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Maternal Exposure to Caffeine and Risk of Congenital Anomalies

A Systematic Review

Marilyn L. Browne

Background: Caffeine is teratogenic in animal studies when administered at high concentrations. Previous review articles have concluded that maternal caffeine consumption does not influence the risk of congenital anomalies. These reviews were narrative rather than systematic. The objective of the current systematic review is to provide a critical appraisal of epidemiologic evidence.

Methods: A search of the MEDLINE/PUBMED database (1966–October 2004) was conducted for all published epidemiologic studies with maternal intake of caffeine as an exposure and major malformations as an outcome. Study characteristics were abstracted, internal validity evaluated, and study findings summarized.

Results: Twenty-five papers met the initial criteria for inclusion, of which 18 were subsequently excluded as a result of other limitations. Effect estimates for the remaining 7 studies were generally close to null. Specific subgroup analyses were summarized across studies (associations between coffee and cardiovascular malformations, coffee and oral clefts, and tea and cardiovascular malformations). Summary point estimates ranged from 1.0 to 1.2; the upper limits of all confidence intervals were less than 1.7.

Conclusions: There is no evidence to support a teratogenic effect of caffeine in humans. Current epidemiologic evidence is not adequate to assess the possibility of a small change in risk of congenital anomalies resulting from maternal caffeine consumption.

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Caffeine is a natural component of coffee, tea, and cocoa products. It is added to many soft drinks and to certain prescription and over-the-counter medications. Caffeine's pharmacologic effects include central nervous system stimulation, bronchodilation, and higher blood pressure, most

likely through antagonism of adenosine receptors in the brain, heart, lungs, and blood vessels.^{1,2} Based on a recent survey by the U.S. Department of Agriculture, coffee, soft drinks, and tea (in that order) are the major sources of caffeine among adults.³ Average caffeine intake is estimated to be 164 mg per day among women 18–34 years and 125 mg per day among pregnant women.³ In a prospective cohort study conducted in Connecticut during 1988–1992, caffeine consumption during the first month of pregnancy was reported by 60% of study participants, with 16% consuming 150 mg or more of caffeine per day.⁴

In their review of the animal literature, Nehlig and Debry⁵ note that teratogenic effects have generally been observed after once-per-day administration of caffeine at doses much higher than human consumption levels. However, when administered in combination with substances such as nicotine or alcohol, teratogenic effects of caffeine were observed at somewhat lower doses. In humans, caffeine and its metabolites easily cross the placenta and reach the fetus.⁶ Decreases in fetal heart rate and placental blood flow have been observed after maternal caffeine ingestion.^{7,8} Human studies have also demonstrated increased homocysteine levels and decreases in insulin sensitivity after intake of caffeine or coffee.⁹ Vascular disruption, increased levels of homocysteine, and oxidative stress associated with hyperglycemia are postulated mechanisms for various congenital malformations.^{10–12} Given the prevalence of caffeine use during pregnancy, even a small increase in the risk of congenital anomalies would have an important effect on public health.

A number of published reports have reviewed the scientific literature regarding maternal caffeine consumption and congenital anomalies.^{5,13–16} However, a systematic review of the epidemiologic literature on this topic has not been published. In a systematic review, specific well-defined criteria are used in searching for papers, selecting studies for inclusion, critically appraising study methods, and summarizing study findings.¹⁷ The methods for this systematic review were based on Mulrow's and Weed's guidelines.^{17,18}

The objectives of this review are to summarize and evaluate methodological aspects of epidemiologic studies of maternal caffeine exposure and risk of congenital anomalies. A critical appraisal of currently available epidemiologic evidence is used to suggest recommendations for future research.

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METHODS

Search Strategy and Selection Criteria

Studies were identified through a search of the MEDLINE/PUBMED database (1966–October 2004). A free-text search limited to human studies was conducted using the terms “caffeine or caffeinated or coffee or tea” and “anomalies or malformations or defects.” The bibliographies of original reports and review articles were searched for additional published studies. No language restriction was imposed; case reports, studies based on a small case group ($n < 10$), and unpublished manuscripts were not included in the search. Only one report describing data for any given study population was selected; when there were multiple reports, the study with the most recent and complete data was selected. The full study reports were examined to determine eligibility for inclusion when citation titles or abstracts did not contain sufficient detail.

