COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

STATEMENT ON THE REPRODUCTIVE EFFECTS OF CAFFEINE

Background

1. Caffeine is present in coffee, tea, chocolate, cocoa, cola drinks, many of the increasingly popular 'energy drinks', and in over-the-counter and prescription medications including many cold and 'flu remedies, headache treatments, diet pills, diuretics and stimulants. Most pregnant women in the UK consume caffeine from one or more sources.

2001 COT Evaluation

2. The Committee last considered possible adverse effects of caffeine consumption on reproduction in 2001 and issued a statement at that time with the following conclusions. ¹

3. “We note that the risk of low birth weight and spontaneous abortion increases with increasing maternal caffeine intake during pregnancy. However, a threshold level of caffeine intake, above which maternal caffeine intake presents a risk to pregnancy, cannot be determined. Different studies assume different caffeine contents of beverages and this leads to some variation in the levels of caffeine intake associated with adverse effects on reproduction in different studies. We consider it prudent to assume that caffeine intakes above 300 mg/day show a plausible association with low birth weight and spontaneous abortion, given the available evidence from studies in experimental animals and epidemiological studies. However, on the basis of the available evidence, it is not possible to define this association as causal. We note that 300 mg/day caffeine is equivalent to four cups of instant coffee or about six cups of tea, assuming average caffeine contents.

4. We note that for caffeine intakes of 150 to 300 mg/day there is less evidence for an association, with greater inconsistency in the results of epidemiological studies than for intakes above 300 mg/day.

5. We note that data on maternal caffeine consumption during pregnancy and associations with adverse effects on reproduction other than low birth weight and spontaneous abortion, such as pre-term birth and adverse effects on the fetus are inconclusive. We do not consider there to be reliable evidence for associations with these parameters at moderate consumption levels (below 300 mg/day).
6. There do not appear to be effects of caffeine consumption on male fertility. Evidence for adverse effects on female fertility is inconclusive.

7. We note that the studies used to establish this association focused on caffeine intake from coffee, and that a possible influence of other constituents of coffee cannot be excluded. We also recognise that coffee and tea are just two sources of caffeine and do not necessarily represent the main sources of caffeine intake for all people.

8. Further studies are required to establish whether the observed association is causal. These might include the use of biomarkers of caffeine intake.”

The FSA funded research projects (T01032 & T01033)

9. In light of the Committee’s conclusions in 2001, the Food Standards Agency issued advice that caffeine intake during pregnancy should be limited to not more than 300 mg/day and offered guidance on amounts of caffeine in different foods and drinks. In addition, the Agency commissioned a prospective study, involving around 2500 pregnant women, in order to reduce uncertainties in the risk assessment and provide a more robust basis for the Agency’s advice to pregnant women on caffeine consumption.

10. This research was funded as two linked projects, ‘Determination of maternal caffeine intakes associated with increased risk to the fetus’ (FSA project code T01032, University of Leicester) and ‘Assessment of caffeine consumption, altered caffeine metabolism and pregnancy outcome’ (T01033, University of Leeds).

11. The FSA-funded research was designed to overcome some of the limitations of earlier studies. It was prospective in design, recruiting women at approximately 12 weeks of gestation, and ascertained caffeine consumption and other relevant exposures through a structured questionnaire. The questionnaire, which was completed on three occasions (once in each trimester of pregnancy), detailed all sources of caffeine, as well as gathering information about other aspects of diet (including alcohol consumption), smoking habits, drug use (medicinal and recreational), work, physical activity and symptoms. The information was recorded for each 4 week period of pregnancy. The main outcome measure was fetal growth restriction (FGR) defined as failure of the baby to attain its growth potential as determined by genetic and environmental factors. A weakness of many of the previous epidemiological studies had been their reliance on birth weight as the endpoint for assessing fetal growth. It is well recognised that low birth weight does not necessarily indicate poor growth, and depends also on gestational age at birth and on other factors such as maternal height, ethnicity and parity. Given that approximately 10% of babies were expected to have FGR, each of the two study sites recruited in the region of 1,250 women in order to ensure sufficient statistical power to detect small differences in the prevalence of FGR births according to caffeine intake.

12. FGR is an important outcome because it is associated with an increased risk of perinatal mortality and morbidity, including perinatal asphyxia. Moreover, there is
epidemiological evidence that FGR correlates with adverse effects in adult life\textsuperscript{2,3}. For example, affected individuals have an increased incidence of metabolic syndrome, manifesting as obesity, hypertension, hypercholesterolemia, cardiovascular disease, and type 2 diabetes\textsuperscript{4,5,6}.

13. Of the four primary routes of caffeine metabolism in humans, 3-demethylation is quantitatively the most important, the caffeine being converted to paraxanthine by CYP1A2. Studies have shown there to be varying levels of CYP1A2 activity in humans. Women recruited to the study were asked to participate in a “caffeine challenge” at approximately 14 and 28 weeks of gestation in order to assess metabolic phenotype for caffeine metabolism. Participants drank a defined volume of caffeine-containing cola and provided saliva samples, which allowed the half-life of caffeine and the ratio of its metabolites to be measured. Cotinine was also measured in these samples to verify reported smoking habits.

14. The Committee was presented with a pre-publication draft of the primary manuscript from these studies. The subjects’ mean caffeine consumption was reported to decrease from 238 mg/day to 139 mg/day during the first trimester of pregnancy, and then increased to 153 mg/day by the third trimester. The major contributions to caffeine consumption in pregnancy were from tea (62%), coffee (14%) and cola drinks (12%), whilst chocolate contributed 8%. After adjustment for various potential confounders, caffeine consumption was associated with an increased risk of FGR which was statistically significant at intakes of 200-299 mg/day and above (Table 1).

