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Rachel Bakker, Liane E Pluimgraaff, Eric Ap Steegers, Hein Raat, Henning Tiemeier, A Hofman, Vincent Wv Jaddoe

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Associations of light and moderate maternal alcohol consumption with fetal growth characteristics in different periods of pregnancy. The Generation R Study.

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3 **Original article**
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8 Associations of light and moderate maternal alcohol consumption with fetal growth
9 characteristics in different periods of pregnancy. The Generation R Study.
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13
14
15 Rachel Bakker, MSc

16
17 The Generation R Study Group, Erasmus Medical Centre, Rotterdam, the
18 Netherlands, and the Department of Epidemiology, Erasmus Medical Centre,
19 Rotterdam, the Netherlands
20
21
22
23

24 Liane E Pluimgraaff, BSc

25
26 The Generation R Study Group, Erasmus Medical Centre, Rotterdam, the
27 Netherlands and the Department of Epidemiology, Erasmus Medical Centre,
28 Rotterdam, the Netherlands
29
30
31
32

33
34 Eric AP Steegers, MD PhD

35
36 Department of Obstetrics and Gynaecology, Erasmus Medical Centre,
37 Rotterdam, the Netherlands
38
39
40

41 Hein Raat, MD PhD

42
43 Department of Public Health, Erasmus Medical Centre, Rotterdam, the
44 Netherlands
45
46
47

48 Henning Tiemeier, MD PhD

49
50 Department of Child & Adolescent Psychiatry, Erasmus Medical Centre,
51 Sophia Children's Hospital, Rotterdam, the Netherlands, and the Department
52 of Epidemiology, Erasmus Medical Centre, Rotterdam, the Netherlands
53
54
55
56

57 Albert Hofman, MD PhD
58
59
60

1
2
3 Department of Epidemiology, Erasmus Medical Centre, Rotterdam, the
4
5 Netherlands
6

7
8 Vincent WV Jaddoe, MD PhD
9

10 The Generation R Study Group, Erasmus Medical Centre, Rotterdam, the
11
12 Netherlands and the Department of Epidemiology, Erasmus Medical Centre,
13
14 Rotterdam, the Netherlands and the Department of Paediatrics, Erasmus
15
16 Medical Centre, Rotterdam, the Netherlands
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1
2
3 **Corresponding author**
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5 Vincent WV Jaddoe, mail: P.O. Box 2040, 3000 CA Rotterdam, the
6
7
8 Netherlands, phone: +31 (0)10 704 34 05, fax: +31 (0)10 704 46 45, e-mail:
9
10 v.jaddoe@erasmusmc.nl
11
12
13
14

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SUMMARY

Background Excessive alcohol consumption during pregnancy has adverse effects on fetal growth and development. Less consistent associations have been shown for the associations of light to moderate maternal alcohol consumption during pregnancy with health outcomes in the offspring. Therefore, we examined the associations of light to moderate maternal alcohol consumption with various fetal growth characteristics measured in different periods of pregnancy.

Methods This study was based on 7333 pregnant women participating in a population-based cohort study. Alcohol consumption habits and fetal growth were assessed in early (gestational age <17.9 weeks), mid- (gestational age 18 – 24.9 weeks) and late pregnancy (gestational age \geq 25 weeks). We assessed the effects of different categories of alcohol consumption (no; 1 drink per week; 2 to 3 drinks per week; 4 to 6 drinks per week; 1 drink per day, 2 to 3 drinks per day) on repeatedly measured fetal head and abdominal circumference and femur length.

Results In total, 37% of all mothers continued alcohol consumption during pregnancy, of whom the majority used less than 3 drinks per week. We observed no differences in growth rates of fetal head circumference, abdominal circumference, and femur length between mothers with and without continued alcohol consumption during pregnancy. Compared to mothers without alcohol consumption, mothers with continued alcohol consumption during pregnancy had an increased fetal weight gain (difference 0.61 (95% confidence interval: 0.18, 1.04) grams per week). Cross-sectional analyses in mid- and late pregnancy showed no consistent associations between the number of alcoholic consumptions and fetal growth characteristics. All analyses were adjusted for potential confounders.

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3 **Conclusions** Light to moderate maternal alcohol consumption during pregnancy
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5 does not adversely affect fetal growth characteristics. Further studies are needed to
6
7 assess whether moderate alcohol consumption during pregnancy influences organ
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9 growth and function in postnatal life.
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15 **Keywords:** alcohol consumption, fetal growth, pregnancy, cohort study
16

17 **Abbreviations:** SD=Standard Deviation, CI=Confidence Interval, OR=Odds Ratio
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INTRODUCTION

Excessive maternal alcohol consumption during pregnancy is associated with various pregnancy complications such as multiple birth defects [1-5], fetal alcohol syndrome [6, 7] and an increased risk of low birth weight [8, 9]. Less is known about the effects of light to moderate maternal alcohol consumption [10-12]. In general, light to moderate alcohol consumption during pregnancy is considered as one or less alcoholic consumption per day on average.

Previous studies focused on the effects of light to moderate alcohol consumption during pregnancy on birth outcomes have shown inconsistent results [2, 3, 11-16]. Most of these studies did not take the effect of potential confounders such as maternal age, smoking habits, weight, height, educational level, ethnicity, and parity into account [15, 17-20]. Recently, we observed in a population-based cohort among more than 7000 subjects that only an average maternal alcohol consumption of more than one drink per day is associated with the risk of low birth weight [21]. To our knowledge, no previous studies focused on the associations of light and moderate maternal consumption with fetal growth characteristics in different trimesters in a population-based prospective cohort design. Such studies would also be able to identify specific critical periods for fetal growth and development.

Therefore, we examined the associations of light to moderate maternal alcohol consumption with fetal growth characteristics measured in different periods of pregnancy. The study was conducted in a population-based prospective cohort among 7333 mothers followed from early pregnancy onwards.

METHODS AND MATERIALS

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life until young adulthood [22, 23]. The cohort includes 9778 mothers and their children of different ethnicities living in Rotterdam, The Netherlands and has been described in detail previously [22, 23]. Our aim was to enrol women at the routine fetal ultrasound examination in early pregnancy (gestational age <17.9 weeks) but enrolment was allowed until birth of the child. Assessments in pregnancy, including physical examinations, fetal ultrasound examinations, and questionnaires, were planned in early pregnancy (gestational age <17.9 weeks), mid-pregnancy (gestational age 18 – 24.9 weeks) and late pregnancy (gestational age ≥25 weeks). The individual timing of these assessments depended on the gestational age at enrolment [22, 23]. The median gestational ages of the early, mid- and late pregnancy measurements for the present study were 13.4 (95% range 9.8 - 17.6), 20.5 (95% range 18.5 – 23.6), and 30.4 (95% range 28.4 – 32.8) weeks, respectively. All children were born between April 2002 and January 2006. Of the total eligible children born in the study area during the enrolment period, 61% was enrolled in the Generation R Study [23]. The Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam, has approved the study. Written informed consent was obtained from all participants.

