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Periconceptional maternal and paternal alcohol consumption and embryonic and foetal development: the Rotterdam periconception cohort

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Abstract

Research Question: What is the impact of maternal and paternal alcohol consumption in the periconception period on embryonic and foetal development assessed using three-dimensional ultrasound and VR techniques?

Design: This is a prospective observational study embedded in the Rotterdam Periconception Cohort (Predict study). Participating women received longitudinal 3D transvaginal ultrasound examinations from week 7 up to week 12 of gestation to measure crown-rump length (CRL) and embryonic volume (EV). Mid-pregnancy foetal size parameters and birthweight were retrieved from medical files. Participants filled out a periconception exposure questionnaire and a validated food frequency questionnaire. Linear mixed models were used to analyse the association between parental alcohol consumption, and embryonic and foetal developmental parameters.

Results: 1141 female and 987 male participants were included in our analyses. Maternal moderate alcohol consumption in the periconception period resulted in a smaller head circumference ($\beta=-1.85$, $SE=0.84$, $P=0.03$), abdominal circumference ($\beta=-2.65$, $SE=0.93$, $P=0.004$), femur length ($\beta=-0.56$, $SE=0.22$, $P=0.01$), and estimated foetal weight ($\beta=-9.36$, $SE=4.35$, $P=0.03$) at 20 weeks of gestation. Paternal alcohol consumption showed significant positive associations, mainly with foetal size parameters (AC: $\beta=0.033$, $SE=0.01$, $P=0.008$; EFW: $\beta=0.131$, $SE=0.06$, $P=0.03$).

Conclusions: Moderate maternal alcohol consumption is negatively associated with foetal growth parameters. Moreover, alcohol is proven a strong teratogen and the consumption before and during pregnancy should be discouraged in both women and men since it affects both several parameters of embryonic and foetal development.

Introduction

Multifactorial processes determine embryonic and foetal development in which lifestyle, environmental exposures and genetic variations of parents play a central role (Steeegers-Theunissen et al., 2013). A well-known teratogen is alcohol, which is associated with a wide variety of foetal developmental defects, including brain abnormalities, dysfunction of the central nervous system, and growth deficiencies of organs and body systems (Caputo et al., 2016).

There is increasing evidence that the earliest developmental period, including gametogenesis,

conception, embryogenesis and placentation, is a vulnerable time-window for environmental influences such as alcohol exposure. This time window, defined as the periconception period, encompasses 14 weeks before until 10 weeks after conception (coinciding with the closure of the secondary palate of the embryo)(Stegers-Theunissen et al., 2013). It is an important period in which reproductive failures, pregnancy complications and adverse pregnancy outcomes originate(Barker, 2004).

What we already know is that excessive prenatal alcohol exposure (PAE) causes foetal alcohol spectrum disorder (FASD)(Caputo et al., 2016). Despite public health efforts to eliminate or reduce alcohol consumption during pregnancy, 10-15% of women worldwide, and in some parts of the world up to 50% of women consume alcohol during pregnancy(Popova et al., 2017). The extent of the impact of PAE on FASD remains unclear and there is a still ongoing and maybe unwanted debate about safe levels and periods of alcohol consumption during pregnancy(Mamluk et al., 2017).

In animal studies, the effects of consuming alcohol in the preconception period or in early pregnancy lead to significant neurobehavioral alterations and growth restriction in the offspring(Brancato et al., 2018; Clarren et al., 1988; Sulik & Johnston, 1983). These findings support that alcohol consumption in this specific period has detrimental effects also in humans. However, to the best of our knowledge, there is only scarce evidence to substantiate these findings(Bakker et al., 2010; Burd et al., 2012; Sawada Feldman et al., 2012).

Crown-rump length (CRL) has been the traditional way to estimate embryonic development and accurately estimate the gestational age (GA) in human pregnancies(Robinson & Fleming, 1975) . We hypothesize that CRL can be used to show the detrimental impact of PAE on embryonic development. The introduction of state-of-the-art imaging modalities like three-dimensional (3D) ultrasound and Virtual Reality (VR) techniques enabled reliable measurements of embryonic volumes (EV) as well(Rousian et al., 2010). Rousian and colleagues demonstrated that when the CRL doubles, the mean EV increases 6.5-fold and when the GA age doubles, the mean EV increases even 500-fold(Rousian et al., 2010). EV might therefore be more sensitive to pick up any influence of PAE on embryonic growth during the first trimester.

Van Uitert and colleagues were the first to observe a negative association between maternal periconception alcohol consumption and embryonic growth (van Uitert et al., 2013). Ninety percent of women consumed 2 or less units of alcohol per day during the periconception period, suggesting that even limited amounts of alcohol consumed during this vulnerable period can have an effect on embryonic development.

However, recently the role of paternal alcohol consumption has also emerged as a topic in human studies after an animal study showed that paternal periconception alcohol consumption has an impact on embryonic growth (Chang et al., 2017). Moreover, the negative effects of maternal alcohol consumption on a variety of aspects of foetal health, such as ovarian function and body composition, have been demonstrated (Steane et al., 2024; Young et al., 2022). From this background, we hypothesize that periconception parental alcohol consumption, both maternal as well as paternal, is negatively associated with embryonic development. Therefore, the aim of this study is to investigate the impact of maternal and paternal alcohol consumption in the periconception period on embryonic and foetal development, assessed using 3D ultrasound and VR techniques.