Teratogenic effects of caffeine would most likely occur at moderate to high levels of exposure and for certain types of congenital anomalies rather than all anomalies. In keeping with the goal of assessing the adequacy of the published epidemiologic literature, the criteria used to include studies for review were as follows:

- Caffeine or caffeinated beverage consumption was examined as a risk factor for major congenital anomalies, defined as “those that have surgical, medical, or serious cosmetic importance.”¹⁹
- Effect estimates were presented for one or more categories of congenital anomalies classified by organ system or subtypes within an organ system; studies with analysis limited to “all malformations combined” were excluded.
- Caffeine exposure assessment included intake from one or more caffeinated beverages (because caffeinated beverages are the main sources of caffeine exposure and of greatest relevance in assessing risk to the general population).
- Effect estimates were presented for moderate to high exposure compared with minimal or no exposure. Moderate to high exposure has customarily been defined as 300 or more mg of caffeine or 3 or more servings of a caffeinated beverage. Low exposure is defined here as less than 100 mg caffeine per day or less than one serving per day. Studies that combined all levels of exposure, grouped moderate to high exposures in the referent group, or only contrasted mean levels of exposure were excluded.

Because bias toward the null value would be expected to result from extensively grouped exposure or outcome categories such as “any exposure” or “all malformations,” the use of these groupings is most problematic in interpreting null findings. Studies excluded based on grouped exposure or outcome are summarized in the appendix available with the online version of this article.

Appraisal of Study Methods

For all studies meeting inclusion criteria, the full study report was examined; study characteristics and results were abstracted using a standard format. Evaluation of selection bias, recall bias, misclassification of exposure, and confound-

ing were included in an assessment of internal validity. No attempt was made to exclude studies based on methodologic quality.

Narrative Summary and Meta-analysis of Study Findings

Summary odds ratios were calculated for studies with the same type of exposure (caffeine, coffee, or tea) and the same type of malformation. Results pertaining to the same exposure and outcome combination were available for a small number of outcomes and mostly for coffee intake. A narrative summary is also presented.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for several studies that did not report measures of association. Odds ratios for high exposure (defined as 3+ servings per day for most studies) versus no exposure were summarized across studies using the general variance-based method described by Petitti.²⁰ When available, adjusted odds ratios were used in the meta-analysis calculations. A general variance-based test of homogeneity²⁰ of effect estimates was performed; significant homogeneity (Q -test $P < 0.05$) was a contraindication for meta-analysis. Heterogeneity was also assessed by the I^2 statistic.²¹ A fixed-effects model was used to estimate the variance of the summary odds ratio when study heterogeneity was low; the DerSimonian and Laird random-effects method was used to estimate the variance of the summary odds ratio in the presence of moderate heterogeneity.²⁰ RevMan 4.2 software²² was used to calculate and graph meta-analysis results.

RESULTS

Literature Search

The search strategy retrieved 304 citations. Of these, there were 21 original research reports describing exposure to a source of caffeine during pregnancy and risk of congenital anomalies. One was a study presented in a letter to the editor;²³ the original study report published in French was translated to English for this review.²⁴ Three additional citations were found in the reference lists of published review articles^{25–27} and one additional study for which results were published in a textbook was identified,²⁸ resulting in 25 selected studies.

Eighteen of these studies were subsequently excluded. Three assessed caffeine exposure from medications only,^{25,26,29} and one evaluated risk of minor anomalies.²⁷ An additional 14 studies were excluded because they did not evaluate the risk of moderate to high exposure compared with low or no exposure ($n = 11$),^{30–40} or they presented results only for all malformations combined ($n = 3$).^{24,41,42} (A summary description of these 14 studies is provided in the electronic appendix.) Six study reports by Tikkanen and Heinonen^{33–37,43} all referred to the same study population. Despite some overlap, all were selected because each contributed quantitative information for different cardiovascular malformation categories. However, 5 of the 6 reports^{33–37} were ultimately excluded from the full review because exposure was categorized as “any versus none.” The Boston University Slone Epidemiology Center Birth Defects Study

contributed data for 2 reports; both are included because each examined congenital anomalies from different organ systems.^{44,45}

Methodology of Included Studies

For the 7 studies retained for analysis, publication dates ranged from 1974 to 1993.^{28,43–48} Four were conducted in the United States or Canada and 3 in European or Scandinavian countries. Six were case-control studies^{28,43–47} and one was a retrospective cohort study.⁴⁸ Study characteristics and results are summarized in Table 1.