Maternal alcohol consumption

Information about maternal alcohol consumption was obtained by postal questionnaires in early, mid-, and late pregnancy [23]. Response rates for these questionnaires were 91%, 80%, and 77%, respectively. In the first questionnaire, the

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3 mothers were asked whether they used any alcoholic drinks in the first three months
4 of pregnancy (no; until pregnancy was known; continued after pregnancy was
5 known). This questionnaire was sent to all mothers, including those enrolled after
6 early pregnancy. In the second and third questionnaires, sent in mid- and late
7 pregnancy, respectively, the mothers were asked whether they drank any alcohol in
8 the past two months (no; yes). Of the mothers who reported in the first questionnaire
9 drinking only until pregnancy was known (n = 1974), those who reported alcohol
10 consumption in the second or third questionnaire (n = 988), were reclassified into the
11 'continued after pregnancy was known' category. The same strategy was used for
12 mothers who reported no alcohol use in the first questionnaire (n = 4174) but who
13 reported drinking in the second or third questionnaire (n = 535). This strategy led to
14 the following groups of alcohol consumption; no alcohol consumption (n=3639),
15 alcohol consumption until the pregnancy was known (n=986), and continued alcohol
16 consumption (n=2708). Mothers who reported any drinking were asked to classify
17 their average alcohol consumption into one of the following six categories: <1 per
18 week; 1 to 3 per week; 4 to 6 per week; 1 per day; 2 to 3 per day; >3 per day. In the
19 Netherlands, the average alcoholic drink (one glass) contains about 12 g of alcohol
20 [24]. Only 12 mothers used more than three alcoholic drinks per day in early
21 pregnancy. In mid- and late pregnancy none of the mothers drank more than three
22 alcoholic drinks per day. In a separate question we asked the mothers to report
23 whether they had drank more than 6 drinks in one day but these numbers were small
24 (n=23 in mid-pregnancy; n=22 in late pregnancy).

57 **Fetal growth characteristics**

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3 Fetal ultrasound examinations were carried out at the research centres in early, mid-,
4
5 and late pregnancy. These fetal ultrasound examinations were used for both
6
7 establishing gestational age and assessing fetal growth characteristics [23].
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10 Gestational age was established by fetal ultrasound examination because using the
11
12 last menstrual period has several limitations, including the large number of women
13
14 who do not know the exact date of their last menstrual period or have irregular
15
16 menstrual cycles [25-27]. Pregnancy dating curves were constructed for subjects with
17
18 complete data on gestational age measured by ultrasonography and the last
19
20 menstrual period [28]. Crown-rump length was used for pregnancy dating up to a
21
22 gestational age of twelve weeks and five days (crown-rump length less than 65 mm),
23
24 and biparietal diameter was used for pregnancy dating thereafter (gestational age
25
26 from twelve weeks and five days onwards, biparietal diameter more than 23 mm) [28].
27
28 Early pregnancy measurements were primarily used to establish gestational age and
29
30 therefore not included in the growth analyses. Growth characteristics were measured
31
32 to the nearest millimeter using standardized ultrasound procedures [29]. Estimated
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34 fetal weight was calculated using the formula of Hadlock with parameters head
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36 circumference, abdominal circumference and femur length [30]. Longitudinal growth
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38 curves were constructed for all fetal growth measurements [28].
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48 **Covariates**

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50 Information about educational level, ethnicity and parity was obtained by a
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52 questionnaire at enrolment in the study. Maternal smoking habits were assessed in
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54 each questionnaire. Maternal distress was assessed by a questionnaire at 20 weeks
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56 of gestation using the Brief Symptom Inventory [31]. Maternal anthropometrics,
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58 including height and weight, were measured without shoes and heavy clothing during
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3 visits at the research centre at enrolment. Date of birth and gender were obtained
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5 from midwife and hospital registries.
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10 **Population for analysis**

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12 In total 8880 mothers were enrolled during pregnancy [23]. Those without information
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14 about alcohol consumption during pregnancy in the first questionnaire were excluded
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16 from the analyses (14%, n = 1241). For the present study, we excluded subjects
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18 without fetal growth data in mid- or late pregnancy and twin pregnancies (n = 190). Of
19
20 the remaining 7449 mothers, those pregnancies leading to fetal deaths (n = 46),
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22 missing birth outcomes (n = 69) or with a delivery less than 25 weeks of gestation (n
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24 = 1) were excluded, since our interest was in low-risk singleton pregnancies. In our
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26 population for analysis, we had 397 mothers with two pregnancies, and 4 mothers
27
28 with three pregnancies. Since, no differences in results were observed between
29
30 associations with and without these second and third pregnancies, we included them
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32 in the analyses. The associations of maternal alcohol consumption during pregnancy
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34 with longitudinally measured fetal growth characteristics were analyzed in the
35
36 remaining 7333 mothers (Figure 1). Analyses focused on the effects of alcohol
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38 consumption levels in mid- and late pregnancy were performed in mothers who were
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40 enrolled in early pregnancy (n = 5612) only, leading to 4836 (86%) and 4654 (83%)
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42 subjects for mid- and late pregnancy, respectively.
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51 **Data analysis**

52 **Fetal growth**

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55 The associations between alcohol consumption during pregnancy and fetal growth
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57 characteristics were analyzed using unbalanced repeated-measurements regression
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2
3 analysis assuming random effects for the intercept and slope. These regression
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5 models enable studies on repeatedly measured outcomes, taking account for the
6
7 correlation between measurements and have an optimal use of available data. Both
8
9 gestational age independent (difference constant over time) and gestational age
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11 dependent (difference not-constant over time) effects were assessed. We used
12
13 unstructured covariance models. First, we constructed best fitting models using
14
15 second-degree fractional polynomials of gestational age [32]. These models have
16
17 been described in detail previously [33]. The best fitting fractional polynomial curves
18
19 were chosen by comparing the deviances and checking the goodness of fit (smallest
20
21 -2 log likelihood). Subsequently, the correctness of the model was assessed by
22
23 plotting the SD scores against gestational age. Second, we included alcohol
24
25 consumption during pregnancy (none; until pregnancy was known; continued after
26
27 pregnancy was known) to these models as additional intercept as interaction with
28
29 gestational age. The interactions of alcohol consumption with gestational age were
30
31 tested with each separate polynomial. Any significant interaction was subsequently
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33 included in the final model for analyses. The final models including gestational age
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35 and alcohol consumption (alcohol) can be written as:

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46 Head circumference = $\beta_0 + \beta_1 * \text{alcohol} + \beta_2 * \text{gestational age}^2 + \beta_3 * \text{alcohol} * \text{gestational}$
47
48 $\text{age}^2 + \beta_4 * \text{gestational age}^2 * \ln(\text{gestational age}) + \beta_5 * \text{alcohol} * \text{gestational}$
49
50 age .