Materials and methods

Study design and participants

The current study was embedded in the Rotterdam Periconception Cohort (Predict study) (Rousian et al., 2021; Steegers-Theunissen et al., 2016), an ongoing observational prospective periconception cohort investigating (epi)genetic and environmental factors in relation to pregnancy course and outcomes. For this study, all women and their male partners were recruited before 10 weeks of gestation between November 2010 and August 2018. Women of at least 18 years of age with ongoing singleton pregnancies were eligible for participation. Recruitment took place at the outpatient clinic of the Erasmus MC, University Medical Centre, Rotterdam, The Netherlands. Women were excluded if ultrasound data was unreliable or missing due to incomplete embryonic or foetal measurements or if pregnancies were conceived through oocyte donation or sperm donation. Dietary (including alcohol

consumption) under-reporters were identified with the Goldberg cut-off method as proposed by Black et al. (Black, 2000), and were excluded from the statistical analyses as well.

The study was approved by the Central Committee on Research in The Hague and the local Medical Ethical Committee of the Erasmus MC in Rotterdam, The Netherlands (MEC-2004-227).

Pregnancy dating

For naturally conceived pregnancies, gestational age (GA) was determined by the last menstrual period (LMP) and adjusted for duration of the menstrual cycle for participants with a regular menstrual cycle (between 21 and 35 days). For participants with an irregular cycle (<21 or >35 days), GA was based on the CRL at the 9 weeks 3D ultrasound scan.

In pregnancies conceived after in vitro fertilization (IVF) treatment with or without intracytoplasmic sperm injection (ICSI), GA was calculated based on the date of oocyte retrieval plus 14 days. If a cryopreserved embryo was used, GA was calculated from the day of embryo transfer plus 19 days. The pregnancies conceived through intrauterine insemination or hormone therapy were considered naturally conceived pregnancies.

Development characteristics

Transvaginal 3D ultrasound examinations were performed longitudinally around the 7th, 9th and 11th week of gestation. The ultrasound examinations were performed by medical doctors who were experienced in the field of maternal foetal medicine and who had followed an internal training program and exam. The ultrasound scans were executed using a 6-12MHz transvaginal probe of the GE Voluson E8 Expert system and 4D View software version 5.0 (GE Medical systems, Austria). All 3D ultrasound datasets were stored and saved as Cartesian volumes using specialized software (4D View) and visualized using the I-Space VR application at the Department of Bioinformatics, Erasmus MC, University Medical Centre, Rotterdam. The I-Space is a so-called four-walled CAVE™-like (Cave Automatic Virtual Environment) VR system (Barco N.V., Belgium) (Rousian et al., 2010; Steegers-Theunissen et al., 2016). The V-Scope application was used in the I-Space to create an

interactive hologram of the ultrasound image which allowed detailed CRL and EV measurements. CRL measurements were performed three times by the same examiner, and the mean value was used for analysis. The EV measurements were performed once. An extensive description of the VR system and measuring methods has been published before (Rousian et al., 2010; Verwoerd-Dikkeboom et al., 2010). Second trimester growth and size parameters were retrieved from the anomaly scan, which is performed between 18 and 22 weeks of gestation. Extracted data included head circumference (HC), abdominal circumference (AC), femur length (FL), and estimated foetal weight (EFW). Birthweight was retrieved from the medical discharge letter written by a midwife or doctor.

Alcohol consumption

Parental alcohol intake was divided in the alcohol intake in the periconception period and first trimester of pregnancy and was assessed using the periconception questionnaire (PQ) and a standardized validated semi-quantitative food frequency questionnaire (FFQ) at inclusion, respectively. The PQ included information on the type of alcoholic beverage and the frequency of consumption during the prior three months and covered periconception alcohol intake. Type of alcohol drink was divided in four different categories, namely: 'beer', 'wine', 'liquors' and 'others'. Alcohol related questions were categorized as; 'no', 'average amount of drinks a day during the week' and 'average amounts of drinks a day in the weekend'. Furthermore, the PQ covered parental details on age, ethnicity, body weight, height, education, obstetric history and lifestyle behaviours prior to conception.

The alcohol related FFQ questions covered the prior four weeks (thus the first trimester of pregnancy) and consisted of six categories, namely: 'beer', 'non-alcohol beer', 'whine, sherry port or vermouth', 'eggnog, 'mixes/long drinks' and 'strong drinks'. After choosing the type of alcohol drink, questions were asked with regards to frequency (categorized from 'nothing' to '6-7 days a week') and the number of glasses consumed per day. Portion sizes of consumed alcoholic drinks were estimated using natural portions and commonly used household measures. Average daily alcohol intakes, during the periconception period (PQ) and during the first weeks of pregnancy (FFQ), were calculated by

multiplying the consumption frequency by portion sizes and alcohol content in grams as indicated by the most recent Dutch food composition table (2016)(Environment), 2011). Maternal alcohol intake was questioned as well at 24 weeks of gestation to assess the length of PAE.