<table>
<thead>
<tr>
<th>Caffeine (mg/day)</th>
<th>OR</th>
<th>(95% CI)</th>
<th>(\rho_{\text{trend}})</th>
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<tbody>
<tr>
<td>Average intake over pregnancy</td>
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<tr>
<td>&lt;100</td>
<td>1</td>
<td></td>
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<td>100-199</td>
<td>1.2</td>
<td>(0.9, 1.6)</td>
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<tr>
<td>200-299</td>
<td>1.5</td>
<td>(1.1, 2.1)</td>
<td></td>
</tr>
<tr>
<td>300+</td>
<td>1.4</td>
<td>(1.0, 2.0)</td>
<td>P=0.02</td>
</tr>
</tbody>
</table>

15. The relation between FGR and caffeine intake during pregnancy was modelled using the best-fitting second-order fractional polynomial (Figure 1). The curve in Figure 1 was derived from a model that took into account other risk factors such as salivary cotinine levels, self-reported alcohol consumption, maternal height, weight, ethnicity, parity, gestation at delivery and gender of the neonate. The results were robust to exclusion of those women with high risk pregnancies, multiparity, and extremely high or low caffeine intakes. For all levels of caffeine intake, lower intakes of caffeine were associated with lower risk of fetal growth restriction. It is possible that the steep decline in risk associated with caffeine intakes of less than 30 mg/day may be attributable to residual confounding. This analysis suggested a continuously increasing risk across the exposure range, and gave no indication of a threshold level.
of exposure, below which risk was not elevated. The Committee requested a repeat
of this analysis, excluding those women who consumed more than 300 mg caffeine
per day. This confirmed that the high level consumers did not materially alter the
shape of the exposure-response curve.

16. Further statistical analysis with regression models (logistic regression for
binary outcomes, e.g. FGR vs no FGR, and linear regression for continuous
outcomes, e.g. birth weight centile) gave no indication of important residual
confounding by smoking.

17. Analysis of the data on half-lives of caffeine (as a proxy for metabolism) in
saliva suggested an increased risk of FGR in fast metabolisers (shorter half life) as
compared with slow metabolisers (longer half life), although the difference was not
statistically significant (P=0.06).

18. It is interesting that among the women with caffeine intakes > 300 mg/day
prior to pregnancy, a subset had chosen to reduce their caffeine intake to <50
mg/day by weeks 5-12 of pregnancy (n=109). The mean birth weight of infants in this
subset was higher than that in women who maintained their caffeine intake above
300 mg/day (n=193) (difference in birth weight=161g, 95% CI: 24 to 297g, p=0.02).
However, these two groups of women may have differed in other ways apart from
their caffeine intakes.

19. The Committee noted that energy intake needed to be considered as a
potential confounder of effects on fetal growth rate. Energy intake had been recorded
in the Leeds arm of the study, but not in Leicester. An analysis of data from Leeds
that adjusted for energy intake indicated that energy intake did not importantly
confound the risk estimates for caffeine in this study.

**Literature review (post-2001 COT statement)**

20. In addition to being presented with the results from the FSA-funded research,
the Committee was provided with an update on relevant research on reproductive
effects of caffeine in humans published since the previous COT review. Table 2
summarises the key data provided to the Committee in tabular form. The references
detailed in Table 2 were sourced through a systematic search of key scientific
databases, details of which are given in Annex A.

21. It was noted that published studies differed substantially in their design, which
may account for some of the variation in the estimated risks of adverse reproductive
outcomes reported for specified levels of caffeine intake.

22. Most studies assessed caffeine intake at various stages of pregnancy,
generally by use of dietary questionnaires. In most reports, caffeine intakes were
assessed by multiplying the number of servings of a beverage or food by an
estimated mean caffeine content, and different studies assumed different caffeine
contents for beverages and foods. Further variation may have been introduced
according to whether participants were asked to estimate serving size or the
researcher assumed a default serving size.
23. Errors in recall would be expected to affect the accuracy of information provided on caffeine intake and on potential confounders, particularly in studies where information was gathered retrospectively. In case-control studies that ascertained caffeine intake after the outcome of pregnancy was known, differential errors may have spuriously exaggerated risk estimates. It should also be noted that many of the studies did not assess caffeine intake from all sources.

24. There is considerable inter-individual variation in caffeine metabolism, and measures of caffeine consumption do not necessarily indicate the levels of caffeine and caffeine metabolites in the maternal or fetal circulation. A small number of studies therefore measured levels of caffeine and its metabolites in maternal or umbilical cord blood rather than assessing caffeine consumption.

25. Further variation in estimates of caffeine effect may have occurred because the range of confounding factors that was taken into account differed between studies. Notably, several studies did not adjust for smoking or nausea during pregnancy.

26. Caffeine consumption greater than or equal to 300 mg/day was reported in several studies\textsuperscript{7-14} to be associated with FGR, decreased mean birth weight, miscarriage, or increased risk of still birth, with one study finding a doubled risk of miscarriage for caffeine intakes above 200 mg/day\textsuperscript{15}. Another study in pregnant women with Type 1 diabetes suggested an increased risk of miscarriage for a caffeine intake of just 1-2 caffeine-containing beverages per day in the first trimester, compared to non-consumers, although the elevation of risk only reached statistical significance for daily intakes of three or more drinks\textsuperscript{16}. On the other hand, there were well-conducted studies that reported no statistically significant association between maternal caffeine intake and miscarriage, FGR, still birth or prematurity, after adjustment for potential confounders\textsuperscript{17-21}. Overall, the findings were consistent with an increased risk of FGR and miscarriage from higher consumption of caffeine, but because of limitations in study designs (e.g. inaccurate assessment of caffeine exposures, potential for recall bias in case-control studies, and possible residual confounding), they do not allow firm conclusions about the relation of risk to levels of exposure.

27. Fewer studies looked at CYP1A2 activity and pregnancy outcomes, due to substantial confounding by smoking status, which is hard to correct for. One investigation suggested an increased risk of FGR in women with fast metabolic phenotype\textsuperscript{22}, while another found an association of caffeine intake with miscarriage only in women with low CYP1A2 activity\textsuperscript{23}.