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53 Abdominal circumference = $\beta_0 + \beta_1 * \text{alcohol} + \beta_2 * \text{gestational age}^2 + \beta_3 * \text{gestational}$
54
55 $\text{age}^2 * \ln(\text{gestational age}) + \beta_4 * \text{alcohol} * \text{gestational}$
56
57 age .

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60 Femur length = $\beta_0 + \beta_1 * \text{alcohol} + \beta_2 * \text{gestational age}^3 + \beta_3 * \text{alcohol} * \text{gestational age}^3$.

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Estimated fetal weight = $\beta_0 + \beta_1 * \text{alcohol} + \beta_2 * \text{gestational age}^{-2} + \beta_3 * \text{gestational age}^{-2} * \ln(\text{gestational age}) + \beta_4 * \text{gestational age}^{-2} * \ln(\text{gestational age})^2 + \beta_5 * \text{alcohol} * \text{gestational age}$.

In these models, ' β_0 ' reflects the intercept and ' $\beta_1 * \text{alcohol}$ ' tests the difference in intercept between alcohol groups. The other beta's (β_2 β_4 β_5), reflect the linear or non linear slope (interaction alcohol consumption with gestational age). These terms test whether the polynomial curves are parallel (whether the groups grow at the same rate as compared to the reference group (no alcohol consumption) between the time points. The main interest for this paper is the beta's which include an interaction with alcohol consumption. Subsequently, we used these models to estimate the estimated differences in fetal growth characteristics between alcohol categories. For all analyses, the unexposed fetus (no maternal alcohol consumption) was used as reference group. We adjusted the models for the following confounders; maternal age, weight, height and distress (all continuous) and smoking, educational level, ethnicity, parity, and infant gender (all categorical) [11]. Analyses were repeated in Dutch and other European mothers only. Since we found similar results, these associations were not presented separately. All levels of association are presented with their 95% confidence intervals. Analyses were performed using the Statistical Analysis System version 8.2 (SAS, Institute Inc. Gary NC, USA), including the Proc Mixed module for unbalanced repeated-measurements.

Dose-response

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3 Dose-response analyses in mid- and late pregnancy were performed using multiple
4 linear regression models. In these analyses also the unexposed fetus (no maternal
5 alcohol consumption) was used as reference group. We adjusted the models for the
6 following confounders; maternal age, weight, height and distress (all continuous) and
7 smoking, educational level, ethnicity, parity, and infant gender (all categorical) [11]. A
8 small proportion of mothers participating in this study had a regular menstrual cycle
9 (28±4 days) and a known and reliable gestational age based on last menstrual period
10 (n=1796). We repeated the analyses focused on the dose-response associations of
11 maternal alcohol consumption in mid- and late pregnancy in this group of women, to
12 exclude underestimation of the effects by ultrasound dating. Tests for trends were
13 performed by using the alcohol consumption categories as continuous variables in
14 the models. All levels of association are presented with their 95% confidence
15 intervals. Analyses were performed using the Statistical Package of Social Sciences
16 version 15.0 for Windows (SPSS Inc, Chicago, IL, USA).
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RESULTS

Subject characteristics

As shown in Table 1, of all mothers, 50% (n=3639) did not use alcoholic drinks in pregnancy, 13% (n = 986) stopped alcohol consumption after their pregnancy was known and 37% continued alcohol consumption during pregnancy (n = 2708). Age of the mothers in the whole cohort ranged from 15.3 to 46.3 years and was significantly higher in mothers who continued alcohol consumption after pregnancy was known compared to mothers who did not use alcohol during pregnancy. The percentages of high educated and Dutch or other European mothers were highest among those who continued alcohol consumption. Of all pregnancies, 5.5% (n = 401) were second or third pregnancies in the study. Since, no differences in results were observed between associations with and without these second and third pregnancies, we included them in the analyses. Mean birth weight of the children was 3417 (95% range 635 – 5310) grams. Gestational age at birth ranged from 25.3 to 43.6 weeks with a median of 40.1 weeks. Of all singleton live births, 5.0% were born before a gestational age of 37 weeks. Analyses were repeated in Dutch and other European mothers only. Since we found similar results, these associations were not presented separately.

Fetal growth

The derived fetal growth curves and estimates for the interactions terms of alcohol with each fractional polynomial for the different fetal growth characteristic are given in the supplement (Figure S1 and Table S1, respectively). Figure 2 shows the associations between maternal alcohol consumption categories with estimated differences in fetal growth characteristics (head circumference, abdominal

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3 circumference, femur length, estimated fetal weight) between the gestational ages of
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5 18 and 35 weeks. Except for estimated fetal weight, these associations were not
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7 significant after adjusting for potential confounders (Table S1). Compared to mothers
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9 without alcohol consumption, mothers with continued alcohol consumption during
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11 pregnancy had an increased fetal weight gain (difference 0.61 (95% CI: 0.18, 1.04)
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13 grams per week).
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20 **Dose-response**

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22 Table 2 showed an association between using one to three drinks per week with
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24 abdominal circumference (increase of 1.02 mm (95% CI: 0.11, 1.92) compared to no
25
26 drinking) in mid-pregnancy. Drinking four to six drinks per week was associated with
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28 a shorter femur length (-0.63 mm (95% CI: -1.15, -0.11)) in mid-pregnancy. After
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30 adjustment for potential confounders, no associations of alcohol consumption with
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32 fetal growth characteristics in mid-pregnancy remained significant. Also, no
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34 significant trends were found. Table 3 shows that in late pregnancy, no significant or
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36 consistent effects of alcohol consumption during pregnancy on any fetal growth
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38 characteristic was observed. We observed no consistent differences between
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40 analyses on the whole cohort using ultrasound for pregnancy dating and subgroup
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42 with pregnancy dating on last menstrual period (see supplementary Tables S2 and
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44 S3).
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DISCUSSION

This population-based prospective cohort study showed no associations of light to moderate maternal alcohol consumption during pregnancy with longitudinally measured fetal head or length growth. Mothers who continued alcohol consumption during pregnancy tended to have an increased fetal weight gain. No consistent associations were observed for the associations between number of alcoholic consumptions and any fetal growth characteristics in different periods of pregnancy.

Methodological considerations

The strength of this study is the large number of subjects in a prospectively studied cohort. To our knowledge, this is the largest study focused on light to moderate alcohol consumption during pregnancy on fetal growth characteristics in different periods of pregnancy. We were also able to control for many possible confounders. A potential limitation of this study is the missing data on alcohol consumption. No differences in maternal age at enrolment, height and birth weight of the offspring were observed between those with and without information about alcohol consumption. Missing information about alcohol consumption might have led to loss of power. The associations might be underestimated if among mothers without alcohol data the percentage of alcohol consumers would be higher than among mothers without missing alcohol data. However, this seems unlikely since no differences in characteristics between those with and without alcohol consumption data were observed. Among mothers with information about alcohol consumption, we had a limited loss-to-follow-up. Therefore, we do not expect biased results due to loss-to-follow-up [33].