The filled out PQ was thoroughly checked by an experienced research nurse and the FFQs were checked by interviewer administration in a standardized manner for completeness and consistency during the first appointment.

An average glass of beer, wine or liquor contains around 10 grams of alcohol. We defined low, moderate and high maternal alcohol consumption during the periconception period as consuming a maximum of 35 grams/week, 70 grams/week, or more than 70 grams/week, respectively. Alcohol consumption during pregnancy was categorized as up to 3 grams/week (low), between 3 and 30 grams/week (moderate), and more than 30 grams/week (high). Low, moderate, and high paternal periconception alcohol consumption was defined drinking up to 70 grams/week, between 70 and 140 grams/week, and more than 140 grams/week, respectively. These alcohol consumption categories were based on a general guideline for alcohol consumption from the World Health Organization((WHO), 2000), however, were adjusted downward for women, since drinking no alcohol in the periconception period is recommended.

Identification of dietary under-reporters

The Goldberg cut-off as proposed by Black(Black, 2000) was used to identify the dietary under-reporters. This calculation relies on the hypothesis that energy intake equals the basal metabolic rate (BMR) multiplied by the physical activity level (PAL). The BMR was calculated using the Schofield equations, which takes sex, age, height and weight into account. For the PAL a fixed value of 1.55 was used, which is equal to a light activity level. Daily energy intake was measured with the FFQ. For the intra-individual variabilities of PAL and BMR we used the proposed values by Black(Black, 2000) of 15% and 8.5% respectively. The calculated 95% lower confidence limit for energy intake provided a cut-off value for each individual. The participant was considered a dietary under-reporter when the reported daily energy intake was below the individuals' energy intake cut-off. Under-reporters were excluded from the analyses.

Directed acyclic graph

We used the R package DAGitty (Textor et al., 2011) to compose a directed acyclic graph (DAG) (Greenland et al., 1999) and to select a minimal sufficient adjustment set of variables (MSAS) that would allow the identification of an unconfounded effect of parental alcohol intake on the prenatal outcomes. The DAG (Figure 1) was built by identifying all known factors affecting parental alcohol intake and growth parameters of the offspring, and then including all common causes of any pair of variables already in the DAG. Additionally, we forced the adjustment of the variable GA. However, this did not change the MSAS. Variables in the MSAS blocked all non-causal, but not the causal pathway between parental alcohol intake and growth parameters of the offspring, and included educational level, geographical background, and GA.

Statistical analyses

First, we compared baseline characteristics between included and excluded participants to investigate if our study sample is representative of the entire cohort, and thereby, to assess potential selection bias. Student t-test was used for continuous variables where normality could be assumed, in case of not normally distributed data Wilcoxon test was used. Chi-square test was used for categorical variables.

CRL and EV showed a skewed distribution and a non-linear relationship with GA. Therefore a Tukey transformation (Osborne, 2010) was applied using the `transformTukey()` function from the R package 'rcompanion'. The Tukey transformed value ("Y") has the following relationship with the original CRL and EV measurement ("X") in mm: $Y = X\lambda$. The Tukey transformation is a simplified form of the boxcox transformation where for a single parameter the λ is identified with the best Shapiro-Wilks test statistic for a range of λ values (-10 till +10). The λ was 0.475 ($W = 0.9659$) for CRL and 0.225 ($W = 0.9702$) for EV. There was an increasing variance for both EV and CRL with GA. This heteroscedasticity needed adjustment, which is achieved by applying an additional variance structure

for GA.

In order to assess the associations between periconception parental alcohol consumption and embryonic development outcomes we performed linear mixed model analyses with the `lme()` function from the R package 'nlme'. In the models we corrected for differences in CRL and EV variance between pregnancies in women with a regular menstrual cycle (21-35 days) and women with an irregular menstrual cycle (<21 or >35 days) using a variance structure.

With this we constructed three maternal models; first, a model only adjusted for GA (model 1). Second, a DAG model in which we used the MSAS, adjusting for GA, educational level, and geographical background (model 2). Education level was divided in low, middle, and high, using low as the reference group. Third, we composed a traditional model consisting of variables that are often included in adjustment sets based on previously published literature (model 3); GA, educational level, geographical background, maternal BMI, maternal smoking, and foetal sex (Bottomley et al., 2009; Jaddoe et al., 2007; Lubchenco et al., 1963; Silva et al., 2010).

Moreover, we constructed two models (model 4-5) with both maternal and paternal covariates. Model 4 included educational level, and geographical background. In addition to model 4, model 5 included maternal and paternal smoking behaviour.

To explore the effects of residual confounding, a sensitivity analysis was performed by excluding smoking participants.

Subgroup analyses were further performed based on mode of conception: naturally conceived pregnancies and IVE/ICSI pregnancies. Data analyses were carried out using R version 1.1.463. A two-sided p-value of <0.05 was considered statistically significant.

Results

Study population and characteristics of participants

In total, 1744 female and 1480 male participants were included and after application of the exclusion criteria the study population included 1141 women and 987 men. Table 1 shows the maternal and

paternal characteristics of included and excluded participants. The analyses on periconception and first trimester alcohol consumption consisted of 1116 women and 953 men, and 649 women and 470 men, respectively. A flowchart of study population selection is depicted in Figure 2.