Response rates were generally high and comparable for cases and controls, so nonresponse was not an obvious source of distortion. Rosenberg et al⁴⁴ and Werler et al⁴⁵ used an affected (malformed) control group. This approach reduces the potential for response bias or recall bias that may occur when a nonmalformed control group is used. In each of the included studies, time to interview was relatively short and similar for cases and controls (generally less than 1 year after the index birth) with the exception of the McDonald et al study.⁴⁹ It is possible that recall bias may have contributed to elevated risk estimates in the studies by Fedrick,⁴⁶ McDonald et al,⁴⁸ and Ferencz et al.²⁸ Inconsistent findings for various types of major congenital anomalies in McDonald et al argue against an important influence of recall bias in that study. However, increased reporting of high tea consumption among case mothers living in medium and high incidence areas but not in low incidence areas in the Fedrick study⁴⁶ could have been the result of heightened concerns about risk factors among women in medium and high incidence areas or, as the author suggested, because of an observed correlation between water softness and anencephaly. The estimates in Table 1 summarize the findings for the entire study area.

Only 3 of the 7 studies evaluated multiple sources of caffeine exposure^{28,43,44} and only one accounted for changes in caffeine intake during early pregnancy. Ferencz et al²⁸ examined average daily caffeinated beverage intake during the period from 3 months before through 3 months after the last menstrual period, whereas the other studies evaluated intake during pregnancy only. Poor measurement of exposure is a particular concern in studies of caffeine consumption during pregnancy.⁵⁰

Control of confounding was limited in some of the included studies. Fedrick⁴⁶ selected control subjects by matching on several variables but did not account for matching in the analysis. Only crude comparisons of caffeine exposure and outcomes were available for the studies by Tikkanen and Heinonen⁴³ and Ferencz et al.²⁸ Confounding from factors including maternal age and smoking was assessed in the 4 remaining studies.^{44,45,47,48} Statistical adjustment by McDonald et al⁴⁸ reduced the excess relative risk associated with 3 or more cups of coffee per day by 24%, 25%, and 71% for heart anomalies, oral clefts, and neural tube defects, respectively (based on crude risk estimates calculated by the present author). Because positive confounding was observed only in the study by McDonald et al and not in the other 3 studies,^{44,45,47} it is uncertain whether uncontrolled confounding contributed to positive associations in the studies by Fedrick⁴⁶ and Ferencz et al.²⁸

The inclusion of previous pregnancies by McDonald et al⁴⁸ posed a number of methodologic problems. First, the contribution of more than one observation (pregnancy) by a study mother violates the assumption of independent observations in standard statistical tests. Second, inaccuracies in outcome and exposure assessment were likely. For previous pregnancies, ascertainment of congenital anomalies relied on self-report and exposure assessment required recall of exposure that occurred years in the past. McDonald et al used separate regression models to estimate effects for current and previous pregnancies. The authors stated that the regression coefficients for previous pregnancies were not significantly different from those for current pregnancies, and they presented odds ratios based on a weighted average of the 2 models.⁴⁸

Results of Included Studies

Narrative Summary

The odds ratios for the 7 included studies were generally close to the null value. Selected elevations in risk were observed in 3 studies. In a study conducted in England and Wales, Fedrick⁴⁶ noted an elevated risk of anencephaly among women who reported drinking 3 or more cups of tea per day (odds ratio = 1.6, 95% confidence interval = 1.1–2.4). McDonald et al⁴⁸ found an adjusted odds ratio of 1.5 (CI = 1.1–2.2) for risk of cardiovascular malformations associated with consumption of 3 or more cups of coffee per day among women in Montreal. Although the authors of the Baltimore-Washington Infant Study²⁸ stated that “no case-control differences were noted” in caffeinated beverage intake, crude odds ratios (calculated by this author) support a dose-response trend for coffee intake and cardiovascular malformations; when intake is categorized as 3 or more cups of coffee per day, the OR was 1.3 (1.0–1.6). An elevated odds ratio for cardiovascular malformations was also observed for 7 or more cups of tea per day (1.7; 1.1–2.8); no dose-response pattern was present.

