks per week by the following rule: one drink per day corresponds to 7-13 drinks weekly, two drinks per day to 14-20 drinks weekly, etc. The harmonized variable for weekly alcohol intake was grouped as: 0; >0 to <1; 1 to <2; 2 to <3; 3 to <4; 4 to <5; 5 to <6; 6 to <7; and ≥7 drinks per week.

Birth outcomes:

Information on gestational age, birth weight and infant sex was primarily obtained from medical records although two cohorts relied on birth registrations and maternal report, Table 1. If more than one estimate of gestational age was available, gestational age estimates based on a combination of last menstrual period (LMP), ultrasound scans and clinical assessment were preferred. Otherwise, gestational age based on LMP was used, unless it varied from ultrasound-based estimate by more than two weeks, in which case the ultrasound estimate was used. Preterm birth was defined as birth <37 completed weeks of gestation. Infants born at term were categorized as term SGA age if they were below the 10^{th} percentile of the cohort specific curves stratified by duration of gestation, sex and parity.

Statistical methods:

Hazard ratios of preterm birth were estimated by a Cox regression model with gestational age as the underlying time variable. The pregnancies were at risk from the time of enrolment and followed until delivery or 36 weeks and 6 days of pregnancy, whichever occurred first. Estimates for birth weight and term SGA were analysed by linear regression and logistic regression, respectively. All analyses were adjusted for cohort and then additionally for maternal education according to International Standard Classification of Education (ISCED 1997(24)) (short (ISCED 0-2); intermediate (ISCED 3-4); long (ISCED 5)), maternal age at enrolment (<20; 20-24; 25-29; 30-34; 35-40; 40+ years), pre-pregnancy BMI (<18.5; 18.5-25; 25-30; 30+ kg/m^2), smoking (never-smokers; smoking 0-10; 10+ cigarettes/day), parity (0;1+), and immigrant status (yes; no). All linear regression models with birth weight in grams as the outcome variable were additionally adjusted for gestational age.

All analyses were repeated in a sub-sample restricted to first-time pregnancies that were either unintended or conceived within 6 months of trying. Furthermore, the data analyses were stratified by year of delivery (<2000; 2000-2004; ≥ 2005), and in these analyses the highest drinking category was ≥3 drinks in the analyses of preterm birth and term SGA. The categorization of calendar time in these three periods was based

on the range and distribution of year of recruitment in the cohorts, and resulted in respectively 20%, 50% and 30% of the pooled sample in each period. As a sensitivity analysis, the pooled data were reanalysed, excluding one cohort at a time, to examine the impact of cohort heterogeneity. We also examined the influence of including cohort as a random effect rather than only a fixed effect as in the main analyses. Data were analysed with the procedure PROC MIANALYSE in SAS 9.3, and the package ggplot2 in R 3.0.2 was used for plots.

Results

We pooled data on average alcohol drinking during pregnancy from birth cohorts recruited from 1984 to 2011 and representing six countries placed in the Northern-, Central-, and Southern part of Europe, Table 1. The four largest cohorts were from Scandinavia, three Danish and one Norwegian, and these four cohorts constitute 93% of the pooled data. All cohorts collected data on alcohol during pregnancy, but data were collected at different gestational ages in the cohorts.

Table 1. Description of the birth cohorts that contributed to the study of low-to-moderate alcohol drinking and pregnancy outcome, Europe 1984-2011

Cohort name (Acronym)	Aarhus Birth Cohort (ABC)(14)	The Danish National Birth Cohort (DNBC)(15)	Generation R (GenR)(16)	Healthy Habits for two (HHf2)(17)	Environment and Childhood Project (INMA)(18)	The Norwegian Mother and Child Cohort (MoBa)(19)	Nascita e INFanzia: gli Effetti dell'Ambiente (NINFEA)(20)	Endocrine disruptors: longitudinal study on pathologies of pregnancy, infertility and childhood (PELAGIE)(21)	Mother Child Cohort in Crete (RHEA) (22)
Country (Cover area)	Denmark (Aarhus)	Denmark	The Netherlands (Rotterdam)	Denmark (Odense and Ålborg)	Spain (Asturias, Gipuzkoa,	Norway	Italy	France (Brittany)	Greece (Crete)

					Sabadell and Valencia)				
Recruitment period	1998-2007[a]	1996-2002	2002-2006	1984-1987	2004-2008	1999-2008	2005-2011[a]	2002-2005	2007-2009
Timing of recruitment	Prenatal care (16 week)	First prenatal care visit (6-12 weeks)	First prenatal care visit (<18 weeks)	Week 35-38	First prenatal care visit (10-13 weeks)	At ultrasound screening (17-18 weeks)	During entire pregnancy	Prenatal care <19 weeks	First major US examination (< 15 weeks)
Source of delivery information	Medical records	Birth registry data	Medical records	Medical records	Medical records	Birth registry data and self-report	Maternal report	Medical record	Medical records
Method of estimating gestational age[b]	US or LMP if US unavailable	Combination of LMP and US	US	LMP and in 50% verified with US, and corrected if necessary	Combination of LMP and US	US or LMP if US unavailable	US and LMP	Combination of LMP and US	LMP and US
Alcohol questionnaire design	Weekly total intake in categories and drinks[c]	Weekly intake by type in drinks	Weekly total intake in categories	Weekly intake by type in categories	Weekly intake by type in categories	Food frequency questionnaire	Weekly intake by type in categories and drinks[c]	Daily intake by type in categories	Food frequency questionnaire
Scheduled gestational week of collecting alcohol data	12	16	At recruitment	At recruitment	At recruitment	17	At recruitment	At recruitment	At recruitment
Imputed alcohol data	Partly	No	Yes	Yes	Yes	No	Partly	Yes	No
N obtained from cohorts	67 988	86 781	9852	11 144	3742	105 144	2949	3438	960
N used in PTB analysis[d]	20 378	83 544	5628	-[e]	1021	67 491	1978	2996	864
N used in BW analysis	20 446	83 544	5630	9432	1021	67 551	2263	2996	864
N used in SGA analysis[f]	19 412	79 786	5357	9290	994	64 288	2167	2886	780