The mean age of included women was 32.0 (± 4.4) and of included men 34.7 (± 6.0). The majority of female and male participants were highly educated, 58.0% and 48.7%, respectively. 84.2% of included women and 69.2% of included men did not smoke tobacco. Regarding mode of conception, 65.2% were naturally conceived pregnancies. In the periconception period, 776 (69.5%) women did not consume alcohol, 216 (19.4%) consumed low amounts of alcohol, 91 (8.2%) consumed moderate amounts of alcohol, and 33 (2.9%) women consumed high amounts of alcohol. No, low, moderate, and high alcohol consumption during pregnancy was reported by 55 (8.6%), 533 (83.3%), 52 (8.1%), and 0 women, respectively.

Maternal alcohol consumption and embryonic and foetal development (model 1-3) (Table S1, and Figure 3)

Periconception period

No significant associations were observed between periconception maternal alcohol consumption and embryonic and foetal development, with alcohol consumption as a dichotomous, and continuous variable. However, alcohol as a categorical variable showed a significantly positive association between high alcohol consumption and CRL ($P=0.05$), and a significantly negative association between moderate alcohol consumption and HC ($P=0.03$), AC ($P=0.004$), FL ($P=0.01$), and EFW ($P=0.03$) in model 2. Results are shown in Table S1 and, additionally, in a forest plot in Figure 3. After excluding smoking participants, the significantly positive association between high alcohol consumption and CRL disappeared. However, the significantly negative association between moderate alcohol consumption and HC, AC, FL, and EFW remained with comparable effect estimates.

First trimester of pregnancy

Maternal alcohol consumption during the first trimester of pregnancy showed no significant associations with embryonic and foetal development. The group that did not consume alcohol during this period consisted of 55 women and the group with moderate alcohol consumption comprised 533 women. Since only 5 women reported that they continued drinking alcoholic consumptions at 24 weeks of gestation, we could not use this information for further analyses.

Parental alcohol consumption and embryonic and foetal development (model 4-5) (Table S2)

Additionally, we composed models that included both maternal and paternal alcohol consumption. Those models showed several significant associations between maternal and/or paternal alcohol consumption and foetal development (Table S2). Since smoking is a strong confounding variable between alcohol consumption and embryonic and foetal development, we analysed the associations again after excluding of the smokers. Still paternal alcohol consumption showed a positive association with multiple foetal development parameters; there was a significant association between low paternal alcohol consumption in the periconception period and birthweight ($\beta=90.86$, $SE=41.69$, $P=0.03$).

Mode of conception

Subgroup analyses in women with naturally conceived pregnancies and women with IVF/ICSI pregnancies showed several significantly positive associations between maternal alcohol consumption and foetal development in the IVF/ICSI subgroup. After excluding smoking women, one significant association remained; periconception alcohol consumption and EFW ($\beta=0.27$, $SE=0.13$, $P=0.03$).

Discussion

Main findings

Maternal moderate alcohol consumption in the periconception period showed a negative association with foetal HC, AC, FL and EFW at 20 weeks GA. These findings remained significant after excluding smoking women. However, no significant associations were shown with embryonic CRL, EV and birth weight. Paternal alcohol consumption in the periconception period as well as during pregnancy demonstrated positive associations with foetal development, mainly in mid gestation (AC and EFW).

Strengths and limitations

This is the first study that included a large sample size, with detailed information from two sources on both maternal and paternal alcohol consumption in the preconception period as well as during the first weeks of pregnancy.

A limitation is that self-administered questionnaires for data collection were used which are susceptible for information bias due to either the stigma to have consumed alcohol, cave underreporting, and recall bias as a consequence of the time interval between alcohol consumption and filling out the questionnaires. In our study, we were not able to investigate the effects of binge drinking behaviour, since the questionnaires did not include questions concerning this subject.

This cohort is embedded in a tertiary care hospital, which includes a large population of high-risk pregnancies. Therefore, our results have a high internal but may have a limited external validity. In addition, our population consisted predominantly of middle and high-educated women and men.

Animal studies were already able to show negative effects of alcohol consumption more convincingly. However, in human studies, initiating research provoking alcohol consumption will lead to ethical concerns, and report bias, since alcohol consumption during pregnancy is severely stigmatized (Tabakoff & Hoffman, 2000). These aspects, inherent to human studies, might explain the less convincing associations compared to findings from animal studies.

Interpretation of embryonic and foetal development

This study demonstrates inverse associations between periconception maternal moderate alcohol consumption and mid-pregnancy foetal development. The analyses in which alcohol consumption is used as a continuous variable have more power, however, failed to show significant associations. This might substantiate the previously suggested hypothesis that maternal alcohol consumption is harmful dependent on the amount and other lifestyle and health conditions (Patra et al., 2011). We are the first to observe a negative association between maternal moderate alcohol consumption in the periconception period and mid-pregnancy foetal size parameters. A systematic review found no convincing evidence of adverse effects of prenatal alcohol consumption at low and moderate levels of consumption on foetal outcomes, such as intra-uterine growth restriction (Henderson et al., 2007). Another study concluded as well that low and moderate maternal alcohol consumption during pregnancy does not adversely affect foetal growth parameters (Bakker et al., 2010). The absence of a significant association between low maternal alcohol consumption is consistent with previous studies (Bakker et al., 2010). In addition, we did not find a significant effect of high maternal alcohol consumption on foetal development. This might be explained by a lack of power, which is illustrated by low numbers of women drinking high amounts of alcohol, the alternating negative and positive associations, and broad standard errors. A recently published study carried out in a cohort with high alcohol consumption in South Africa confirms that periconceptional and prenatal alcohol exposure were associated with reduced fetal growth (Pielage et al., 2023).