A dose-response relationship was generally lacking in the Rosenberg et al⁴⁴ study findings (only slight support for a positive trend for cleft lip with or without cleft palate). However, there is some evidence of inverted U-shaped trends for inguinal hernia, cardiovascular malformations (CVMs), and neural tube defects, and an inverse trend for isolated cleft palate. Odds ratios (calculated by this author) for daily caffeine intake of none, 1–199 mg, 200–399 mg, and 400 mg or more were 1.0, 1.6, 1.5, and 1.2 for inguinal hernia; 1.0, 1.8, 1.7, and 1.2 for CVMs; 1.0, 1.5, 0.9, and 0.6 for neural tube defects; and 1.0, 1.0, 0.8, and 0.5 for isolated cleft palate, respectively. These estimates were imprecise as a result of small numbers in the nonexposed and high exposure categories.

Elevations in relative risk were observed for some of the anomaly categories other than cardiovascular malformations examined by McDonald et al.⁴⁸ Evidence of a relationship between coffee consumption and various congenital anomalies was absent in the following studies: Kurppa et al⁴⁷ (oral clefts, skeletal, cardiovascular, or central nervous system anomalies), Werler et al⁴⁵ (gastroschisis), and Tikkanen and Heinonen⁴³ (hypoplastic left heart syndrome).

TABLE 1. Summary of Epidemiologic Studies of Maternal Caffeine Consumption and Congenital Anomalies Included in the Review

Author, Date, Study Design	Location, Time Period	Study Population	Exposure Measure	Covariates Evaluated*	Odds Ratios by Daily Caffeine/Caffeinated Beverage Intake; (95% CI)	Methods Comments†
Fedrick, 1974 ⁴⁶ Case-control	England and Wales, 1969	464 anencephaly cases; 1785 matched controls; 2 stillbirths without anencephaly and 2 live births per case	Usual amount tea/d	Matched on social class, time of delivery, age, parity; analysis did not account for matching	Crude OR, referent = 0 cups per day [‡] 1-2 cups tea/d 1.04 (0.62-1.74) 3-4 cups tea/d 1.74 (1.12-2.69) 5-8 cups tea/d 1.63 (1.08-2.45) 9+ cups tea/d 1.62 (1.05-2.50)	83% and 80% response rate, cases and controls, respectively; recruited 6-9 mo postdelivery; stratification by social class and by region; no other control of confounding
Ferencz, 1993 ²⁸ Case-control	District of Columbia, Maryland, North Virginia, 1981-1989	3377 CVM cases; 3572 randomly sampled controls, same hospitals	Coffee, tea, cola, cocoa, drugs; 3 mo before through 3 mo after the last menstrual period	None [§]	Crude OR, referent = 0 cups per day [‡] Coffee 1-2 cups/d 1.01 (0.90-1.14) 3-4 cups/d 1.18 (0.92-1.53) 5-6 cups/d 1.51 (0.87-2.62) 7+ cups/d 1.61 (0.85-3.04) Cocoa 1-2 cups/d 1.00 (0.91-1.11) 3-4 cups/d 1.01 (0.86-1.20) 5-6 cups/d 1.01 (0.76-1.35) 7+ cups/d 1.22 (0.84-1.77)	90% participation cases, 78% of "first choice" controls in final control group; over 90% both cases and controls interviewed within 9 mo postdelivery; adjusted analyses presented for xanthine intake only; xanthine score was not associated with CVM, but xanthine is not equivalent to caffeine (eg, heavily weights theobromine in cocoa)
Kurppa, 1983 ⁴⁷ Case-control	Finland, 1980-1982	706 case-control pairs 241 oral clefts 210 skeletal defects 143 CVM 112 CNS	Coffee; tea drinkers excluded; before and during pregnancy; "during pregnancy"	Age, smoking, alcohol; matched on delivery date and region	Unadjusted ORs (for 465 discordant pairs), referent = 0 cups 1-3 cups/d 4+ cups/d Overall 1.2 (0.9-1.5) Clefts 1.0 (0.6-1.5) Skeletal 1.2 (0.7-1.9) CVM 1.2 (0.7-2.2) CNS 1.4 (0.8-2.8)	>95% participation, mean time until interview = 84 d and 91 d for case and control mothers, respectively; authors suggest recall bias unlikely; no negative publicity or known relationship; 96% were coffee drinkers before pregnancy; many stopped or reduced intake during pregnancy as a result of taste aversion
McDonald, 1992 ⁴⁸ Retrospective cohort	Montreal, 1982-1984	56,000 women; 80,319 pregnancies 552 club foot 271 CVM 197 musculoskeletal 191 renal/urinary 162 NTD 97 gastrointestinal or respiratory 87 clefts	Coffee; first trimester	Age, education, ethnicity, smoking, alcohol	Adjusted OR, referent = 0 cups per day 1-2 cups/d 3+ cups/d Clubfoot 1.01 (0.8-1.2) CVM 1.08 (0.8-1.4) Musculoskeletal 0.89 (0.6-1.2) Renal/urinary 0.96 (0.7-1.3) NTD 1.12 (0.8-1.6) GI/respiratory 1.17 (0.7-1.8) Clefts 1.42 (0.9-2.3)	90% participation; interviewed in-hospital soon after delivery, included more than one pregnancy per subject; long lag between first trimester and interview for past pregnancies