[a] Recruitment for the ABC and NINFEA cohorts is on-going, but the delivered data sets included the birth year 2007 and 2011, respectively.
[b] US: Ultrasound and LMP: 1 day of Last Menstrual Period
[c] In the ABC and NINFEA cohorts, later questionnaire versions, version 10+ of the ABC questionnaire asked for alcohol intake in drinks rather than in categories.
[d] The analyses of preterm birth were restricted to women who entered the study before 37 completed weeks' gestation.
[e] The HHf2 cohort is excluded from the analyses of preterm birth because of the late recruitment and the pregnancies were not at risk of early preterm birth.
[f] The analyses of small-for-gestational age were restricted to deliveries after 36 completed weeks' gestation.

The average alcohol intake during pregnancy was low; two thirds of the women reported to abstain during pregnancy, and only 7% consumed two or more drinks of alcohol per week, Table 2. The alcohol intake varied between cohorts with the highest proportion of abstainers in MoBa, INMA, and PELAGIE. Drinking more than one drink per week was most common in HHf2, DNBC, ABC and GenR. Less than one third of the included pregnancies were first time pregnancies conceived within 6 months of trying. NINFEA, followed by INMA and GenR, was the cohort with highest proportion of this type of pregnancies. Preterm birth and low birth weight (<2500g) were most common in RHEA with 10% and 5%, respectively, compared to around 3% preterm births in INMA and 3% low birth weight infants in MoBa, which were the cohorts with the lowest proportions of preterm birth and low birth weight children, respectively.

Table 2. Characteristics of study population according to cohort. The characteristics are presented in percentages, except for maternal age and birth weight.

Cohort name	Total		ABC	DNBC	GenR	HHf2	INMA	MoBa	NINFEA	PELAGIE	RHEA
Lifestyle and maternal characteristics		193 747	20 446	83 544	5630	9432	1021	67 551	2263	2996	864
Weekly alcohol intake in drinks[a]	N										
0	127 138	65.6	54.0	55.2	56.0	18.2	87.0	88.4	58.3	85.3	67.7
>0 to <1	31 456	16.2	35.0	15.8	26.0	16.8	6.2	11.2	12.0	.	21.6
1 to <2	21 093	10.9	5.5	17.3	6.9	45.4	3.9	0.3	17.6	5.1	5.4
2 to <3	8312	4.3	3.8	7.2	4.6	9.9	1.4	0.0	6.1	3.9	2.0
3 to <4	2821	1.5	0.9	2.4	1.2	4.3	0.5	0.1	1.8	2.3	1.5
4 to <5	1334	0.7	0.3	1.1	1.8	1.7	0.2	0.0	1.2	1.0	0.3
5 to <6	602	0.3	0.2	0.5	1.1	0.8	.	.	0.5	0.4	0.2
6 to <7	335	0.2	0.0	0.2	0.3	1.0	0.1	0.0	0.8	0.2	.
≥7	656	0.3	0.1	0.3	2.1	1.8	0.8	0.0	1.8	1.7	1.2

Daily smoking in cigarettes											
No	166 060	85.7	89.1	83.6	82.9	61.9	90.1[b]	91.1	92.2	73.1	82.1
<10	16857	8.7	6.7	8.9	14.3	18.4	[b]	6.8	6.0	18.0	16.0
≥ 10	10 830	5.6	4.2	7.5	2.9	19.7	9.9	2.1	1.9	8.9	2.0
Pre-pregnancy BMI											
<18.5	8845	4.6	6.7	4.5	4.5	9.4	5.6	3.1	8.4	7.3	4.6
18.5-25	131 018	67.6	67.5	68.0	67.9	78.3	66.7	65.2	71.8	75.6	63.4
25-30	38 068	19.6	20.1	19.3	18.8	9.3	20.1	21.9	15.2	12.3	20.1
30+	15 816	8.2	5.6	8.2	8.7	3.0	7.6	9.7	4.6	4.8	11.8
Socio-demography											
Maternal age (median)		30.0	30.0	30.0	30.0	27.0	31.0	30.0	33.0	29.0	30.0
Maternal education											
Basic	7642	6.9	8.6	-[c]	26.3	16.0	27.9	2.7	5.1	17.1	19.9
Further	35 688	32.4	23.5	-[c]	31.8	48.7	41.2	31.8	35.4	45.5	49.9
Long	66 873	60.7	67.9	-[c]	41.9	35.3	30.9	65.5	59.5	37.4	30.2
Maternal immigrant status[d]	4609	2.4	11.8	~0	33.1	~0	10.7	~0	4.0	2.1	7.8
Reproductive history											
Primigrav (%)	75 054	38.7	38.8	34.7	45.9	36.5	42.6	42.8	59.5	36.1	33.7
Primiparous (%)	98 989	51.1	49.4	46.9	58.2	49.0	54.5	55.9	76.0	45.3	42.2
Time-to-pregnancy <6 months (%)	148 056	76.4	76.3	73.6	79.1	78.1[e]	80.6[e]	79.7	72.5	69.8	86.1
Planned pregnancy	160 154	82.7	71.5	88.5	67.8	77.4	64.8	80.8	84.1	94.5	56.4
First-time pregnancy with time-to-pregnancy < 6 months	54 682	28.2	28.0	24.1	35.0	27.5[e]	35.7[e]	32.5	42.4	24.5	27.7
Birth outcomes											
Preterm birth (PTB) (<37 weeks)	8787	4.5	5.1	4.5	4.8	1.5[f]	2.6	4.8	4.2	3.7	9.7