When comparing the effect sizes found for the association between alcohol consumption and foetal development in similar studies, some similarities were found. The effect size that we found for the association between low periconception maternal alcohol intake and CRL is comparable to the effect size of the association between increased maternal serum homocysteine and CRL (Parisi et al., 2017).

No associations between alcohol consumption during pregnancy and foetal development were observed, for which methodological and biological explanations are possible. The absence of significant effects of high alcohol consumption might be explained by the fact that nearly no women with high alcohol consumption participated in the study. This might be an underestimation, because PAE during pregnancy is even more stigmatized than during the preconception period (Stengel,

2014). Additionally, as pregnancy progresses, other factors may become more important like smoking.

Furthermore, during the first weeks of pregnancy, the developing embryo is still contained within the amniotic sac, receives nutrients from the yolk sac and endometrial glands, and is not yet connected with the mother by the materno-foetal circulation via the placenta (Burton et al., 2001). Whether PAE in this stage of pregnancy is harmful and the potential underlying mechanisms, have still to be elucidated. However, it is known in animals that extraembryonic tissues such the parietal yolk sac and the placenta are affected by alcohol, which impairs placentation and eventually embryonic development (Padmanabhan, 1985; Xu et al., 2005).

Previous studies showed respectively a negative association with foetal growth and birth weight or failed to show any effect (Bakker et al., 2010; Windham et al., 1995). It is hypothesized that paternal alcohol consumption affects epigenetic mechanisms, mainly the noncoding RNA milieu in sperm, and, thereby, might influence foetal growth (Rompala & Homanics, 2019). However, to the best of our knowledge, this is the first study that showed positive effects of paternal alcohol consumption on foetal growth parameters. We can only speculate what might have caused these findings, and it cannot be excluded that we found the positive association as a result of multiple testing. We carefully interpreted these findings and more research is needed in settings with high alcohol exposure in men. Second, there might have been differences between study groups that we did not take into account, and not adjust for, leading to this positive association (e.g., unmeasured confounding factors such as stress).

Recommendation for practice and further research

Alcohol is a strong teratogen and drinking alcohol during pregnancy is associated with, among others, congenital heart defects (Mateja et al., 2012), oral clefts (Yin et al., 2019), and foetal alcohol syndrome (Popova et al., 2017). Moreover, moderate maternal alcohol consumption affects foetal growth parameters. For that reason, not drinking alcohol before and during pregnancy should be strongly advised.

However, we did not provide conclusive evidence on the harmful effects of paternal alcohol consumption.

Preconception health promotion should include counselling on the detrimental effects of alcohol consumption during pregnancy. A recent study in the Dutch population reported that one in nineteen women continued to consume alcohol during early pregnancy, of which 89% did not report this use to their obstetric care provider (Breunis et al., 2021). This finding illustrates the stigma of drinking alcohol during pregnancy and underlines the importance for the health care professional to actively bring this subject up for discussion during preconception counselling or the first antenatal visit.

Moreover, in countries with the highest reported prevalence of alcohol consumption, United Kingdom (41.3%, CI: 32.9–49.0%), and Denmark (45.8%, CI: 30.9–61.2) (Popova et al., 2017), this problem deserves even more attention from health care professionals as well as from policy makers.

A biomarker can provide objective information on alcohol consumption and may be included in future research on this subject (Breunis et al., 2021). Several biomarkers to detect PAE have been used in both clinical and research settings. Traditionally, maternal urine and blood samples have been used to determine prenatal alcohol use (C. F. Bearer, 2001). However, the biomarkers measured from these samples mostly reflect alcohol exposure within 2 to 3 days before delivery. Samples from amniotic fluid, umbilical cord blood, placenta, neonatal hair, breast milk, vernix, or meconium have also been proposed as biomarkers for PAE. Meconium in particular, has been studied to measure fatty acid ethyl esters (FAEE) as a biomarker for prenatal alcohol use that may reflect exposure since the 13th week of pregnancy when meconium first begins to form (Cynthia F. Bearer, 2001; DeJong et al., 2019).

Phosphatidylethanol (PEth) is a promising biomarker in maternal blood that can detect even low levels of alcohol consumption over a longer period of time (Gustavsson, 1995; Helander et al., 2019; Wassenaar & Koch, 2015). With a mean half-life of four days, this biomarker remains detectable for two weeks after consumption of a single unit of alcohol and for a longer period after larger amounts of alcohol intake.