(Continued)

TABLE 1. (Continued)

Author, Date, Study Design	Location, Time Period	Study Population	Exposure Measure	Covariates Evaluated*	Odds Ratios by Daily Caffeine/Caffeinated Beverage Intake; (95% CI)	Methods Comments†
Rosenberg, 1982 ⁴⁴ Case-control	Boston, Philadelphia, Toronto, 1976-1980	712 malformed controls Cases: 380 inguinal hernia 299 cleft lip ± palate 277 CVMs 194 pyloric stenosis 101 NTD	Decaffeinated/caffeinated coffee, tea, soda: "during pregnancy"	Age, education, income, parity, medical conditions, caffeine-containing drugs, smoking	200 mg/d 400 mg/d OR vs no caffeine 1.4 (0.8-2.6) 1.2 (0.6-2.5) 1.3 (0.7-2.5) 1.4 (0.7-2.9) 1.2 (0.5-2.7) 1.5 (0.7-3.2) 1.2 (0.5-3.1) 1.8 (0.8-3.9) 1.2 (0.5-3.1) 0.8 (0.3-1.7) 0.5 (0.2-1.4) 0.8 (0.3-2.2) 0.6 (0.2-2.1)	Use of an affected control group reduced potential for response bias or recall bias; small numbers in nonexposed and high exposure categories; no confounding observed; crude odds ratios presented
Tikkanen and Heinonen, 1994 ⁴³ Case-control	Finland, 1982-1983	34 hypoplastic left heart syndrome cases 756 controls	Coffee, tea, cola; first trimester	None [§]	Crude OR, referent = 0 cups per day, 3+ cups coffee/d: 1.38 (0.51-3.72) [‡]	88% participation among controls, not mentioned for cases; interviewed 92-96 d postdelivery; coffee intake was not evaluated in multivariable models
Werler, 1992 ⁴⁵ Case-control	Boston, Philadelphia, Ontario, Iowa, 1976-1990	59 gastrochschisis cases 2581 malformed controls (anomalies other than abdominal wall or chromosomal)	Coffee; first 4 mo of pregnancy	Age, education, parity, smoking, alcohol, race, nausea/vomiting	Age-adjusted OR coffee, referent = 0 cups per day 1-2 cups/d 3+ cups/d 1.0 (0.5-1.7) 0.7 (0.3-1.7)	Use of an affected control group reduced potential for response bias or recall bias; small number of cases in high exposure category

*Maternal characteristics unless otherwise specified.

†Lack of adjusted analyses refers specifically to caffeine effect estimates.

‡Odds ratios and 95% confidence intervals were calculated by the author of this review based on numbers presented in the study report.

§As a result of nonsignificant crude associations, caffeine exposure was not included in multivariable models.