Very PTB (<32 weeks)	1084	0.6	0.6	0.6	0.4	0.0	0.0	0.6	0.4	0.5	0.3
Spontaneous preterm birth[g]	4536	2.3	2.8	2.2	2.5	.	0.6	2.8	2.0	.	.
Caesarean section	23 528	12.1	18.3	15.2	11.2	.	17.2	7.1	25.7	16.7	48.7
Birth weight (mean)		3567	3551	3585	3419	3484	3259	3602	3273	3393	3198
Low birth weight (<2500 g)	5813	3.0	3.1	3.0	4.6	2.3	4.1	2.8	4.6	3.1	5.2
Small-for-gestational age[h]	18 554	9.6	7.9	10.0	9.4	9.9	9.8	9.6	9.1	8.9	8.3

[a] Alcohol intake with imputed values for interval censored data. Presented is the first imputation out of five.
[b] In the INMA cohort, smoking was categorized in <10 and ≥10 cigarettes a day, and it was impossible to distinct no smokers from daily smokers.
[c] Maternal education was not available for DNBC. Instead, occupation-based socio-economic status was used as a proxy in the adjusted analyses.
[d] Maternal immigrant status was not available in DNBC, HHf2 and MoBa. Due to the recruitment procedures that almost precluded immigrants due to required language skills, everyone was assumed to be non-immigrants.
[e] In the INMA and HHf2 information on time to pregnancy was only available in categories of 0-6 months and 7+ months.
[f] In the HHf2, women were recruited late in pregnancy and therefore not at risk of early preterm birth.
[g] Spontaneous preterm birth was defined as vaginal preterm birth where delivery was not induced. Spontaneous PTB was only defined when both information on the onset of delivery and caesarean section was available. This information was available for n=178,589.
[h] Infants were categorized as small-for-gestational age if they were below the 10th percentile of the cohort-specific curves stratified by gestational length, sex and parity (nulliparous vs. multiparous).

Women who consumed alcohol during pregnancy were more often smokers and less often obese or overweight. The median age was highest in women drinking four or more drinks per week, and the proportion of first-time pregnancies conceived within six months of trying was highest among the abstainers and women with an intake of <1 drink per week, Table 3.

Table 3. Characteristics of the study population according to weekly alcohol intake in drinks. The characteristics are presented in percentages, except for maternal age.

	Alcohol intake per week [a]									
	Total	**0**	**>0 to <1**	**1 to <2**	**2 to <3**	**3 to <4**	**4 to <5**	**5 to <6**	**6 to <7**	**≥7**
Lifestyle and maternal	193 747	127 138	31 456	21 093	8,312	2,821	1,334	602	335	656

characteristics										
Daily smoking in cigarettes										
No[b]	85.7	87.3	85.7	81.1	81.2	78.0	72.7	68.8	62.1	59.1
<10	8.7	7.9	9.1	10.5	10.6	13.0	13.7	15.6	16.1	17.2
≥ 10	5.6	4.7	5.1	8.4	8.1	9.0	13.6	15.6	21.8	23.6
Pre-pregnancy BMI										
<18.5	4.6	4.5	4.5	5.0	4.7	4.3	4.3	3.8	6.9	6.4
18.5-25	67.6	65.3	69.8	72.9	74.9	76.2	77.5	77.2	74.6	78.0
25-30	19.6	20.7	19.1	16.9	16.2	15.3	14.7	14.3	15.2	12.7
30+	8.2	9.5	6.5	5.2	4.2	4.2	3.4	4.7	3.3	2.9
Socio-demography										
Maternal age (median)	30.0	30.0	31.0	30.0	31.0	31.0	32.0	32.0	32.0	32.0
Maternal education[c]										
Basic	6.9	6.8	5.6	11.3	7.7	9.7	7.8	10.8	9.4	12.6
Further	32.4	32.4	28.2	41.4	35.7	36.2	34.9	33.5	31.5	32.2
Long	60.7	60.8	66.2	47.4	56.6	54.0	57.2	55.7	59.1	55.2
Maternal immigrant status [d]	2.4	2.7	2.5	0.7	1.0	1.1	1.3	1.5	2.7	3.8
Reproductive history										
Primigrav	38.7	41.0	36.7	33.6	31.4	30.3	26.5	28.7	28.7	31.9
Primiparous	51.1	52.7	52.5	45.6	42.9	42.1	39.2	38.2	40.0	42.7
Time-to-pregnancy <6 months[e]	76.4	76.4	77.1	75.9	75.9	77.6	75.6	77.1	73.7	76.4
Planned pregnancy	82.7	82.4	81.0	85.6	86.4	83.6	81.5	81.1	80.3	72.3
First-time pregnancy with time-to-pregnancy < 6 months[e]	28.2	29.9	27.1	24.1	22.4	22.2	19.9	20.3	20.6	22.6