**Related observations from studies using experimental animals**

28. The potential reproductive effects of caffeine have been studied in a wide range of species and strains of animals. In studies administering repeat doses of caffeine (12.5 mg/kg body weight per day and higher) to rats throughout pregnancy, significantly decreased birth weights have been noted\textsuperscript{24}. It is not possible to determine whether this was due to a direct effect of caffeine on the fetus or secondary to decreased maternal body weight gain since it was observed only when there was a decrease in maternal body weight gain. In mice administered caffeine in
drinking water at levels equating to consumption of 22, 44 and 88 mg/kg/day a
reduction in number of live pups/litter of 15 and 20% was observed in the medium
and high dose level group, respectively. For the F0 animals there were no effects on
body weight, but alopecia occurred in 55% of the medium dose and 50% of the high
dose animals25.

29. Studies in the Cynomolgus monkey, Macaca fascicularis, have shown a high
rate of still births and miscarriage with maternal caffeine intakes of 10-15 mg/kg body
weight per day, given via drinking water26. In 2001 the COT noted “that the main
serum metabolite of caffeine in monkeys is theophylline, whereas in humans it is
paraxanthine and that information on the comparative toxicities of these metabolites
is not available.” It should be noted that the Cynomolgus monkey does not
constitutively express CYP1A2 (which is the main enzyme responsible for caffeine
metabolism) 27. Thus, for a given dose of caffeine, the monkeys’ systemic exposure
is likely to be higher. Furthermore, there were limitations in the study design and
therefore this study is not informative for assessing the risks of caffeine intake in
humans.

Committee discussion

30. With regard to the new FSA-funded research, FGR was considered to be a
relatively robust endpoint, unlike miscarriage, which is difficult to ascertain reliably as
it often occurs before women know they are pregnant, or before they have been
recruited to a study. Members noted that decreases in birth weight of as little as 10-
15 g can have implications for future health outcomes, particularly in pre-term babies.

31. Caffeine consumption was assessed retrospectively by means of a
questionnaire completed at interview at the end of each of the three trimesters of
pregnancy, women being asked to recall their caffeine consumption during 4 week
periods. Data on caffeine intake from all sources were recorded (tea, coffee, hot
chocolate, soft drinks, chocolate) including information on brand, serving size and
preparation of product. Caffeine consumption is likely to have been estimated with
reasonable accuracy as, because of the repeated administration of the questionnaire,
recall was recent and for most before pregnancy outcome or birth weight were
known. Salivary cotinine measurement confirmed the accuracy with which the
women reported their smoking habits.

32. The half-life of caffeine was measured in women in a “caffeine challenge” the
a priori hypothesis being that an increased half-life would be associated with an
increased risk of FGR, based upon the assumption that clearance would remove the
potential hazard. However, this was not found. Rather, the analysis suggested that if
anything, risk of FGR was higher in faster metabolisers than in slower metabolisers.
This result is consistent with the findings of Grosso et al22, who reported increased
risk of intrauterine growth retardation (IUGR) in association with serum paraxanthine
levels >149 ng/ml and higher paraxanthine/caffeine ratios. There are no reports of
animal studies investigating reproductive effects of paraxanthine.

33. It was noted that adjustment for various potential confounding factors had little
impact on risk estimates.
34. The fact that repeat modelling of the risk of FGR according to caffeine intake showed a similar dose-response relation after exclusion of women with caffeine intakes in excess of 300 mg per day suggested that the modelled relationship was not unduly influenced by findings for women with the highest caffeine intakes. The Committee noted the possibility that fitting a different mathematical model to the data may have importantly influenced the dose-response relationship observed in Figure 1, and that there was considerable uncertainty about the shape of the dose-response relationship at lower intakes. They noted that the model used placed weight on those with intakes below 50 mg/day (who may have differed in their exposure to confounding lifestyle factors) and questioned whether it was the most appropriate choice. Hence it would be inappropriate to attempt to determine a threshold dose from this figure.

Committee conclusions

35. We consider that the FSA-funded research contributes usefully to the body of evidence on the relation between caffeine intake and adverse birth outcomes.

36. From this work and from the other studies that have been published, we conclude that caffeine intake during pregnancy is associated with an increased risk of FGR. It is still not possible to be confident that the association is causal rather than a consequence of residual confounding, but it would be prudent to assume causation.

37. The evidence that is now available does not make it possible to identify a threshold level of caffeine intake below which there is no elevation of risk, and it seems likely that risk is increased in association with intakes in the order of 200 mg per day and perhaps even lower. However, if the relation is indeed causal, then the absolute increase in incidence of FGR from intakes less than 200 mg per day is likely to be less than 2% of infants.

38. The literature suggests a positive association of caffeine intake with miscarriage, but there are uncertainties relating to possible recall bias and residual confounding.

39. Data on maternal caffeine consumption during pregnancy and associations with adverse effects other than FGR and spontaneous miscarriage, such as pre-term birth and congenital malformations, are inconclusive.

COT statement 2008/04
September 2008
Figure 1 Modelled relation between risk of fetal growth restriction (FGR) and caffeine intake (mg/day) during pregnancy.

The relation is modelled by the best-fitting second-order fractional polynomial, with 95% confidence intervals. For clarity, the graph is restricted to caffeine intakes <500mg/day. Horizontal dotted lines mark national average risk of FGR (10%) and the average risk in the cohort (13%).
References