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3 Information on alcohol consumption habits during pregnancy was collected by
4 postal questionnaires. If any, misclassification would be most likely due to
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6 underreporting and subsequently lead to underestimation of differences between
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8 those not using and using alcoholic consumptions. Previous studies suggested use
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10 of biomarkers of alcohol consumption such as carbohydrate-deficient transferrin and
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12 gamma-glutamyl transferase. However, currently these biomarkers have a low
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14 sensitivity in subjects with light to moderate alcohol consumption [34]. In our study
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16 we had only information about the average number of alcoholic drinks per week,
17
18 without information on drinking patterns. Our estimation of the amount of alcohol per
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20 consumption might be imprecise since both alcohol percentages and serving sizes
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22 may differ between mothers.
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29 Gestational age was established by fetal ultrasound examination. This method
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31 seems to be superior to use of the last menstrual period [24]. The major
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33 disadvantage of establishing gestational age by ultrasonography is that the growth
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35 variation of the fetal characteristics used for pregnancy dating is assumed to be zero.
36
37 Therefore, in our study, crown-rump length and biparietal diameter were used for
38
39 pregnancy dating but not for assessing fetal growth [25, 26]. Since pregnancy dating
40
41 characteristics and growth characteristics are correlated throughout pregnancy,
42
43 growth variation in head circumference, abdominal circumference, and femur length
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45 may be reduced by dating the pregnancy on the other fetal characteristics. This may
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47 have led to underestimation of our effect estimates. However, we expect this effect to
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49 be small in our results. First, the longitudinal analyses were focused on fetal growth
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51 or change in size during pregnancy within individuals. This change in size is unlikely
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53 to have been materially affected by our pregnancy dating method. Second, the
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55 analyses assessing the associations of maternal alcohol consumption with fetal
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3 growth characteristics in mid- and late pregnancy were restricted to mothers who
4 were enrolled and had their pregnancies dated in early pregnancy (76.5 % of the
5 population for analysis). Since gestational age and fetal growth were not established
6 concurrently, we believe that we minimized the effect of pregnancy dating on growth
7 variation. Our analysis in a subgroup of mothers with pregnancy dating on their last
8 menstrual period, did not show consistent stronger effects. However, results based
9 the last menstrual period shown in Table S2 tended to show larger differences than
10 that in Table 2. This might be due to some underestimation of the main results due to
11 correlation between ultrasound dating and growth characteristics.
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27 **Maternal alcohol consumption and fetal growth characteristics**

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29 Previous studies focused primarily on the associations between maternal alcohol
30 consumption during pregnancy and birth weight and showed inconsistent
31 associations [2, 8, 12-18, 21]. Smaller studies assessing the effect of maternal
32 alcohol consumption during pregnancy on fetal growth retardation [18, 35] also
33 showed inconsistent results. Windham et al. [18] showed an association of moderate
34 maternal alcohol consumption with an increased risk of fetal growth retardation (odds
35 ratio (OR) = 2.3, 95% CI: 1.2, 4.6) while Yang et al. [35] showed no effect of
36 moderate alcohol consumption on fetal growth retardation. Most studies used low
37 birth weight or fetal growth retardation as outcome measurement and showed
38 conflicting results. Moreover, most of these studies did not adjust for potential
39 confounders [8, 15, 17-20]. Examining fetal growth characteristics instead of birth
40 weight enables identification of specific critical periods during pregnancy for the
41 exposure on various patterns of fetal growth and development.
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3 In 2006, Handmaker et al. [36] examined the effect of maternal alcohol
4 consumption during pregnancy on fetal growth characteristics. This study, comprised
5 of 167 subjects, showed an association between heavy drinking and the ratio of head
6 circumference and abdominal circumference. However, no adjustments were made
7 for potential confounders. We did not find any consistent effects of moderate
8 maternal alcohol consumption on fetal growth characteristics. However, studies in
9 larger numbers of subjects might be able to identify smaller effects. Differences in
10 results from the cross-sectional analyses compared to the repeated measurement
11 analysis can be explained by less power and smaller numbers in the alcohol
12 consumption groups in the cross-sectional analyses. From our results, it seems that
13 any trend for positive associations between alcohol consumption during pregnancy
14 and fetal growth characteristics is explained by socio-demographic and life style
15 related variables. After adjustment, none of the positive associations remained
16 significant. Other potential confounders that might be important include dietary habits
17 and folate acid supplementation [37]. However, including maternal folic acid use in
18 early pregnancy into the current analyses did not have an effect on our findings (data
19 not shown).
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43 Previous studies also suggested effects of maternal alcohol consumption on
44 postnatal growth and development. It was shown that the rate of postnatal growth is
45 reduced in children who were prenatally exposed to alcohol. Weight, length and head
46 circumference were negatively affected by alcohol exposure during pregnancy [38].
47 However, a more recent study showed that moderate maternal alcohol consumption
48 during pregnancy was not associated with either weight or head circumference at the
49 age of five years [20]. Also, inconsistent results were found on behavioural
50 development and cognitive processing in children prenatally exposed to alcohol [39,
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3 40]. A study of Faden et al. [41] showed a higher activity level, a greater difficulty in
4 following instructions and have eating problems among offspring exposed to alcohol
5 during pregnancy. Furthermore, binge drinking during pregnancy was shown to be
6 associated with increased odds for the appearance of psychiatric disorders [1]. Our
7 study was focused on the effects of light and moderate maternal alcohol
8 consumption. We also asked the mothers if they drank occasionally more than 6
9 glasses of alcohol in one day (yes; no), which is considered as binge drinking. In
10 total, 23 mothers in mid-pregnancy and 22 mothers in late pregnancy reported that
11 they drank occasionally more than 6 glasses of alcohol in one day. No differences in
12 fetal growth were observed between binge drinking and non-drinking mothers (data
13 not shown), however, future studies with more power are needed for this analysis.
14 Although, previous studies did not show consistent associations either of binge
15 drinking during pregnancy with several outcomes, except for neurodevelopmental
16 outcomes [8], future studies with larger numbers are needed. Whether light to
17 moderate alcohol consumption in this or any other cohort is related to postnatal
18 growth and development needs to be examined in follow-up studies. The effects of
19 alcohol consumption are dependent of the absorption and metabolism in the mother
20 and fetus. This may be partially genetically determined. Therefore, the effects of
21 alcohol consumption in specific groups of women should still be studied.
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50 **Conclusion**