CVM indicates cardiovascular malformation; NTD, neural tube defect; CNS, central nervous system.

Quantitative Synthesis

Odds ratios for single types of exposure (caffeine, coffee, or tea) and specific malformations were summarized through meta-analysis methods. There were overlapping exposure–outcome combinations for coffee and neural tube defects (2 studies), coffee and oral clefts (3 studies), coffee and cardiovascular malformations (4 studies), and tea and cardiovascular malformations (2 studies).

Summary odds ratios were calculated for risk of high exposure, defined as 3 or more servings per day (4 or more for Kurppa et al⁴⁷ estimates) versus no exposure (Fig. 1). A test of homogeneity was of borderline statistical significance for studies of coffee and neural tube defects; therefore, a summary estimate was not calculated. Although the Q-test was not statistically significant, 2 of the 4 risk estimates for the association between coffee and cardiovascular malformations were below the null value and 2 were above the null value; the I^2 statistic (52%) indicated moderate heterogeneity. A summary estimate using a random-effects variance model is presented with reservation. Slight elevations were observed for associations between coffee intake and cardiovascular malformations (OR = 1.1; CI = 0.9–1.5) and coffee intake and oral clefts (1.2; 0.9–1.6), but not for the association between tea and cardiovascular malformations (1.0; 0.9–1.2).

There is limited ability to evaluate study heterogeneity given the few studies contributing to each summary estimate. Even so, recall bias is a possible source of heterogeneity in the estimates for the association between coffee and cardiovascular malformations. The Rosenberg et al⁴⁴ study took place before the 1981 U.S. Federal Drug Administration

(FDA) advisory⁵¹ to limit caffeine intake during pregnancy. In addition, the use of affected controls was expected to reduce recall bias. Kurppa et al⁴⁷ stated that public concern about harmful effects of caffeine did not exist in Finland at the time of their study. For these reasons, recall bias was unlikely for the 2 studies with effect estimates below the null value. The 2 studies with risk estimates above the null value took place after the FDA advisory and may have been more vulnerable to recall bias.

DISCUSSION

Studies with extensive grouping by exposure and outcome were not selected for review. Classifying caffeine intake as “any versus none” is problematic because grouping low exposures with high exposures could hide a true effect that happens only at high levels of exposure. Different types of congenital anomalies have diverse etiologies; grouping all anomalies as a single outcome can mask an effect that occurs for only particular categories of anomalies.⁵² With a few exceptions, the studies excluded for these reasons did not find associations between caffeine intake and congenital anomalies. In the few instances in which a positive association was observed,^{24,30} selection bias and confounding were possible alternative explanations.

The 7 included studies were well-conducted studies and provide the best available epidemiologic evidence about caffeine teratogenicity. Inaccuracies in exposure assessment and the relatively small number of specific exposure–outcome relationships that have been studied limit conclusions based on these data. Meta-analysis was possible for associations between coffee and oral clefts, coffee and cardiovascular malformations, and tea and cardiovascular malformations. Summary estimates could not be calculated for total caffeine intake (versus coffee or tea consumption) because only one of the 7 included studies reported findings for caffeine exposure from multiple sources. The few exposure–outcome combinations suitable for quantitative synthesis emphasize the relative scarcity of published research on this topic. The possibility of publication bias is a concern in interpreting the results restricted to published reports. Findings of little or no increased risk in early studies of this topic may have reduced interest on the part of both investigators and editors in publishing additional studies with null results.

The results of the studies included in this review suggest that a large increase in the risk of congenital anomalies is unlikely to result from consumption of caffeinated beverages during pregnancy. The 10% to 20% excess risk associated with coffee intake suggested by the summary estimates for cardiovascular malformations and oral clefts would be important if the relative risks reflected a true effect of coffee consumption. However, these small increases might also be explained by recall bias or confounding. Conversely, sources of nondifferential exposure misclassification were likely to have attenuated risk estimates. Therefore, these slight increases and the null results for other anomaly categories may warrant further attention. The few available studies for each anomaly category do not provide adequate negative evidence regarding risk.