### Table 2. Key data from relevant human studies published since the previous COT review

<table>
<thead>
<tr>
<th>Author + location</th>
<th>Study period</th>
<th>Outcome variables</th>
<th>Study sample</th>
<th>Measure of caffeine exposure</th>
<th>Study authors description of results</th>
<th>OR/RR (95% CI)</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Studies on Birth Weight</strong></td>
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<tr>
<td>Balat et al (2003)(^7) Turkey</td>
<td>Not stated</td>
<td>BW, length and head circumference, weight and diameter of placenta</td>
<td>63 pregnant non-smokers + 60 pregnant smokers with spontaneous vaginal deliveries in gestational wks 37-41</td>
<td>Daily consumption of tea and coffee (#cups) Participants grouped as daily caffeine intake &lt; or &gt; 300 mg/day</td>
<td>Non-smokers and smokers consuming &gt;300 mg/day had significantly lower newborn and placental weights than those consuming &lt;300 mg/day. No differences in other parameters.</td>
<td>Not reported</td>
<td>No adjustment reported.</td>
</tr>
<tr>
<td>Bech et al (2007)(^25) Denmark</td>
<td>1998-2002</td>
<td>Birth weight and length of gestation</td>
<td>1207 pregnant women drinking at least 3 cups of coffee/day, recruited before 20 wks gestation</td>
<td>Randomised to drink caffeinated (n=568) or decaffeinated (n=629) instant coffee at usual consumption levels Interviewed throughout pregnancy on daily consumption coffee, tea, cola and cocoa</td>
<td>No significant differences in mean bw or mean length of gestation between caffeinated and decaffeinated groups. Mean bw of babies of women in the decaffeinated group was 16 g (95% CI: -40, +73) higher than those from the caffeinated group.</td>
<td>Not reported</td>
<td>Adjustment for length of gestation, parity, prepregnancy BMI and smoking at entry to study. Women were not asked to avoid intake of other caffeinated beverages.</td>
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<td>Author + location</td>
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<td>Bicalho and Barros Filho (2002)</td>
<td>1994-1995</td>
<td>LBW, prematurity and IUGR</td>
<td>354 newborns with bw &lt;2,500 g (cases) 354 newborns ≥3,000 g (controls)</td>
<td>Daily consumption of coffee, tea and soft drinks</td>
<td>No association between caffeine consumption during pregnancy and low birthweight, prematurity and intrauterine growth restriction.</td>
<td>Caffeine (mg/day)</td>
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<td>Adjustment for age, schooling, income, marital status, skin colour, parity, smoking, previous lbw child, pre-pregnancy weight, employment status, interval between pregnancies, prenatal care and high blood pressure</td>
</tr>
<tr>
<td>Bracken et al (2003)</td>
<td>1996-2000</td>
<td>IUGR LBW</td>
<td>2,291 women with singleton live births</td>
<td>Interviews on coffee, tea and soda consumption - Interview on trimester 1 intake conducted before gestation wk 25 - Post natal interview on trimester 3 intake Urine analysis at interview 1</td>
<td>No significant association of caffeine consumption in trimesters 1 or 3 or urinary caffeine with the various endpoints. Mean bw reduced by 28 g per 100 mg caffeine consumed daily in trimester 1 [vs 178g reduction for smoking 10 cigarettes daily in trimester 3].</td>
<td>Trimester 1 Caffeine (mg/Day) Reference: average 0 mg/day</td>
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<td>Author + location</td>
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<td>Study sample</td>
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<td>Clausson et al (2002)</td>
<td>1996-1998</td>
<td>BW, gestational age, BW standardised for gestational age (BW ratio)</td>
<td>873 women with singleton live births</td>
<td>Interviews in gestational wks 6-12 and 32-34 on intake of coffee, tea, soft drinks, cocoa, chocolate and caffeine containing medication</td>
<td>No associations between caffeine consumption and the endpoints assessed, neither when caffeine exposure averaged from conception to gestational wks 32-34, nor when stratified by trimester</td>
<td>Not reported</td>
<td>Adjustment for age, height, BMI, country of birth, parity, previous LBW infant, education, work, nausea, vomiting, fatigue, diabetes and hypertensive disorders</td>
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<tr>
<td>Grosso et al (2006)</td>
<td>1996-2000</td>
<td>IUGR</td>
<td>Pregnant women at ≤24 gestational wks: 718 consuming ≥150 mg/day caffeine in previous wk 2,915 consuming &lt;150 mg/day in previous wk</td>
<td>Caffeine and primary metabolites measured in umbilical cord blood</td>
<td>Higher serum caffeine levels associated with reduced risk IUGR. Paraxanthine levels ≥149 ng/ml associated with increased risk. Increase in paraxanthine:caffeine ratio increased likelihood of IUGR.</td>
<td>Standard deviation increase in paraxanthine:caffeine ratio</td>
<td>1.21 (1.07, 1.37)</td>
</tr>
<tr>
<td>Infante-Rivard, (2007)</td>
<td>1998-2000</td>
<td>SGA</td>
<td>493 SGA cases, 480 controls</td>
<td>Interview within 2 days of delivery on number of cups of coffee, tea and cans of cola daily for each trimester, and month before pregnancy</td>
<td>No association caffeine consumption and SGA overall (smokers and non-smokers combined). ORs for caffeine intake in trimester 1 statistically heterogeneous between smokers and non, authors suggest an increased risk for non-smokers</td>
<td>Caffeine (mg/day) ≥300 in trimester 1 vs &lt;300 Reference category: &lt;300 mg/day</td>
<td>Smokers 0.43 (0.18, 1.03) Non smokers 2.13 (0.82, 1.03) Heterogeneity: p=0.01</td>
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<tr>
<td>Author + location</td>
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<td>Outcome variables</td>
<td>Study sample</td>
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<tr>
<td>Klebanoff et al (2002)</td>
<td>1959-1966</td>
<td>SGA</td>
<td>2,515 women</td>
<td>Paraxanthine levels in serum collected in trimester 3 (&gt;26 wks of gestation)</td>
<td>Mean levels higher in women with SGA babies (754 ng/ml) vs women with NGA babies (653 ng/ml) Significant linear trend for smokers but not non-smokers before adjustment</td>
<td>Not reported</td>
<td>Adjustment for maternal age, pre-pregnancy weight, education, parity, ethnicity and no. cigarettes smoked per day</td>
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<tr>
<td>Ørskou et al (2003)</td>
<td>1990-1999</td>
<td>High birth weight (&gt;4,000 g)</td>
<td>24,093 non-diabetic pregnant women</td>
<td>Questionnaire at approx. 16 wks gestation on average daily coffee intake</td>
<td>Women with a caffeine intake of &gt;200 mg/day had a statistically reduced ‘risk’ of giving birth to an infant weighing &gt; 4,000 g compared to women with an intake of &lt;200 mg/day. OR for high BW</td>
<td>Caffeine (mg/day)</td>
<td>Adjustment for pre-pregnancy weight and height, parity, smoking, alcohol, marital status, education level, gestational age and infant gender</td>
</tr>
<tr>
<td>Parazzini et al (2005)</td>
<td>Not stated</td>
<td>SGA</td>
<td>555 women with SGA babies [&lt;10th percentile based on Italian standard] (cases) 1966 women with term babies of normal weight (controls)</td>
<td>Interviews on tea, cola and coffee intake prior to pregnancy and in each trimester</td>
<td>No significant associations between tea, cola, caffeinated coffee or decaffeinated coffee consumption and SGA</td>
<td>Coffee (≥3 cups/day)</td>
<td>Adjustment for age, education, parity, smoking in trimester 3, gestational hypertension and history of SGA birth</td>
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<tr>
<td>Author + location</td>
<td>Study period</td>
<td>Outcome variables</td>
<td>Study sample</td>
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<td>Vik et al (2003)</td>
<td>1986-1988</td>
<td>SGA</td>
<td>111 mothers of small for gestational age (SGA) babies, 747 mothers of non-SGA babies</td>
<td>3-day food records collected in Trimesters 2 and 3. Caffeine intake calculated from tea, coffee, soft drinks and chocolate, classed as high or low based on median</td>
<td>Mean caffeine intake higher in SGA mothers than controls in trimester 3 (281 vs 212 mg/day) but not in trimester 1</td>
<td><strong>OR</strong> 1.1(0.6,2.1) <strong>1.6(1.0,2.5)</strong> <strong>1.5(1.0,2.4)</strong></td>
<td>Adjustment for smoking at conception, pre-pregnancy wt, low education, previous SGA birth</td>
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<tr>
<td>Xue et al (2007)</td>
<td>Inform-collected from mothers in 2001-2002</td>
<td>BW, IUGR</td>
<td>34,063 women in Nurse’s Mother Cohort</td>
<td>Interviews conducted on coffee intake when pregnant with their nurse daughters</td>
<td>Daily consumption of each additional cup of coffee associated with a 10g decrease in bw</td>
<td>Coffee (cups/day) <strong>1.00(0.82,1.21)</strong> <strong>1.28(1.12,1.47)</strong> <strong>1.30(1.10,1.55)</strong> <strong>1.63(1.25,2.12)</strong></td>
<td>Interviews with mothers conducted a long time after pregnancy - when their offspring were adults</td>
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<td></td>
<td>Trend test (cup/day) <strong>1.09(1.05,1.13)</strong></td>
<td>Adjustment for maternal BW, height, BMI, birth order, maternal weight gain, diabetes in pregnancy, smoking, gestational age, occupation, maternal milk consumption, paternal BMI, maternal infertility</td>
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<td>Author + location</td>
<td>Study period</td>
<td>Outcome variables</td>
<td>Study sample</td>
<td>Measure of caffeine exposure</td>
<td>Study authors description of results</td>
<td>OR/RR (95% CI)</td>
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<tr>
<td>Bech et al (2005)</td>
<td>1996-2002</td>
<td>Fetal death (miscarriage or stillbirth)</td>
<td>88,482 pregnant women recruited into Danish National Birth Cohort by GPs</td>
<td>Telephone interview at approx gestational wk 16 on daily coffee consumption</td>
<td>High levels of coffee consumption associated with an increased risk of fetal death</td>
<td>OR/RR (95% CI)</td>
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<td>0.5-3 cups coffee/day:</td>
<td>1.03 (0.89, 1.19)</td>
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<td>4-7 cups coffee/day:</td>
<td>1.33 (1.08, 1.63)</td>
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<td>≥8 cups coffee/day:</td>
<td>1.59 (1.19, 2.13)</td>
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<td>0 cups coffee/day</td>
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</table>