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52 Our results suggest that in a Western population-based cohort moderate maternal
53 alcohol consumption during pregnancy does not adversely affect fetal growth. Future
54 studies are needed to examine whether the effects differ among subjects with
55 different absorption and metabolism patterns and to examine the effects on organ
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3 growth and function in postnatal life. Furthermore, studies are needed in developing
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5 countries or populations with different nutritional status. Also, we had small numbers
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7 of women using more than 2 alcoholic consumptions per day. Results for these
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9 groups should be interpreted carefully.
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41 Rotterdam.
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TABLE 1. Maternal characteristics according to alcohol consumption during pregnancy category (n = 7333 mothers)

	No alcohol consumption n=3639	Alcohol consumption until the pregnancy was known n=986	Continued alcohol consumption n=2708
Age (years)	28.4 (5.3)	29.5 (5.2)**	31.6 (4.7)**
Height (cm)	165.5 (7.3)	168.1 (7.1)**	169.6 (6.9)**
Weight at enrolment (kg)	70.0 (14.4)	68.6 (12.9)**	69.0 (11.8)**
Parity ≥ 1 (%)	46.1	30.6**	43.3*
Education (%)			
Primary school	17.8	4.5**	5.2**
Secondary school	56.6	50.2**	32.5**
Higher education	25.6	45.3**	62.3**
Ethnicity (%)			
Dutch and other-European	41.1	68.6**	76.0**
Surinamese	10.4	11.1	6.5**
Turkish	16.5	1.7**	1.7**
Moroccan	12.8	0.4**	0.6**
Other	19.2	18.2	15.2**
Smoking (%)			
No smoking in pregnancy	79.5	66.2**	71.1**
Smoking until pregnancy was known	4.3	16.7**	10.4**
Continued smoking in pregnancy (%)	16.2	17.1	18.5*
Maternal stress, index [#]	0.19 (0.00, 1.25)	0.15 (0.00, 1.01)	0.13 (0.00, 0.85)
First child of same mother in study (%)	96.0	94.3*	92.6**
Enrolment in study in early pregnancy (%)	71.0	84.4**	81.1**
Ultrasonography for fetal growth (%)			
Mid-pregnancy	93.5	97.4**	96.5**
Late pregnancy	96.5	96.8	97.6**
Birth outcomes			
Birth weight (g)	3396 (552)	3354 (571)*	3468 (559)**
Gestational age (wk) [#]	40.0 (36.9-42.0)	40.0 (36.5-42.0)	40.3 (37.1-42.1)**
Gender (% boys)	49.7	51.5	51.0

* $P < 0.05$, ** $P < 0.01$

[#] Median (90% range)

Values are means (standard deviation) or percentages unless listed otherwise.

Differences in maternal characteristics (compared with the no alcohol consumption category) were evaluated using independent-sample t tests for continuous variables and chi-squared tests for proportions.

Data were missing on height (n=12), weight (n=28), body mass index (n=39), parity (n=11), educational level (n=151), ethnicity (n=36), smoking (n=65), maternal stress (n=1461), and first child of same mother in study (n=7).

TABLE 2. Dose-response associations between maternal alcohol consumption during pregnancy and fetal growth characteristics in mid-pregnancy (18 – 24.9 weeks) (n = 5612 mothers)

Difference in head circumference (mm)			
Alcohol consumption	Number of subjects	Crude	Adjusted
None	n=3081	<i>Reference</i>	<i>Reference</i>
< 1 drink/week	n=1235	-0.00 (-0.41, 0.40)	-0.31 (-0.74, 0.12)
1 to 3 drinks/week	n=327	0.50 (-0.20, 1.20)	0.32 (-0.40, 1.04)
4 to 6 drinks/week	n=43	-0.10 (-1.94, 1.74)	-0.08 (-1.98, 1.81)
1 drink/day	n=19	0.92 (-1.84, 3.68)	1.33 (-1.36, 4.02)
2 to 3 drinks/day	n=3	5.14 (-1.79, 12.08)	6.77 (-0.01, 13.55)
		$P_{\text{trend}} = 0.21$	$P_{\text{trend}} = 0.59$
Difference in abdominal circumference (mm)			
Alcohol consumption	Number of subjects	Crude	Adjusted
None	n=3092	<i>Reference</i>	<i>Reference</i>
< 1 drink/week	n=1237	-0.01 (-0.52, 0.53)	-0.54 (-1.10, 0.02)
1 to 3 drinks/week	n=329	1.02* (0.11, 1.92)	0.54 (-0.40, 1.48)
4 to 6 drinks/week	n=41	-1.70 (-4.14, 0.75)	-2.11 (-4.64, 0.43)
1 drink/day	n=19	2.29 (-1.29, 5.86)	1.97 (-1.54, 5.48)
2 to 3 drinks/day	n=3	6.02 (-2.96, 15.00)	5.88 (-2.95, 14.71)
		$P_{\text{trend}} = 0.13$	$P_{\text{trend}} = 0.94$
Difference in femur length (mm)			
Alcohol consumption	Number of subjects	Crude	Adjusted
None	n=3088	<i>Reference</i>	<i>Reference</i>
< 1 drink/week	n=1235	-0.01 (-0.21, 0.02)	-0.03 (-0.15, 0.10)
1 to 3 drinks/week	n=329	-0.05 (-0.25, 0.15)	0.00 (-0.21, 0.21)
4 to 6 drinks/week	n=43	-0.63* (-1.15, -0.11)	-0.36 (-0.91, 0.19)
1 drink/day	n=19	-0.48 (-1.26, 0.30)	-0.53 (-1.31, 0.25)
2 to 3 drinks/day	n=3	-0.42 (-2.39, 1.55)	-0.26 (-2.22, 1.69)
		$P_{\text{trend}} < 0.05$	$P_{\text{trend}} = 0.26$
Difference in estimated fetal weight (grams)			
Alcohol consumption	Number of subjects	Crude	Adjusted
None	n=3078	<i>Reference</i>	<i>Reference</i>
< 1 drink/week	n=1228	-0.80 (-3.44, 1.85)	-1.98 (-4.82, 0.86)
1 to 3 drinks/week	n=329	4.17 (-0.38, 8.71)	3.29 (-1.46, 8.04)
4 to 6 drinks/week	n=41	-10.04 (-22.36, 2.28)	-9.78 (-22.59, 3.04)
1 drink/day	n=19	4.94 (-13.09, 22.97)	3.07 (-14.65, 20.78)
2 to 3 drinks/day	n=3	23.98 (-21.31, 69.28)	25.55 (-19.05, 70.14)
		$P_{\text{trend}} = 0.54$	$P_{\text{trend}} = 0.97$

* $P < 0.05$. Values are regression coefficients (95% confidence interval) and reflect the difference for each growth characteristic.

Crude model: adjusted for gestational age. Adjusted model: Crude model + maternal age, weight, height, smoking, distress, educational level, ethnicity, parity, and infant gender.