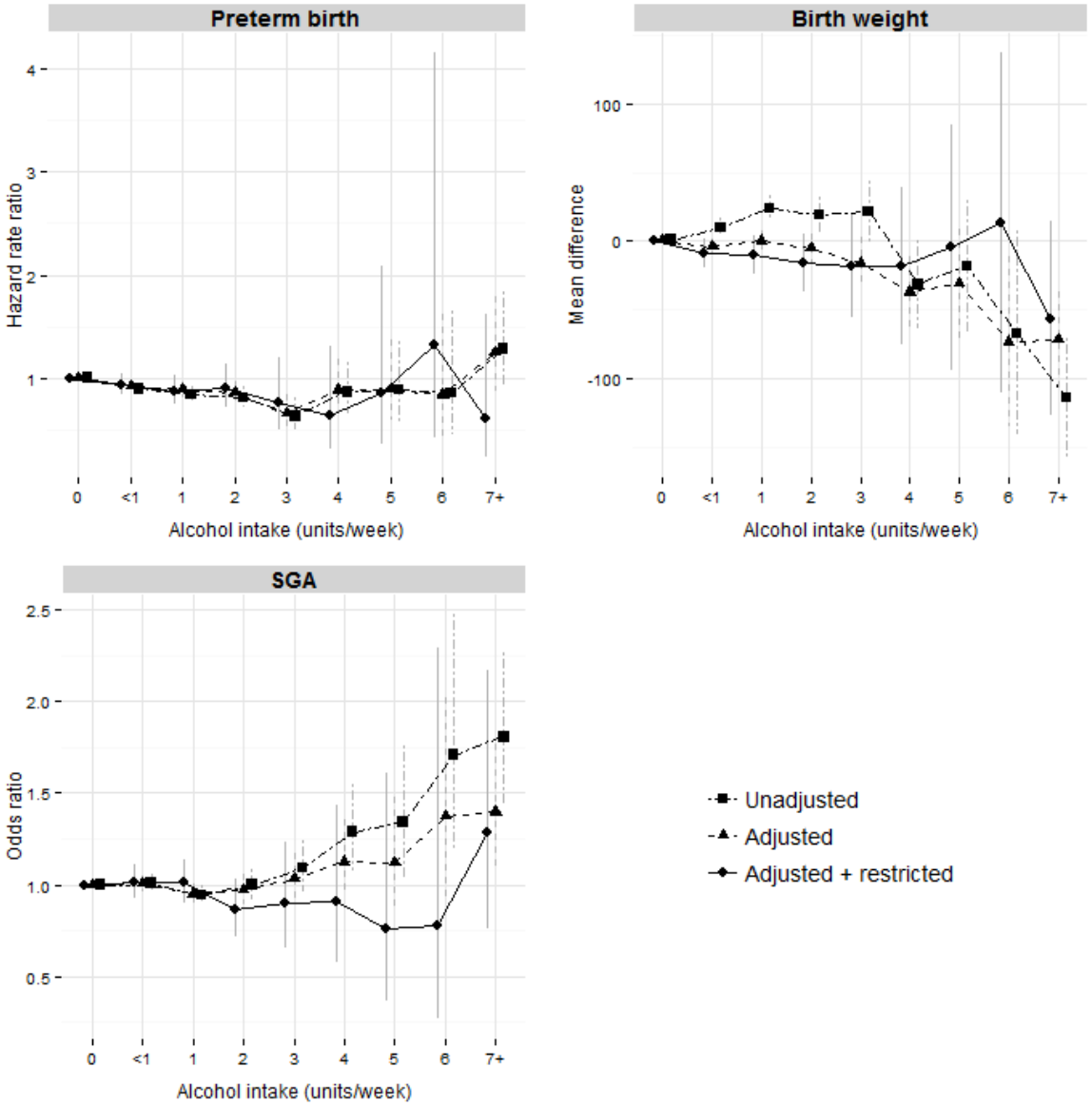
[a] Alcohol intake with imputed values for interval censored data. Presented is the first imputation out of five.

[b] In the INMA cohort, smoking was categorized in <10 and ≥10 cigarettes a day, and it was impossible to distinct no smokers from daily smokers.

[c] Maternal education was not available for DNBC. Instead, occupation-based socio-economic status was used as a proxy in the adjusted analyses.
[d] Maternal immigrant status was not available in DNBC, HHf2 and MoBa. Due to the recruitment procedures that almost precluded immigrants due to required language skills, everyone was assumed to be non-immigrants.
[e] In the INMA and HHf2 information on time to pregnancy was only available in categories of 0-6 months and 7+ months.