| George et al (2006)      | 1996-1998    | Repeated miscarriage | 108 women with ≥2 consecutive miscarriages (cases) 953 control women matched by wks of gestation | Interviews within 2-6 wks of miscarriage on intake of coffee, tea, cocoa, chocolate, soft drinks and caffeine-containing medication | Mean caffeine intake 311 mg/day in cases, 240mg/day for controls | Mean caffeine intake in pregnancy (mg/day) | 0.5 (0.04, 6.9) | 0.4 (0.05, 4.1) |
|                          |              |                   |              |                              |                                     | Smokers         |          |
|                          |              |                   |              |                              |                                     | Non smokers     |          |
|                          |              |                   |              |                              |                                     | 1.9 (0.8, 4.3)  | 2.7 (1.1, 6.2) |
|                          |              |                   |              |                              |                                     | Reference:      |          |
|                          |              |                   |              |                              |                                     | 0-99 mg/day     |          |

Adjustment for age, parity, smoking, prepregnancy BMI, alcohol consumption, socio-occupational status
<table>
<thead>
<tr>
<th>Giannelli et al. (2003)</th>
<th>1987-1989</th>
<th>Miscarriage</th>
<th>160 nulliparous women with miscarriage (cases) 314 nulliparous pregnant women attending for antenatal care in trimester 3.</th>
<th>Interview 3 wks after miscarriage or at antenatal appointment on coffee, tea and cola consumption</th>
<th>Caffeine consumption &gt;300 mg/day during pregnancy associated with an increased risk of miscarriage</th>
<th>Caffeine intake in pregnancy (mg/day)</th>
<th>151-300</th>
<th>301-500</th>
<th>&gt;500</th>
<th>Reference: ≤ 150 mg/day</th>
<th>Adjustment for maternal age, severity of nausea and gestational age.</th>
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<tr>
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<td>Caffeine intake in pregnancy (mg/day)</td>
<td>1.19(0.67, 2.12)</td>
<td>1.94(1.04, 3.63)</td>
<td>2.18(1.08, 4.40)</td>
<td>≤ 150 mg/day</td>
<td>1.19(0.67, 2.12)</td>
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<tr>
<td>Author + location</td>
<td>Study period</td>
<td>Outcome variables</td>
<td>Study sample</td>
<td>Measure of caffeine exposure</td>
<td>Study authors description of results</td>
<td>OR/RR (95% CI)</td>
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<tr>
<td>Karypidis et al (2006)</td>
<td>1996-1998</td>
<td>First trimester miscarriage</td>
<td>507 women with miscarriage in trimester 1 (cases) 908 women with a normal trimester 1 pregnancy (controls)</td>
<td>Interview on intake of coffee, tea, caffeine-containing soda and hot chocolate. Consumption based on women’s estimate of cup size</td>
<td>Significant association between caffeine intake of 100-299 and &gt;500 mg/day and miscarriage in women with CYP1B1 Val/Val genotype.</td>
<td>Caffeine intake (mg/day)</td>
<td>Val/Val genotype</td>
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<td>100-299: 2.63 (1.39, 4.98)</td>
<td>300-499: 1.82 (0.84, 3.93)</td>
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<td>&gt;500: 3.61 (1.36, 9.61)</td>
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<td>Reference:</td>
<td>Leu/Leu genotype &amp; &lt;100 mg/day intake</td>
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<td>Adjust for age, smoking, alcohol, previous miscarriage, parity, pregnancy symptoms</td>
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<tr>
<td>Khoury et al (2004)</td>
<td>1978-1993</td>
<td>Wide range including, miscarriage, congenital malformation, pre-eclampsia, delivery at &lt;37wks.</td>
<td>191 pregnant women with type 1 diabetes</td>
<td>Monthly interviews; caffeine consumption based on number cups caffeinated beverages/day</td>
<td>Significant associations observed for spontaneous miscarriage (+ve), pre-eclampsia and infant hypoglycaemia (-ve)</td>
<td>Drinks/day</td>
<td>Spont. miscarriage</td>
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<td>1-2: 3.8 (0.8, 16.9)</td>
<td>5.2 (1.2, 22.0)</td>
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<td>Reference: 0 drinks/day</td>
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<td>Caffeine intake at &gt;20 wks gestation</td>
<td>Pre-eclampsia 0.3 (0.1, 1.0)</td>
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<td>Infant hypoglycaemia 0.2 (0.1, 1.0)</td>
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<td>Adjust for age, yrs since diagnosis of diabetes, nephropathy, retinopathy, glycaemic control, cigarette smoking</td>
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<td>Author + location</td>
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</table>
| Maconochie et al (2007) | 1980-2002 | Trimester 1 miscarriage | 603 women with most recent pregnancy ending in trimester 1 miscarriage (cases) 6116 women with most recent pregnancy progressing beyond 12 wks (controls) | Questionnaire on reproductive history sent to UK women in 2001. Caffeine intake determined by tea, coffee and caffeinated drink consumption | Apparent association between caffeine intake and risk of miscarriage not significant after adjustment for nausea | Caffeine (mg/day)  
<151: 1.03 (0.71, 1.49)  
151-300: 0.93 (0.64, 1.33)  
301-500: 1.04 (0.72, 1.50)  