P-values for trend were based on multiple linear regression models with alcohol consumption categories as a continuous variable.

TABLE 3. Dose-response associations between maternal alcohol consumption during pregnancy and fetal growth characteristics in late pregnancy (≥ 25 weeks) (n = 5612 mothers)

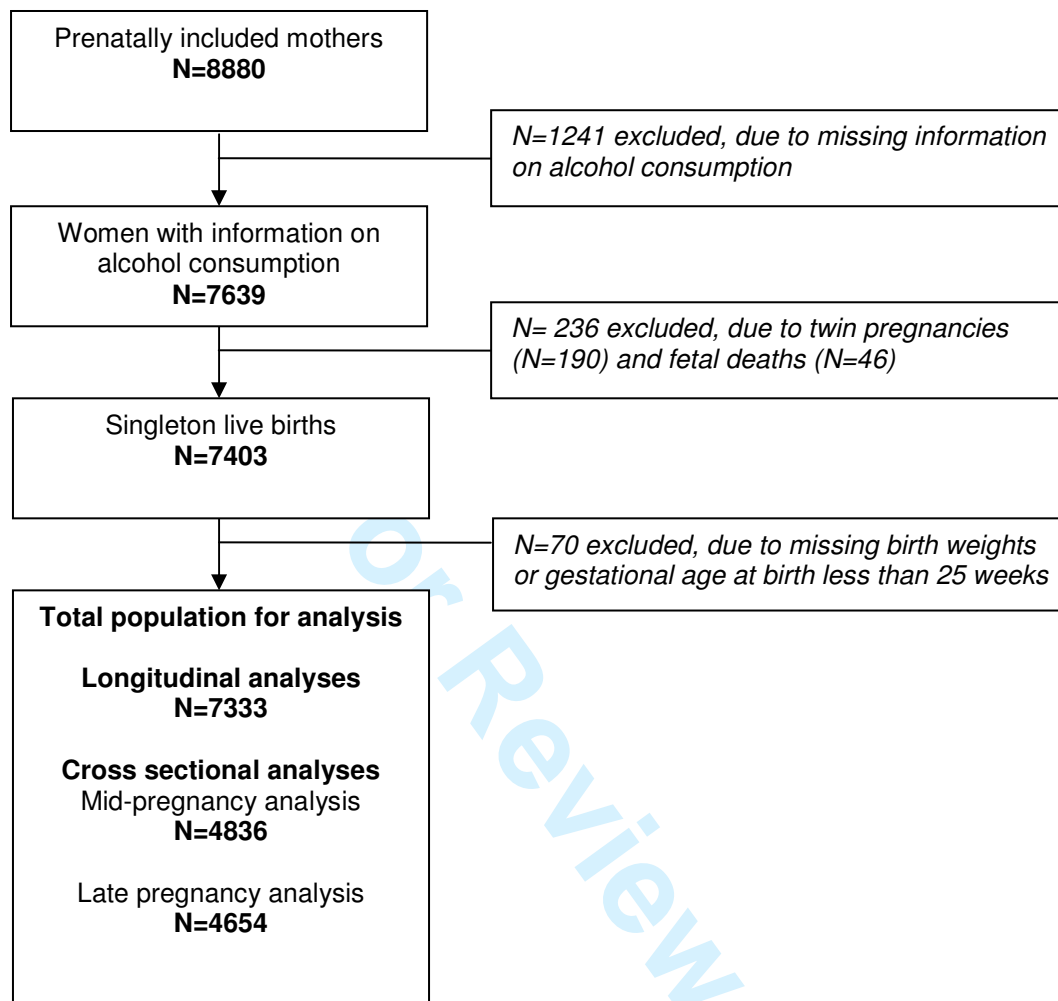
Difference in head circumference (mm)			
Alcohol consumption	Number of subjects	Crude	Adjusted
None	n=2890	<i>Reference</i>	<i>Reference</i>
< 1 drink/week	n=1227	0.73* (0.11, 1.34)	-0.37 (-1.04, 0.30)
1 to 3 drinks/week	n=396	1.48** (0.50, 2.45)	0.28 (-0.74, 1.30)
4 to 6 drinks/week	n=43	-0.53 (-3.32, 2.27)	-0.76 (-3.65, 2.12)
1 drink/day	n=16	-1.45 (-6.00, 3.11)	-2.74 (-7.23, 1.74)
2 to 3 drinks/day	n=4	1.41 (-7.68, 10.50)	1.64 (-8.33, 11.62)
		$P_{\text{trend}} < 0.01$	$P_{\text{trend}} = 0.61$
Difference in abdominal circumference (mm)			
Alcohol consumption	Number of subjects	Crude	Adjusted
None	n=2904	<i>Reference</i>	<i>Reference</i>
< 1 drink/week	n=1235	0.42 (-0.45, 1.28)	-0.22 (-1.18, 0.75)
1 to 3 drinks/week	n=398	1.37 (0.00, 2.74)	0.03 (-1.44, 1.50)
4 to 6 drinks/week	n=43	-2.97 (-6.90, 0.97)	-3.13 (-7.29, 1.02)
1 drink/day	n=16	-1.13 (-7.54, 5.29)	-2.52 (-8.99, 3.94)
2 to 3 drinks/day	n=4	11.95 (-0.85, 24.74)	10.99 (-3.38, 25.36)
		$P_{\text{trend}} = 0.16$	$P_{\text{trend}} = 0.56$
Difference in femur length (mm)			
Alcohol consumption	Number of subjects	Crude	Adjusted
None	n=2909	<i>Reference</i>	<i>Reference</i>
< 1 drink/week	n=1238	-0.00 (-0.15, 0.15)	-0.07 (-0.23, 0.10)
1 to 3 drinks/week	n=397	-0.07 (-0.30, 0.16)	-0.09 (-0.34, 0.16)
4 to 6 drinks/week	n=43	-0.49 (-1.15, 0.18)	-0.40 (-1.10, 0.31)
1 drink/day	n=16	0.06 (-1.03, 1.14)	-0.28 (-1.38, 0.82)
2 to 3 drinks/day	n=4	-0.54 (-2.71, 1.62)	-0.60 (-3.04, 1.84)
		$P_{\text{trend}} = 0.36$	$P_{\text{trend}} = 0.18$
Difference in estimated fetal weight (grams)			
Alcohol consumption	Number of subjects	Crude	Adjusted
None	n=2899	<i>Reference</i>	<i>Reference</i>
< 1 drink/week	n=1233	3.44 (-8.65, 15.54)	-5.44 (-18.84, 7.97)
1 to 3 drinks/week	n=397	13.65 (-5.39, 32.70)	-1.14 (-21.57, 19.28)
4 to 6 drinks/week	n=43	-47.71 (-102.37, 6.95)	-46.04 (-103.69, 11.61)
1 drink/day	n=16	-12.29 (-101.46, 76.88)	-38.14 (-127.88, 51.59)
2 to 3 drinks/day	n=4	122.26 (-55.71, 300.23)	116.76 (-82.74, 316.26)
		$P_{\text{trend}} = 0.46$	$P_{\text{trend}} = 0.36$

* $P < 0.05$, ** $P < 0.01$. Values are regression coefficients (95% confidence interval) and reflect the difference for each growth characteristic.