Alcohol intake up to three drinks per week was associated with lower hazard ratios for preterm birth compared to abstaining, and women who drank three drinks per week had the lowest hazard ratio (HR) of 0.66 with 95% confidence interval (CI): 0.52; 0.84, Figure 2 and supplementary Table 1. Drinking between four to six drinks per week was also associated with risk estimates below unity, although no longer statistically significantly different from abstaining. Women with an intake of seven or more drinks per week had a hazard ratio for preterm birth of 1.25 (95 % CI: 0.87; 1.79) compared with abstainers. Regarding birth weight, no mean differences were found for intake up to around three drinks per week when compared to abstaining. Tendencies toward reduced birth weight were observed for women with an intake of at least three drinks per week, and birth weight were on average 73 g (95% CI: -135; -11) and 72 g (95% CI: -107; -37) lower in children exposed to six and at least seven drinks per week, respectively. The SGA analyses, as for birth weight, showed that the estimates for intake up to around three drinks per week were close to unity, and thereafter above unity with an OR of 1.40 (95 % CI: 1.10; 1.77) in women with an intake of at least seven drinks per week. Restriction to first-time pregnancies conceived within six months of trying did not consistently change the results, but widened the confidence intervals, and (if anything at all) attenuated the tendencies of detrimental effects of drinking minimum four drinks a week on birth weight and term SGA, respectively (Figure 2). There was evidence for an interaction between alcohol intake and being first time pregnant within six months of trying (yes vs. no) only in the analysis of birth weight ($p < 0.05$), not in the analysis of preterm birth nor term SGA.

Figure 1. Adjusted* hazard ratios for preterm birth, mean differences for birth weight, and odds ratios for Small-for-Gestational-Age (SGA) in term born children according to weekly alcohol intake in pooled data of n=193,747 pregnancies from 9 European birth cohorts



Adjusted for cohort, maternal socioeconomic status/maternal education, maternal age, pre-pregnancy BMI, smoking, parity and immigrant status. Birth weight was additionally adjusted for gestational age. The analyses were restricted to n=54,682 first-time pregnancies conceived within 6 months. In the INMA and HHf2 information on time to pregnancy was only available in categories of 0-6 months and 7+ months.

The reported maternal alcohol intake decreased dramatically across the studied time period. The proportion of abstainers increased from approximately 50% before 2000 to 61% in 2000-2004 and 86% in 2005-2011, Table 4. The association between weekly average alcohol intake and birth weight changed markedly across time, as before 2000, the mean birth weight decreased with increasing intake. In 2000-2004, only intake above three drinks per week was associated with decreased birth weight, and in 2005-2011, the mean birth weight increased with increasing alcohol intake up to an intake of six drinks per week compared with abstaining. For SGA, where the highest intake category was minimum three drinks per week, we observed a similar pattern across the three time periods as drinking two or more drinks was associated with higher OR of SGA before 2000, no difference in 2000-2004 and 2005-2011. No differences over time were observed for preterm birth. Only ABC, DNBC and MoBa contributed to more than one of the calendar periods. The period before 2000 mainly consisted of DNBC and HHf2 data, the period from 2000-2004 DNBC, MoBA, ABC, GenR and PELAGIE, and the latest period again MoBA and ABC, but also the Southern European cohorts; INMA, NINFEA and RHEA.

Table 4. Adjusted[a] hazard ratios for preterm birth, mean differences for birth weight, and odds ratios for Small-for-Gestational-Age (SGA) in term born children according to weekly alcohol intake stratified by birth year. In pooled data of n=193,747 pregnancies from 9 European birth.

	1984-1999[b]		2000-2004[c]		2005-2011[d]	
Weekly alcohol intake in drinks						
Preterm birth	N	HR (95% CI)		HR (95% CI)		HR (95% CI)
0[e]	16 140	1	58,863	1	50,179	1

	(54.7%)		(61.4%)		(85.8%)	
>0 to <1	4972 (16.8%)	0.96 (0.82, 1.11)	17,922 (18.7%)	0.93 (0.86, 1.01)	6899 (11.8%)	0.83 (0.72, 0.94)
1 to <2	4918 (16.7%)	0.9 (0.77, 1.05)	11,021 (11.5%)	0.89 (0.8, 0.98)	818 (1.4%)	0.82 (0.57, 1.17)
2 to <3	2112 (7.2%)	0.9 (0.72, 1.12)	4902 (5.1%)	0.82 (0.7, 0.95)	342 (0.6%)	1.07 (0.63, 1.82)
≥3	1386 (4.7%)	0.78 (0.59, 1.04)	3189 (3.3%)	0.83 (0.69, 1.00)	237 (0.4%)	0.59 (0.27, 1.31)
Birth weight	N	MD (95% CI)		MD (95% CI)		MD (95% CI)
0	17 855 (45.8%)	0	58,897 (61.4%)	0	50,386 (85.7%)	0
>0 to <1	6567 (16.9%)	-11.6 (-24.4, 1.1)	17,945 (18.7%)	-6.5 (-14.2, 1.2)	6,944 (11.8%)	-9.9 (-21.0, 1.3)
1 to <2	9203 (23.6%)	-16.1 (-28.1, -4.1)	11,025 (11.5%)	-0.5 (-10.0, 9.1)	865 (1.5%)	26.3 (-4.4, 57.0)
2 to <3	3045 (7.8%)	-22.5 (-40.5, -4.5)	4,902 (5.1%)	-7.9 (-21.7, 5.9)	365 (0.6%)	57.8 (7.4, 108.2)
3 to <4	1140 (2.9%)	-46.2 (-76.1, -16.2)	1,579 (1.6%)	-8.1 (-31.8, 15.5)	102 (0.2%)	30.4 (-60.5, 121.3)
4 to <5	515 (1.3%)	-66.8 (-108.8, -24.7)	774 (0.8%)	-32.5 (-66.3, 1.3)	45 (0.1%)	72.9 (-93.4, 239.2)
5 to <6	221 (0.6%)	-57.9 (-127.6, 11.8)	357 (0.4%)	-36.4 (-86.5, 13.8)	24 (0%)	121.7 (-59.8, 303.1)
6 to <7	170 (0.4%)	-90.6 (-174.6, -6.5)	145 (0.2%)	-104.2 (-186.9, -21.6)	20 (0%)	218.7 (7.2, 430.2)