>500: 1.14 (0.79, 1.66) | Adjustment for year of conception, maternal age, previous miscarriage, previous live birth and nausea |
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<th>Author + location</th>
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<th>Outcome variables</th>
<th>Study sample</th>
<th>Measure of caffeine exposure</th>
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<th>OR/RR (95% CI)</th>
<th>Comments</th>
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<tr>
<td>Matijasevich et al (2006)35 Uruguay</td>
<td>2002-2003</td>
<td>Fetal death</td>
<td>382 women with fetal death ≥20wks gestational age or weighing &gt;350g (cases) 792 women with live term NGA births (controls)</td>
<td>Questionnaire on coffee and mate consumption</td>
<td>Mean caffeine intake significantly higher in cases than controls (156.5 mg/day vs 113.6)</td>
<td>Mean caffeine (mg/day) 1-59 60-149 150-299 ≥300</td>
<td>0.74(0.42,1.31) 0.93(0.51,1.67) 1.22(0.69,2.17) 2.33(1.23,4.41)</td>
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<tr>
<td>Rasch et al (2003)33 Denmark</td>
<td>1994</td>
<td>Miscarriage</td>
<td>330 women with miscarriage in gestational wks 6-16 (cases) 1168 women with live fetuses in gestational wks 6-16 (controls)</td>
<td>Questionnaire on daily tea, coffee, cola and chocolate bar consumption during pregnancy</td>
<td>Consumption of ≥375 mg caffeine/day associated with increased risk of miscarriage</td>
<td>Caffeine (mg/day) 200-374 ≥375</td>
<td>1.31(0.92,1.86) 2.21(1.53,3.18)</td>
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<tr>
<td>Author + location</td>
<td>Study period</td>
<td>Outcome variables</td>
<td>Study sample</td>
<td>Measure of caffeine exposure</td>
<td>Study authors description of results</td>
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<tr>
<td>Sata et al (2005)</td>
<td>2003-2004</td>
<td>Recurrent pregnancy loss</td>
<td>58 women with two or more miscarriages (cases) 147 women with live births (controls)</td>
<td>Questionnaire on coffee, tea and cola consumption during pregnancy</td>
<td>CYP1A2*1F (AA vs CA CC) genotype found to influence risk</td>
<td>Caffeine (mg/day) All women 100-299 ≥300 1.29(0.66,2.50) 1.82(0.72,4.58) CYP1A2 CC+CA 100-299 ≥300 1.03(0.42,2.52) 1.03(0.29,3.70) CYP1A2 AA 100-299 ≥300 1.94(0.57-6.66) 5.23(1.05-25.9)</td>
<td>Adjustment for age and smoking status in pregnancy</td>
</tr>
<tr>
<td>Author + location</td>
<td>Study period</td>
<td>Outcome variables</td>
<td>Study sample</td>
<td>Measure of caffeine exposure</td>
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<tr>
<td>Savitz et al (2008)(^{20}) USA</td>
<td>2000-2004</td>
<td>Miscarriage at &lt;20 gestational wks</td>
<td>2407 women recruited at &lt;12 gestational wks</td>
<td>Interview before 16 weeks on caffeine-containing coffee, tea and soda consumption pre-pregnancy, 4 wks after last menstrual period (LMP), + at time of interview or when still pregnant</td>
<td>Coffee and caffeine consumption at all 3 timepoints were unrelated to overall risk of miscarriage.</td>
<td>Caffeine (mg/day)</td>
<td>Pre-preg 1.6 (0.7,3.4) 1.2 (0.6,2.6) 1.1 (0.4,2.6) 4wks post LMP 1.2 (0.6,2.2) 1.0 (0.5,2.0) 0.5 (0.2,1.4) Time of interview 1.1 (0.6,2.2) 1.9 (1.1,3.5) 2.3 (1.2,4.5)</td>
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<td>Author + location</td>
<td>Study period</td>
<td>Outcome variables</td>
<td>Study sample</td>
<td>Measure of caffeine exposure</td>
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| Signorello et al (2001) | 1996-1998 | Miscarriage | 101 women with normal karyotype miscarriages (cases) 953 pregnant women at 6-12 gestational wks (controls) | Interviews within 2 wks of miscarriage or 6 days of enrolment (controls). Coffee, tea, cocoa, chocolate, soft drinks + caffeine-containing medication | Caffeine found to be a significant risk factor among women with low, but not high, CYP1A2 activity. Association with NAT2 genotype less clear. | Caffeine (mg/day)  
100-299 ≥300  
100-299 ≥300  
100-299 ≥300  
100-299 ≥300  
Reference: 0-99 mg/day for each group | Low CYP1A2 activity  
0.32(0.08,1.23)  
0.46(0.12,1.73)  
High CYP1A2 activity  
2.42(1.01,5.80)  
3.17(1.22,8.22)  
Slow acetylators  
2.38(1.04,5.49)  
1.65(0.67,4.06)  
Fast acetylators  
1.07(0.39,2.95)  
1.93(0.67,5.51) | Adjustment for age, gestational week, smoking + nausea |
<table>
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<tr>
<th>Author + location</th>
<th>Study period</th>
<th>Outcome variables</th>
<th>Study sample</th>
<th>Measure of caffeine exposure</th>
<th>Study authors description of results</th>
<th>OR/RR (95% CI)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Tolstrup et al (2003)</td>
<td>1991-1995</td>
<td>Miscarriage</td>
<td>303 women from a population-based cohort with miscarriage (cases) 1381 women in cohort who gave birth (controls)</td>
<td>Interview on tea and coffee intake at enrolment into cohort and again 2 yrs later</td>
<td>High pre-pregnancy caffeine intake (&gt;900 mg/day) associated with an increased risk of miscarriage</td>
<td>Caffeine intake pre-pregnancy (mg/day) 75-300: 1.26 (0.77-2.06) 301-500: 1.45 (0.87,2.41) 501-900: 1.44 (0.87,2.37) &gt;900: 1.72 (1.00,2.96) Reference category: &lt;75 mg/day</td>
<td>Only considers pre-pregnancy caffeine intake. Adjustment for age, marital status, smoking and alcohol intake.</td>
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<tr>
<td>Weng et al (2008)</td>
<td>1996-1998</td>
<td>Miscarriage at &lt;20 gestational wks</td>
<td>1063 pregnant women recruited at ≤15 gestational wks</td>
<td>Interview on intake of coffee, tea, caffeine-containing soda and hot chocolate</td>