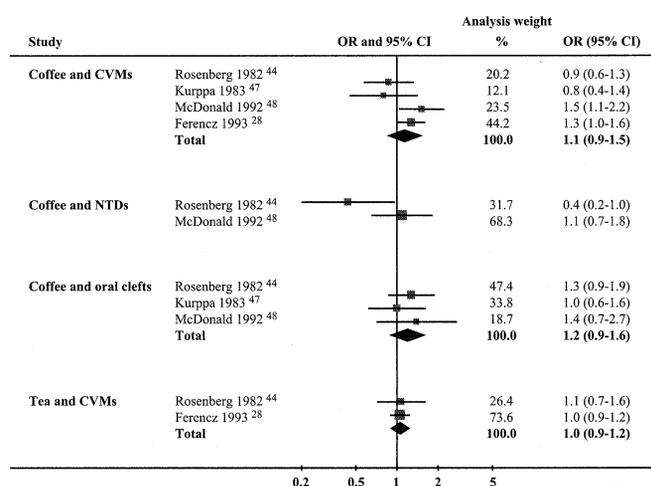


FIGURE 1. Meta-analysis results for consumption of specific caffeinated beverages (high consumption vs. none) and selected congenital anomalies. High consumption defined as 4+ cups per day for the Kurppa et al study⁴⁷ and 3+ cups per day for each of the other studies. Test for heterogeneity for coffee and CVMs: $P = 0.10$; $I^2 = 52\%$. Test for heterogeneity for coffee and NTDs: $P = 0.05$; $I^2 = 73\%$. Test for heterogeneity for coffee and oral clefts: $P = 0.65$; $I^2 = 0\%$. Test for heterogeneity for tea and CVMs: $P = 0.92$; $I^2 = 0\%$.

Misclassification of exposure is a special concern in studies of caffeine exposure. Wide variations in the caffeine content of a beverage serving⁵³ and changes in caffeine consumption during pregnancy⁵⁴ are 2 prominent difficulties. In addition, interindividual differences in caffeine metabolism represent a source of error in measuring caffeine exposure. The rate of caffeine clearance among smokers is approximately twice that in nonsmokers as a result of metabolic enzyme induction by cigarette smoke.^{55,56} Grosso and Bracken⁵⁰ recently provided a detailed description of sources of misclassification in measuring caffeine intake during pregnancy. The authors proposed measurement of caffeine biomarkers as a remedy to the deficiencies of questionnaire-based methods. Unfortunately, prospective study methods are not practical in studies of congenital anomalies. However, validation studies comparing prospectively measured exposure information with questionnaire-based estimates collected after delivery would be helpful in estimating uncertainty in retrospective study results and in guiding development of improved exposure assessment methods.

A list of recommendations for future research follows:

- Collect information on multiple sources of caffeine. To separate any effect of caffeine from that of other components of coffee, tea, and soda, analyze exposure–outcome relationships for individual caffeinated beverages in addition to total caffeine.
- Avoid extensive grouping of different malformations; define malformation outcome categories that are “embryologically or pathogenetically meaningful.”⁵²
- Through validation studies, identify questionnaire methods that could improve exposure assessment accuracy. For example, questions on brew strength (tea and coffee), portion size, and changes in caffeine consumption during the period starting before pregnancy through the first trimester.
- In the analysis, form categories of exposure that allow assessment of dose–response; avoid grouping high exposures with low exposures.
- Assess potential effect modification by smoking status and other factors that affect caffeine metabolism.
- To reduce concerns about spurious findings from multiple analyses, use a priori relationships and mechanisms to guide the choice of outcome categories and potential effect modifiers. However, exploratory analyses in the absence of mechanistic hypotheses, when reported as such, are also useful in guiding subsequent research efforts.

SUMMARY

The 7 studies included in this review do not provide adequate evidence on which to base conclusions about the safety of maternal caffeine consumption during pregnancy. There is no evidence that caffeine intake causes a large increase in the risk of various types of congenital anomalies, but there is greater uncertainty about small elevations in risk. Given the relatively high prevalence of maternal caffeine exposure, even a small increase in the risk of congenital anomalies would have an important effect on public health. Large study populations and improved exposure assessment methods would be necessary to rule out small risks for

specific categories of congenital anomalies after maternal exposure to caffeine.

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