A lifestyle intervention provided to women and their partner in the preconception period could prevent the teratogenic effects of alcohol. This intervention should contain information on healthy

lifestyle habits, counselling and, preferably, follow-up during a certain period. Several effective lifestyle interventions have been developed and tested at the Erasmus MC during the previous years: lifestyle counselling at the outpatient clinic (Hammiche et al., 2011), lifestyle coaching through digital coaching www.smarterpregnancy.co.uk (Dutch www.slimmerzwanger.nl), and a blended intervention consisting of face-to-face counselling combined with digital lifestyle coaching through a mobile app (van der Windt et al., 2020; Van Dijk et al., 2016).

Conclusion

Moderate maternal alcohol consumption in the periconception period detrimentally affects mid-pregnancy foetal development. Moreover, first trimester embryonic development is impaired although non-significantly.

Investigating the effects of parental alcohol consumption is complicated, since alcohol consumption during pregnancy is highly stigmatized, which might lead to report bias. Additionally, the association between alcohol consumption and foetal development is strongly confounded by smoking.

Furthermore, since in animal studies the detrimental effects of periconception alcohol consumption are irrefutably demonstrated and it is certain that alcohol is a strong teratogen, alcohol consumption before and during pregnancy should be discouraged in both parents-to-be.

Author contributions

Conceptualisation: MR, RS-T. Methodology: ET, MR. Statistical analysis: ET, MW, IC. Drafting of the paper: MW. Critical revision of the paper for important intellectual content: All authors.

Conflicts of interest statement

All authors have no conflicts of interest to declare.

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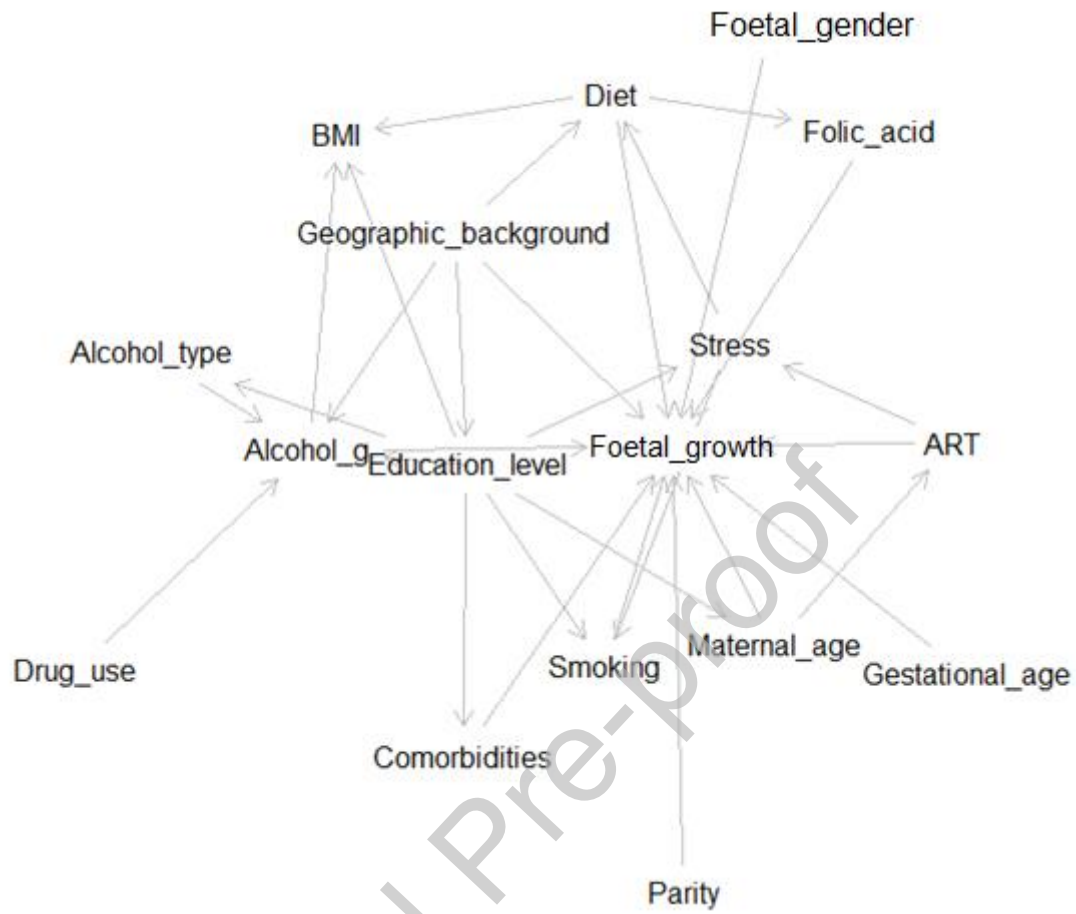
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Table 1. Baseline characteristics of included and excluded participants**Figure 1.** Embryonic and foetal development causal diagram