<td>Increasing caffeine consumption associated with an increased risk of miscarriage</td>
<td>Caffeine mg/day &lt;200: 1.42 (0.93,2.15) ≥200: 2.23 (1.34,3.69) Baseline: Non-user</td>
<td>Adjustment for maternal age, race, education, family income, marital status, previous miscarriage, nausea and vomiting since LMP, smoking status, alcohol consumption, Jacuzzi use and magnetic field exposure.</td>
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<tr>
<td>Wisborg et al (2003)</td>
<td>1989-1996</td>
<td>Stillbirth and infant death in 1st yr of life</td>
<td>18,478 singleton pregnancies</td>
<td>Questionnaire at approx 16 wks of gestation on coffee intake</td>
<td>Drinking coffee during pregnancy associated with an increased risk of stillbirth but not infant death</td>
<td>Coffee (cups/day) 1-3: Stillbirth 0.6 (0.3, 1.1) 4-7: 1.4 (0.8, 2.5) ≥8: 2.2 (1.0, 4.7) Infant death 1-3: 0.9 (0.6, 1.6) 4-7: 0.2 (0.1, 0.7) ≥8: 1.6 (0.7, 3.6) Baseline: 0 cups/day</td>
<td>Caffeine exposure from tea, cola or drinking chocolate considered insignificant so not included in analysis. Adjustment for smoking and alcohol, parity, age, marital status, BMI, yrs education and employment status in pregnancy.</td>
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<td>Author + location</td>
<td>Study period</td>
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<td>Study sample</td>
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Denmark | 1998-2002 | Birth weight and length of gestation | 1207 pregnant women drinking at least 3 cups of coffee/day, recruited before 20 wks gestation | Randomised to drink caffeinated (n=568) or decaffeinated (n=629) instant coffee at usual consumption levels  
Interviewed throughout pregnancy on daily consumption coffee, tea, cola and cocoa | No significant differences in mean bw or mean length of gestation between caffeinated and decaffeinated groups. | Not reported | Adjustment for length of gestation, parity, prepregnancy BMI and smoking at entry to study.  
Women were not asked to avoid intake of other caffeinated beverages. |
| Bicalho and Barros Filho (2002)  
Brazil | 1994-1995 | LBW, prematurity and IUGR | 354 newborns with bw <2,500 g (cases)  
354 newborns ≥3,000 g (controls) | Daily consumption of coffee, tea and soft drinks | No association between caffeine consumption during pregnancy and low birthweight, prematurity and intrauterine growth restriction. | Caffeine (mg/day)  
<300 | 0.59(0.32,1.09)  
≥300 | 0.32(0.15,0.72) | Abstract only in English.  
Adjustment for age, schooling, income, marital status, skin colour, parity, smoking, previous lbw child, pre-pregnancy weight, employment status, interval between pregnancies, prenatal care and high blood pressure |
<table>
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<tr>
<th>Study</th>
<th>Country</th>
<th>Timeframe</th>
<th>Outcome Description</th>
<th>Study Design</th>
<th>Coffee/Tri. 1 Caffeine (mg/day)</th>
<th>Preterm delivery (95% CI)</th>
<th>Adjustment Factors</th>
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<tbody>
<tr>
<td>Bracken et al (2003)</td>
<td>USA</td>
<td>1996-2000</td>
<td>Preterm delivery</td>
<td>Interviews on coffee, tea and soda consumption - Interview on trimester 1 intake conducted before gestation wk 25 - Post natal interview on trimester 3 intake Urine analysis at interview 1</td>
<td>No significant association of caffeine consumption in trimesters 1 or 3 or urinary caffeine with preterm delivery</td>
<td>Trimester 1 Caffeine (mg/day)</td>
<td>Preterm del 1.20(0.80,1.76) 1.74(0.93,3.27) 1.67(0.76,3.81) Reference: average 0 mg/day</td>
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<tr>
<td>Chiaffarino et al (2006)</td>
<td>Italy</td>
<td>1989-1999</td>
<td>Preterm birth of SGA or normal for gestational age babies</td>
<td>Post pregnancy interview on coffee, tea and cola consumption</td>
<td>No significant association with overall intake of caffeine Inverse association coffee consumption (≥2 servings/day) disregarding caffeine from other sources and risk of SGA preterm babies (OR= 0.5 [0.3,0.8])</td>
<td>Caffeine servings/day</td>
<td>Preterm SGA 1.1 (0.7,1.8) 1.0 (0.6,1.7) Preterm NGA 0.9 (0.6,1.3) Reference category: 0 servings/day</td>
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<td>de Souza + Sichieri (2005)</td>
<td>Brazil</td>
<td>Not stated</td>
<td>Prematurity</td>
<td>'Semi-quantitative’ food frequency questionnaire on coffee, tea + powdered chocolate</td>
<td>Total caffeine consumption during pregnancy not associated with prematurity</td>
<td>Caffeine (mg/day)</td>
<td>50-99 1.58(0.32,2.84) 1.35(0.48-3.80) Baseline: Below 50 mg/day</td>
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<tr>
<td>Author + location</td>
<td>Study period</td>
<td>Outcome variables</td>
<td>Study sample</td>
<td>Measure of caffeine exposure</td>
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<tr>
<td>Browne et al (2007) USA</td>
<td>1997-2002</td>
<td>Cardio-vascular malformations (CVMs)</td>
<td>4,196 mothers of infants with cardio-vascular malformation 3,957 controls</td>
<td>Telephone interviews on consumption of caffeinated coffee, tea, soda or soft drinks and chocolate in year prior to pregnancy</td>
<td>No significant positive associations between maternal caffeine consumption and CVMs</td>
<td>Caffeine (mg/day) 10-&lt;100 100-&lt;200 200-&lt;300 ≥300 Baseline: &lt;10 mg caffeine/day</td>
<td>All CVM 1.17(0.91,1.50) 1.05(0.80,1.38) 1.23(0.91,1.66) 1.24(0.91,1.68)</td>
</tr>
</tbody>
</table>
Search strategy for review of research on reproductive effects of caffeine