≥7	253 (0.6%)	-130.5 (-189.6, -71.3)	335 (0.3%)	-34.8 (-83.0, 13.5)	68 (0.1%)	-51.0 (-152.9, 50.9)
Term SGA	N	OR (95% CI)		OR (95% CI)		OR (95% CI)
0	17 039 (45.5%)	1	55 897 (61.2%)	1	48 027 (85.6%)	1
>0 to <1	6323 (16.9%)	1.01 (0.91, 1.11)	17 105 (18.7%)	1.03 (0.97, 1.09)	6672 (11.9%)	1.01 (0.93, 1.11)
1 to <2	8939 (23.9%)	1.03 (0.94, 1.13)	10 577 (11.6%)	0.92 (0.86, 1)	830 (1.5%)	0.95 (0.73, 1.22)
2 to <3	2943 (7.9%)	1.13 (0.99, 1.3)	4713 (5.2%)	0.92 (0.83, 1.03)	347 (0.6%)	0.64 (0.39, 1.03)
≥3	2233 (6%)	1.28 (1.11, 1.48)	3064 (3.4%)	1.08 (0.96, 1.22)	251 (0.4%)	0.80 (0.51, 1.27)

[a] Adjusted for cohort, gestational age, maternal socioeconomic status/maternal education, maternal age, pre-pregnancy BMI, smoking, parity and immigrant status.
[b] Including data from the following cohorts HHf2 (100%), DNBC (34%), MoBa (0,02%), ABC (7%).
[c] Including data from the following cohorts DNBC (66%) MoBa (31%), ABC (53%), GenR[f](100%), PELAGIE[f] (100%).
[d] Including data from the following cohorts MoBa (69%), ABC (40%), INMA[f](100%), NINFEA (100%), RHEA (100%).
[e] The HHf2 was not included in the analysis of preterm birth, resulting in a changed distribution across calendar time, as 16%, 52% and 32% of the pooled data were in respectively the periods: <2000; 2000-2004; ≥ 2005. The exclusion of HHf2 also resulted in a higher proportion of abstainers before 2000in the analyses of preterm birth.
[f] Information on year of birth was not available. Period of recruitment was 2002 to 2006 for GenR, 2002 to 2005 for PELAGIE and 2004 to 2008 for INMA and these cohorts were categorised in the strata with most overlap with the recruitment period.

A sensitivity analysis, excluding each cohort one at a time, showed that DNBC had a high influence on the results. When DNBC was excluded, we found slightly higher birth weight for infants of women who drank one to two drinks a week compared to abstainers, and birth weight remained on average higher for these intake groups when restricted to first-time pregnancies conceived within six months of trying (data not shown). In contrast,

although MoBa was the largest cohort, the prevalence of drinking during pregnancy was very low, and excluding the MoBa did not influence the results. Including a random effect of cohort in all analyses had negligible impact on the standard errors and p-values.

Discussion

In this European multi-cohort study including almost 200,000 pregnancies we found that compared to abstaining, drinking a maximum of three alcohol drinks per week during pregnancy was associated with reduced risk of preterm birth, while no association was found with birth weight or term SGA. Drinking more than three drinks per week was associated with lower birth weight and slightly higher risk of term SGA, especially among women drinking at least seven alcoholic drinks per week. No difference in risk of preterm birth was observed in women drinking more than three drinks per week compared with abstainers. Restriction to first-time pregnancies conceived within six months of trying had negligible impact on the results, and if anything attenuated the tendencies of detrimental effects on birth weight and SGA of prenatal exposure to more than three drinks per week. Finally, the associations between light-to-moderate drinking and birth weight and SGA changed markedly across calendar period.

Comparison with existing literature and interpretation of the results:

Our findings of reduced birth weight and higher risk of term SGA in children exposed to at least six to seven drinks per week are comparable with the most recent meta-analysis; showing that the risk of low birth weight and SGA increased linearly with every increase in intake after exposure to an average of one drink or more per day. Below this threshold level for alcohol drinking no associations with low birth weight and SGA were observed (2). The same meta-analysis showed that the threshold intake was on average half a drink per day higher for preterm birth, which support our finding of no increased risk of preterm birth, even in the group drinking seven or more drinks per week, as the majority in this category consumed less than

an average of one and a half drinks per day (2). In general findings on light-to-moderate drinking in relation to preterm birth, birth weight and SGA are inconclusive (3), which is supported by our findings of period-specific associations for birth weight and term SGA. In further support of our findings, a systematic review published in 2007 concluded that most existing studies on light-to-moderate drinking in relation to these three outcomes have shown either no association or lower risk in light drinkers compared to abstainers (3). Previously published findings based on HHf2, ABC and DNBC were included in both the meta-analysis and the systematic review, while the findings from GenR were only included in the meta-analysis (25). Recently published results from MoBa on preterm birth are likewise in line with our findings as they find no association with drinking during pregnancy among primi-parous women(26). Alcohol drinking during pregnancy in relation to preterm birth and SGA has furthermore been addressed in two Western-European cohorts, not included in our study, which showed no association with SGA and lower risk of preterm birth (27).