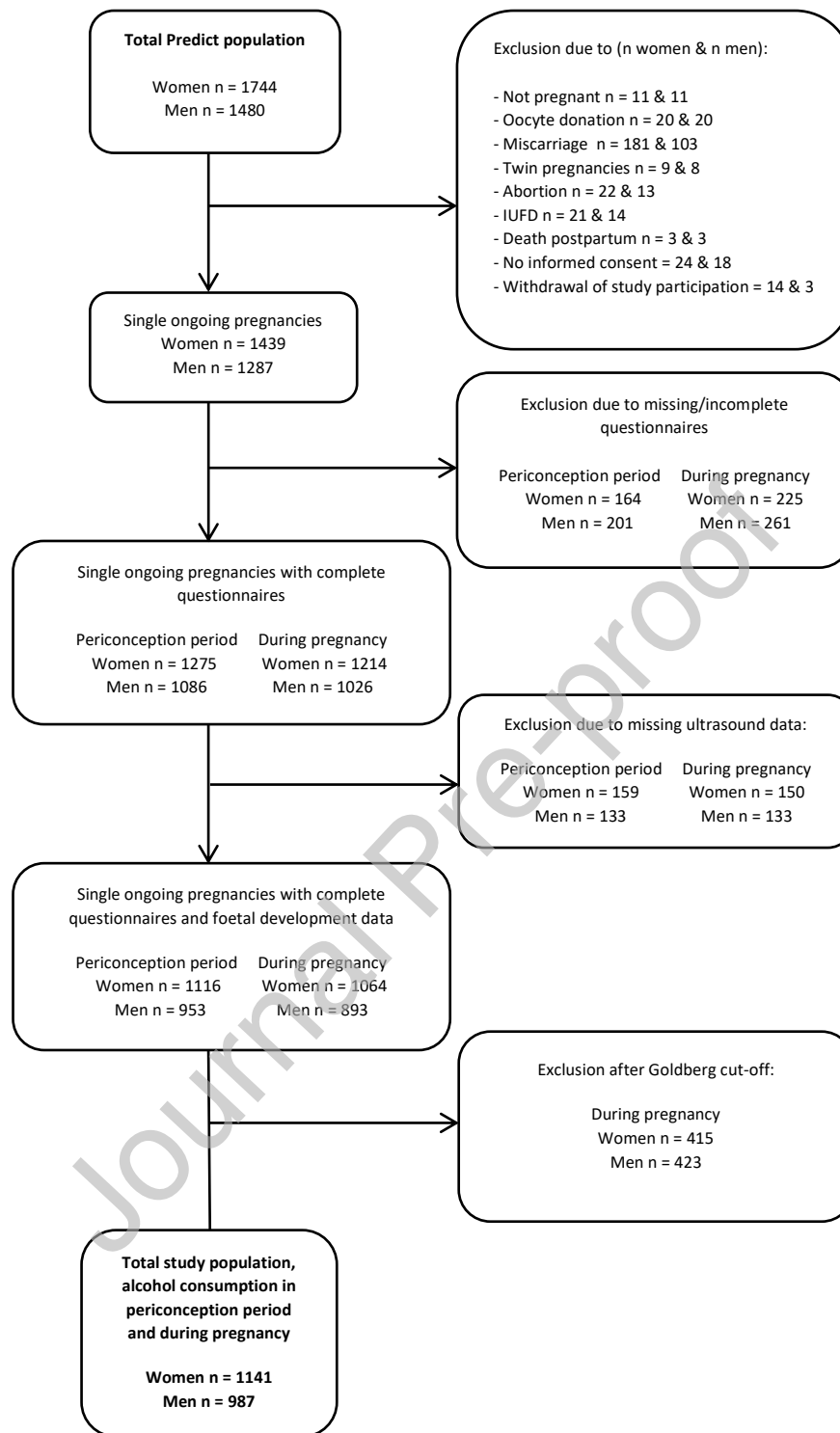


Figure 2. Flowchart of study population selection

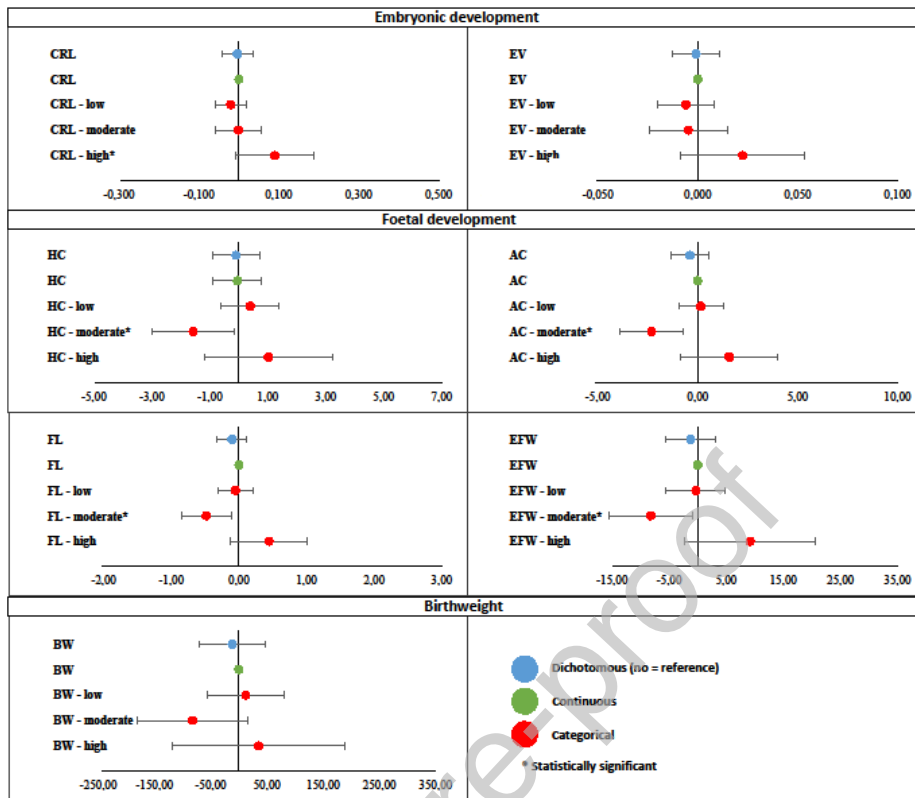


Figure 3. Forest plot of effect estimates of the association between embryonic and foetal development parameters and maternal periconception alcohol consumption, analysed as a dichotomous, continuous or categorical variable (low – moderate – high). CRL: crown-rump length, EV: embryonic volume; HC: head circumference; AC: abdominal circumference; FL: femur length; EFW: estimated foetal weight; BW: birth weight

	Maternal		P-value	Paternal		P-value
	Included (N=1141)	Excluded (N=603)		Included (N=987)	Excluded (N=757)	
Age (years), mean [±SD]	32.0 [± 4.4]	32.8 [± 4.8]	0.001	34.7 [± 6.0]	35.2 [± 6.3]	0.12
missings	0	0		0	0	
BMI (kg/m ²), mean [±SD]	25.4 [± 5.1]	26.5 [± 5.4]	<0.001	26.2 [± 4.1]	26.8 [± 4.1]	0.02
missings	16	78		115	306	
Geographic origin, n (%)			<0.001			<0.001
Western	964 (84.5)	306 (50.7)		848 (87.3)	287 (84.9)	
Non-Western	177 (15.5)	297 (49.3)		123 (12.7)	51 (15.1)	
missings	0	0		16	419	
Level of education, n (%)			0.008			0.50
Low	88 (7.8)	42 (11.1)		132 (13.7)	50 (15.1)	
Middle	385 (34.2)	149 (39.5)		364 (37.6)	113 (34.1)	
High	653 (58.0)	186 (49.3)		471 (48.7)	168 (50.8)	
missings	15	226		20	426	
Smoking			.90			.39
No, n (%)	948 (84.2)	295 (84.5)		661(69.2)	221 (71.5)	
Yes, n (%)	72 (6.4)	20 (5.7)		223 (23.4)	72 (23.3)	
Quit, n (%)	106 (9.4)	34 (9.8)		71 (7.4)	16 (5.2)	
missings	15	254		32	448	
Comorbidities (yes), n (%)	282 (32.2)	50 (33.3)	0.08	NA	NA	
missings	265	453				
Multivitamin use (yes)	693 (61.7)	261 (68.0)	0.03	142 (15.2)	57 (18.9)	0.15