Crude model: adjusted for gestational age. Adjusted model: Crude model + maternal age, weight, height, smoking, distress, educational level, ethnicity, parity, and infant gender.

P-values for trend were based on multiple linear regression models with alcohol consumption categories as a continuous variable.

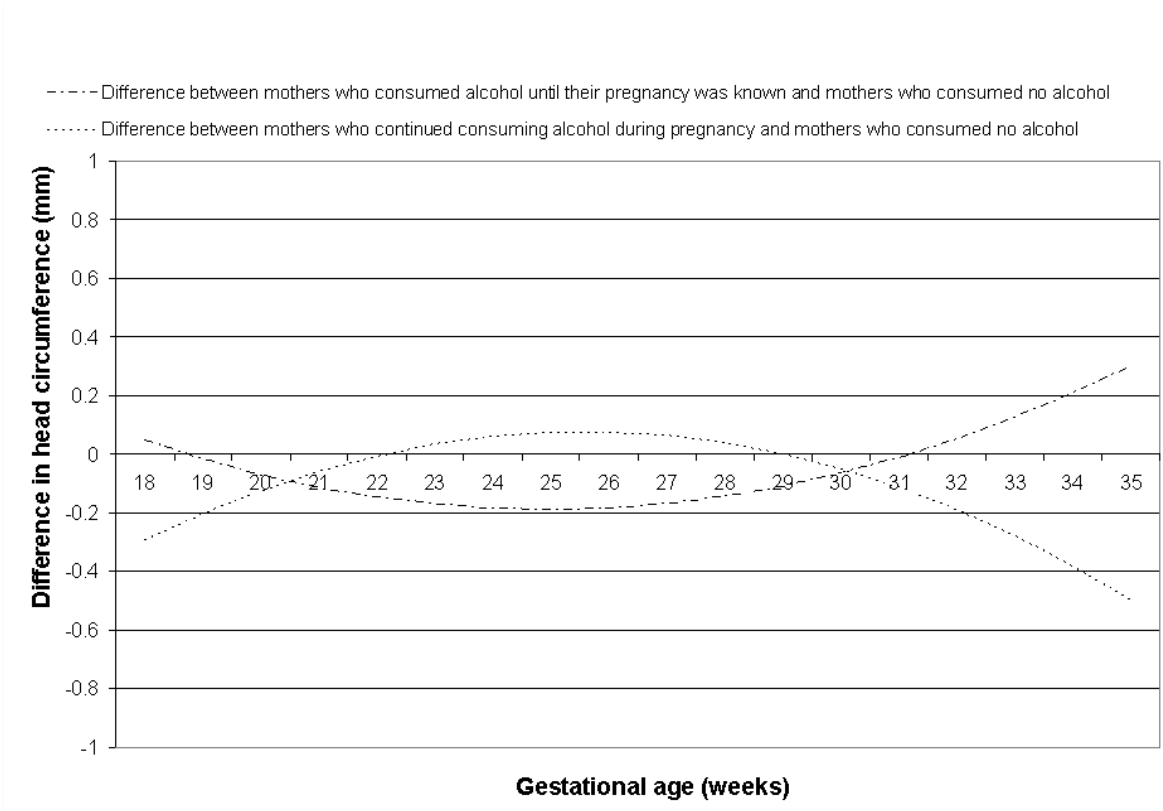
FIGURE 1. Flow chart of participants included for analysis.



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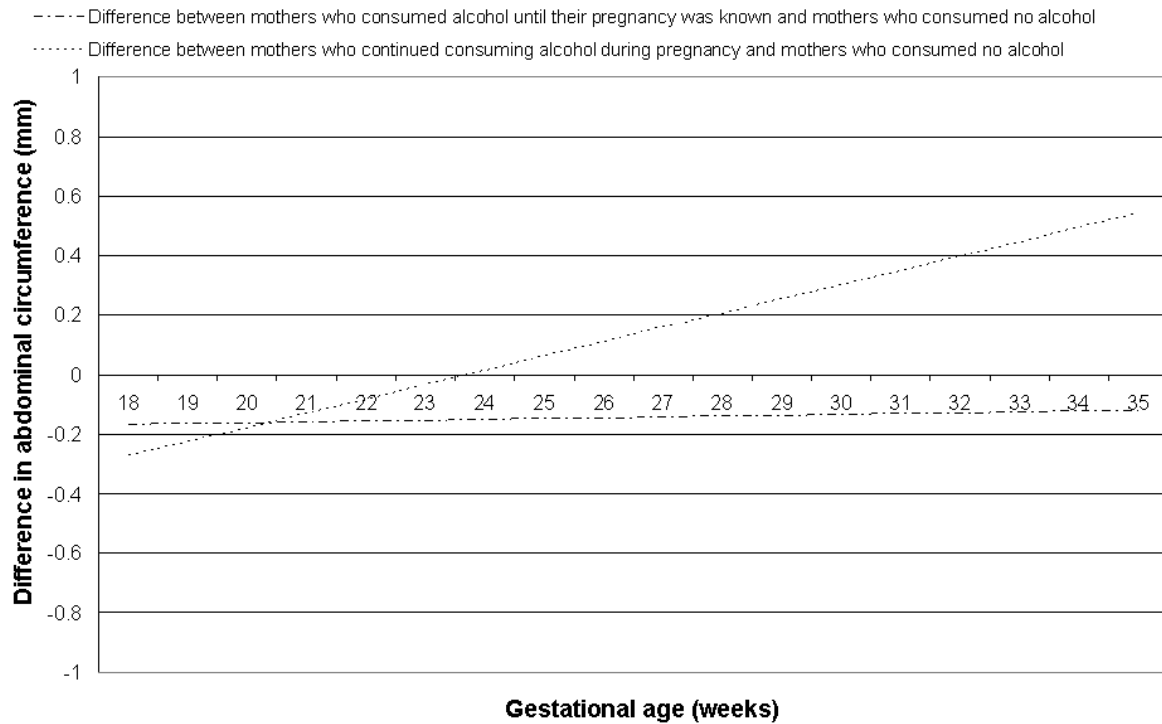
FIGURE 2. Differences in fetal growth measures between alcohol consumption categories.