The proportion of women drinking alcohol (any amount) in Europe have recently been shown to be one of the highest worldwide as about one quarter of pregnant women in year 2012 was estimated to drink alcohol in pregnancy (28). This is substantially higher than the drinking prevalence of <15% in 2005-2011 in our pooled sample. The estimation of the European prevalence of drinking during pregnancy was based on country-specific prevalence covering the late 1980s to the late 1990s, and the estimation did not account for reductions across time in prevalence of alcohol drinking during pregnancy, and this might have resulted in a seriously overestimation (29), as our findings indicate a dramatic decline in women drinking any amount of alcohol during pregnancy across time. A similar marked reduction in intake have been shown among Danish pregnant women, as the proportion reporting no alcohol intake during pregnancy increased from 31% in 1998 to 83% in 2013 (30). This marked reduction in drinking during pregnancy over time may also imply that unmeasured characteristics of pregnancy drinkers have changed across time, which could be an explanation for the period-specific associations. Our findings add little weight to the hypothesis that properties related to reproductive experience

account for the apparently beneficial effects of drinking during pregnancy, since restricting the analysis to women without any knowledge of their reproductive ability had negligible impact on the results.

Strengths and limitations:

The present study invited all European birth cohorts with prospectively collected information on light-to-moderate alcohol drinking and analysed individual-level data after developing an analysis plan in collaboration with cohort representatives. In contrast to previously published meta-analyses, our results are not influenced by potentially publication bias, and we were able to reduce some of the between-cohort heterogeneity by harmonizing variables and by using the same adjustment model for all cohorts. In meta-analyses, it is not uncommon to use interval midpoints to harmonize categories but given that alcohol intake is strongly left-skewed, midpoints are unlikely to reflect the true unobserved distribution. We have used interval-imputations to get a better estimate of values within intervals, which make data more comparable across cohorts, and also introduce a more valid variance in the dataset.

Nevertheless, there was important and inevitable between-cohort heterogeneity. A key challenge was that information on alcohol consumption during pregnancy was collected in different ways using different questionnaires addressing different periods of pregnancy. Differences in periods of pregnancy covered, as well as sparse data on timing of drinking limited us from examining effects of windows of exposure or cumulative alcohol exposure during pregnancy. Other differences contributing to the between-cohort heterogeneity were different selection and participation procedures, as well as ways of collecting, registering and cleaning data on other variables included in the analyses. The limited sample size of half of the cohorts, and the low drinking frequency in many of the cohorts made it impossible to address the cohort-specific effects, and thereby evaluate to what extent the results from this pooled analysis of individual level data differed from a meta-analysis of the cohort-specific associations. Including a

fixed effect of cohort impacted the results, but adding a random effect had minor impact on our results. We further approached the cohort heterogeneity by addressing how much the results changed when removing one cohort at a time. The three Danish cohorts, ABC, HHf2 and DNBC, were the ones with the highest proportion of moderate drinkers and omitting the DNBC from the analyses had, due to its size and the proportion of drinking > one drink/week, the largest impact on our findings. On the other hand, leaving out MoBa, the largest cohort, had little influence on the results due to the low prevalence of drinking during pregnancy. Two thirds of the cohorts only contributed to one of the time periods, in the analysis stratified by birth year, which limited the possibilities to disentangle if the period-specific associations were attributable to time-changes of the characteristics of the drinkers or if it is solely caused by differences between the cohorts. However, no matter if the marked variation across time is attributable to between-cohort heterogeneity instead of period-effects, it illustrates that the observed associations are biased and not reflecting the causal effects of low-to-moderate drinking during pregnancy.

We compared proportions of preterm births and low birth weight infants with data from the Peristat 2008 report (31). In general, proportions in each cohort were similar or slightly lower than the national prevalence. Higher socio-economic profile and healthier life style are presumed to explain these differences, as women enrolled in the cohorts have been shown to be healthier and more well-off (32-35). Thus the cohorts are selected samples, but baseline-selection is by definition independent of outcome, and thereby not introducing selection bias in the exposure-outcome associations. However, baseline-selection may impact the confounding pattern, so it is different from the pattern in the source population of each cohort (35). The period-specific associations indicate unmeasured confounding, and thus it is hard to predict whether and how sample selection might have distorted our findings. We applied a complete case analysis, which implied that 15% of the pooled sample was excluded because of no information on gravidity, time to pregnancy, or at least one of the confounders. The proportion with missing on these variables varied between the cohorts and the complete case sample therefore not constitutes a random sample. However, it is unlikely to have introduced bias, as the

missingness in the pooled sample is not expected to be associated with alcohol or any of the outcomes, in addition to the clear cohort heterogeneity we showed in Table 2.

Differential, as well as depended, misclassification is unlikely as information on alcohol was obtained during pregnancy and data on the outcomes were retained from medical records or birth registry records, except in the NINFEA cohort. In this cohort the mothers reported birth weight and gestational age of delivery, which is assumed to be based on the information the mothers received in a booklet when discharged from the hospital.