missings	17	219		35	456	

Folic acid supplement use (yes)	895 (81.1)	285 (81.4)	0.91	64 (6.7)	32 (10.6%)	<0.001
Preconception period	208 (18.9)	65 (18.6)				
First-trimester	38	253		28	445	
<i>missings</i>						
Nulliparous (yes)	576 (50.5)	245 (47.3)	0.23	NA	NA	
<i>missings</i>	0	85				
Mode of conception			<0.001	NA	NA	
Natural/IUI	743 (65.2)	283 (76.7)				
IVF/ICSI	398 (34.8)	66 (17.9)				
Oocyte donation	0	20 (5.4)				
<i>missings</i>	0	234				
Foetal gender (male)	577 (51.2)	189 (48.8)	0.43	NA	NA	
<i>missings</i>	13	216				
Periconception alcohol consumption	n=1116	n=346		n=953	n=791	
Periconception, mean[±SD]	10.4 [± 21.9]	9.4 [± 22.2]	.22	32.9 [± 35.8]	38.5 [± 73.6]	.69
None, n (%)	776 (69.5)	253 (73.1)	.47	268 (28.1)	95 (31.8)	.27
Low, n (%)	216 (19.4)	57 (16.5)		561 (58.9)	165 (55.2)	
Moderate, n (%)	91 (8.2)	29 (8.4)		108 (11.3)	30 (10.0)	
High, n (%)	33 (2.9)	7 (2.0)		16 (1.7)	9 (3.0)	
<i>Missing</i>	0	257		0	492	
Alcohol consumption during pregnancy	n=640	n=770				
First trimester, mean[±SD]	0.81 [± 2.6]	0.32 [± 1.3]	.19	NA	NA	
None, n (%)	55 (8.6)	95 (12.4)	<0.001	NA	NA	
Low, n (%)	533 (83.3)	654 (84.9)				
Moderate, n (%)	52 (8.1)	21 (2.7)				
High, n (%)	0	0				



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Key Message

Moderate maternal alcohol consumption is negatively associated with foetal growth parameters. Moreover, alcohol is proven a strong teratogen and the consumption before and during pregnancy should be discouraged in both women and men since it affects both several parameters of embryonic and foetal development.