**Pubmed**

Colleagues at the Food Standards Agency’s Information Centre searched using the following search terms:

(caffeine OR coffee) AND [("adverse effects" AND "pregnancy") OR "fetal growth restriction" OR "fetal growth retardation" OR "FGR" OR "fetal growth" OR "miscarriage" or "outcomes" OR "birth weight" OR "intrauterine growth retardation" OR "IUGR" OR "small for gestational age" OR "SGA" OR "fetus" OR "preterm birth")]

Limits imposed on search: Published between 2001-2008, limited to ‘humans’

Total number of papers: **32**

Of these, 2 papers were not ordered as they were review articles, 2 reported studies performed in rodents, 1 described a study of factors affecting IVF fertility and 6 referred to caffeine only as a confounder in irrelevant studies.

Search conducted on PubMed using the following search string:

(caffeine OR coffee) AND ("adverse effects" AND "pregnancy")

Limits imposed on search: Published between 2001-2008, limited to ‘humans’

Total number of papers: **88**

This search yielded 24 potentially useful references that were not identified in the previous search. All of the other references in this search were duplicates of those already obtained, or were disregarded primarily as they described studies where pregnancy outcome was not the main focus of the study, or focussed on different species such as primates, rats or mice, or for one of the reasons stated previously.

**British Library Inside**

Search conducted on British Library Inside using the following search string:

(caffeine OR coffee) AND pregnancy

Limits imposed on search: Published ≥2001 only.

Total number of papers: **72**
Of these 18 had not been previously identified. All of the other references in this search were either duplicates of papers already obtained, duplicates within the search, or were disregarded for the reasons outlined above.

**Current Contents**

Colleagues at the Information Centre searched using the following search terms:

(caffeine OR coffee) AND [(“adverse effects” AND “pregnancy”) OR “fetal growth restriction” OR “fetal growth retardation” OR “FGR” OR “fetal growth” OR “miscarriage” or “outcomes” OR “birth weight” OR “intrauterine growth retardation” OR “IUGR” OR “small for gestational age” OR “SGA” OR “fetus” OR “preterm birth”)]

**Limits imposed on search:** Published ≥2001 only.

Total number of papers: **175**

From the results of this search only 2 had not been previously identified. Most references were duplicates of those already found and some related to studies conducted in rodents and primates.

From the references (n = 75) obtained, 42 were excluded once the full paper was retrieved: as they were reviews (9), letters in response to papers (7), included in the 2001 COT review (3), studies reporting on maternal health outcomes/fertility (5), reported health issues in young children (6), reporting intake estimates (4), described the use of caffeine for apnoea of prematurity (2), in a foreign language (2), or duplicates (4).