Conclusion

Our findings of period-specific associations for light-to-moderate drinking during pregnancy in relation to birth weight and term SGA indicate that bias seems to be in play when examining safety levels of drinking during pregnancy. We were unable to separate bias attributable to unmeasured characteristics of the drinkers that might have changed over time and cohort heterogeneity, as few of the cohorts spanned more than one of the periods. Finally, our findings do not support behaviour-modification bias as an important driver for the counterintuitive findings of mildly protective effects of light drinking, which have been shown for several health outcomes.

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Supplementary Table 1. Adjusted[a] hazard ratios for preterm birth, mean differences for birth weight, and odds ratios for Small-for-Gestational-Age (SGA) in term born children according to weekly alcohol intake in pooled data of n=193 747 pregnancies from 9 European birth

Weekly alcohol intake in drinks	Total, adjusted for cohort only		Total, adjusted[a]	Restricted to first-time pregnancies conceived within 6 months[b], adjusted[a]	
Preterm birth[c]	N	HR (95% CI)	HR (95% CI)	N	HR (95% CI)
0	125 182	1	1	37 367	1
>0 to <1	29 793	0.89 (0.84, 0.95)	0.92 (0.87, 0.98)	8008	0.94 (0.84, 1.04)
1 to <2	16 757	0.84 (0.77, 0.91)	0.89 (0.81, 0.96)	3927	0.88 (0.75, 1.03)
2 to <3	7356	0.81 (0.72, 0.92)	0.86 (0.76, 0.97)	1644	0.90 (0.71, 1.13)
3 to <4	2404	0.63 (0.49, 0.80)	0.66 (0.52, 0.84)	506	0.77 (0.49, 1.20)
4 to <5	1168	0.86 (0.65, 1.15)	0.88 (0.66, 1.18)	220	0.64 (0.31, 1.31)
5 to <6	520	0.88 (0.58, 1.35)	0.89 (0.58, 1.36)	103	0.86 (0.35, 2.08)
6 to <7	239	0.86 (0.44, 1.65)	0.84 (0.43, 1.61)	42	1.33 (0.42, 4.16)
≥7	481	1.28 (0.89, 1.84)	1.25 (0.87, 1.79)	117	0.60 (0.22, 1.61)
Birth weight	N	MD (95% CI)	MD (95% CI)	N	MD (95% CI)
0	127 138	0	0	37 996	0
>0 to <1	31 456	10.2 (3.2, 17.3)	-3.9 (-9.6, 1.7)	8510	-8.6 (-19.0, 1.7)
1 to <2	21 093	24.2 (15.3, 33.0)	0.0 (-7.1, 7.2)	5080	-9.9 (-23.7, 3.8)
2 to <3	8312	19.0 (6.0, 32.0)	-5.1 (-15.5, 5.3)	1866	-15.7 (-36.7, 5.4)
3 to <4	2821	21.3 (-1.4, 44.1)	-15.9 (-34.3, 2.6)	626	-18.3 (-55.8, 19.3)
4 to <5	1334	-31.5 (-63.4, 0.5)	-36.9 (-63.2, -10.6)	265	-18.3 (-75.0, 38.5)
5 to <6	602	-18.1 (-65.9, 29.8)	-30.9 (-71.0, 9.2)	122	-4.7 (-93.8, 84.5)
6 to <7	335	-66.8 (-140.7, 7.1)	-73.3 (-135.2, -11.4)	69	13.2 (-110.8, 137.2)
≥7	656	-113.7 (-157.3, -70.2)	-71.6 (-106.7, -36.5)	148	-56.1 (-126.8, 14.7)

Term SGA[d]	N	OR (95% CI)	OR (95% CI)	N	OR (95% CI)
0	120 963	1	1	35 861	1
>0 to <1	30 100	1.01 (0.97, 1.05)	1.00 (0.96, 1.05)	8080	1.01 (0.93, 1.11)
1 to <2	20 346	0.94 (0.89, 1.0)	0.95 (0.90, 1.01)	4878	1.01 (0.90, 1.14)
2 to <3	8003	1.00 (0.92, 1.09)	0.97 (0.89, 1.06)	1773	0.86 (0.72, 1.04)
3 to <4	2744	1.09 (0.96, 1.24)	1.03 (0.91, 1.17)	604	0.90 (0.66, 1.24)
4 to <5	1283	1.29 (1.07, 1.55)	1.13 (0.93, 1.36)	258	0.91 (0.57, 1.44)
5 to <6	579	1.34 (1.03, 1.75)	1.12 (0.85, 1.48)	116	0.76 (0.36, 1.61)
6 to <7	322	1.71 (1.18, 2.48)	1.37 (0.93, 2.02)	65	0.78 (0.27, 2.29)
≥7	620	1.81 (1.44, 2.27)	1.40 (1.10, 1.77)	142	1.28 (0.76, 2.17)

[a] Adjusted for cohort, maternal socioeconomic status/maternal education, maternal age, pre-pregnancy BMI, smoking, parity and immigrant status. Birth weight was additionally adjusted for gestational age.
[b] In the INMA and HHf2 information on time to pregnancy was only available in categories of 0-6 months and 7+ months.
[c] The analyses of preterm birth were restricted to women who entered the study before 37 completed weeks' gestation.
[d] The analyses of small-for-gestational age were restricted to deliveries after 36 completed weeks' gestation.