A. Head circumference



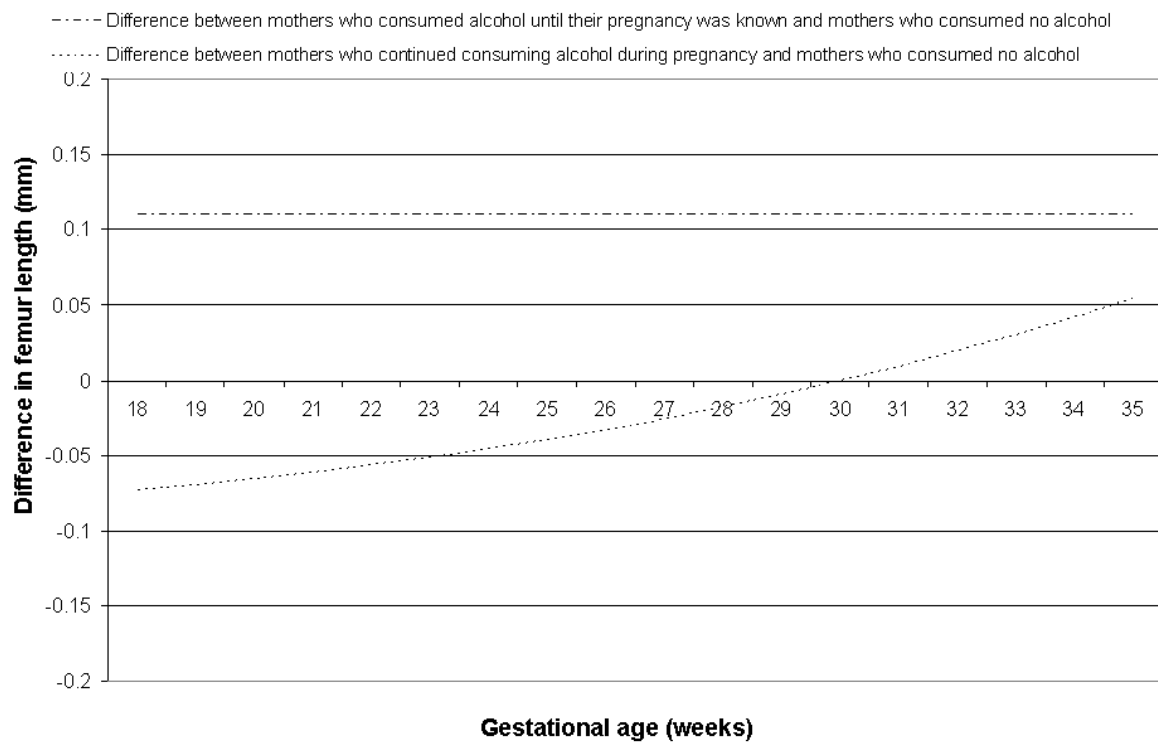
Values reflect difference in fetal growth characteristics of mothers with different alcohol consumption categories and were based on repeated regression models (*P<0.05). The corresponding effect estimates of the differences in the slopes are presented in Table S1. All models are adjusted for maternal age at enrolment, weight at enrolment, height, educational level, parity, ethnicity, fetal gender, smoking habits, maternal stress.

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3 **B. Abdominal circumference**
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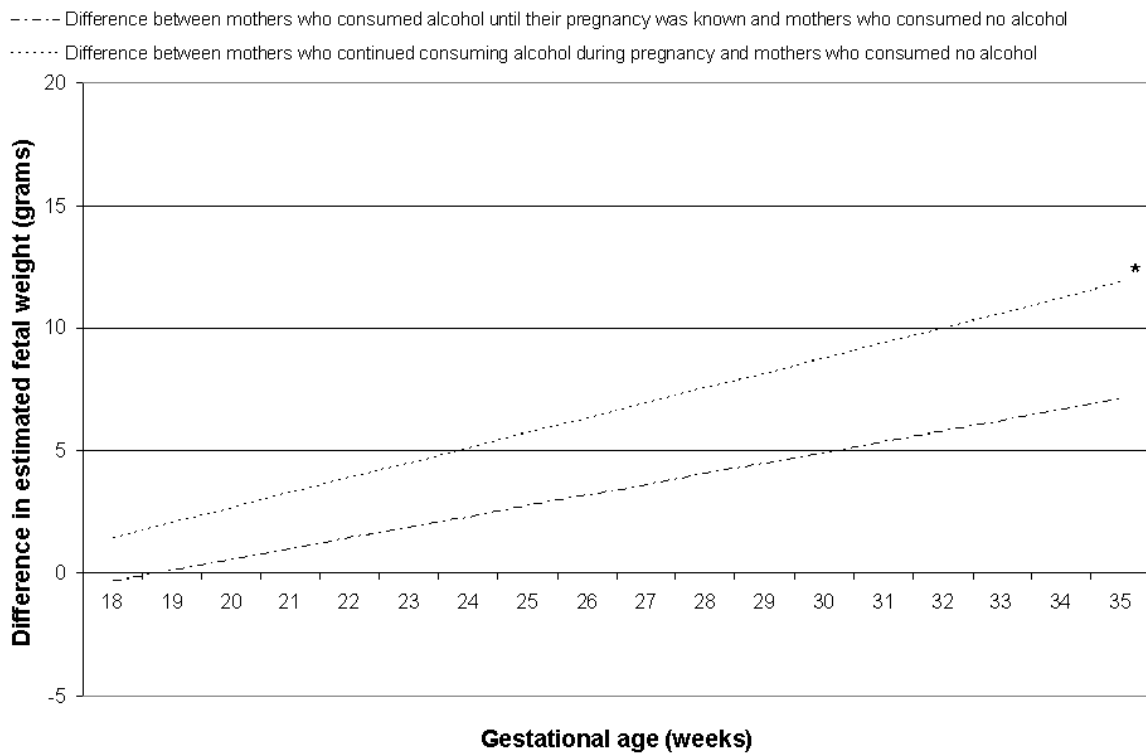
Values reflect difference in fetal growth characteristics of mothers with different alcohol consumption categories and were based on repeated regression models (* $P < 0.05$). The corresponding effect estimates of the differences in the slopes are presented in Table S1. All models are adjusted for maternal age at enrolment, weight at enrolment, height, educational level, parity, ethnicity, fetal gender, smoking habits, maternal stress.

C. Femur length



Values reflect difference in fetal growth characteristics of mothers with different alcohol consumption categories and were based on repeated regression models (*P<0.05). The corresponding effect estimates of the differences in the slopes are presented in Table S1. All models are adjusted for maternal age at enrolment, weight at enrolment, height, educational level, parity, ethnicity, fetal gender, smoking habits, maternal stress.

D. Estimated fetal weight



Values reflect difference in fetal growth characteristics of mothers with different alcohol consumption categories and were based on repeated regression models (* $P < 0.05$). The corresponding effect estimates of the differences in the slopes are presented in Table S1. All models are adjusted for maternal age at enrolment, weight at enrolment, height, educational level, parity, ethnicity, fetal gender, smoking habits, maternal stress.