

Caffeine intake and pregnancy outcomes: a meta-analytic review

Consumo de cafeína na gravidez
e desfechos perinatais

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Abstract *Epidemiological publications on the relationship of caffeine to birth weight and duration of human pregnancy, from 1966 to 1995, were searched through Medline. Each study was treated as the stratification variable, and its weight in the weighted average was proportional to the inverse of its variance. Twenty-six studies were located. Among the twenty-two studies on birth weight, eleven were on mean birth weight, nine on low birth weight (LBW), and four on intrauterine growth retardation (IUGR). Combined analysis of mean birth weight study results showed a significant decrease in birth weight of nearly 43g among newborns of the heaviest caffeine-consuming mothers. LBW, IUGR, and preterm delivery displayed significant homogeneity in the test results, indicating that a pooled estimate should not be taken as an adequate measure. The high heterogeneity of the available literature on the effects of caffeine on LBW, IUGR, and preterm delivery prevents estimation of reliable pooled estimates through meta-analysis. Further assessment of caffeine intake during pregnancy is needed in future research.*

Key words Caffeine; Low Birth Weight; Fetal Growth Retardation; Premature Infant

Resumo *Foram rastreadas as publicações epidemiológicas de 1966 a 1995 sobre a associação entre cafeína e peso ao nascer e duração da gestação humana através de pesquisa em Medline. Cada estudo foi tratado como uma categoria de uma variável e seu peso foi proporcional ao inverso de sua variância. Foram localizados vinte e seis estudos. Entre os vinte e dois estudos sobre peso ao nascer, onze foram sobre peso médio ao nascer, nove sobre baixo peso ao nascer (BPN) e quatro sobre retardo do crescimento intra-uterino (RCIU). O efeito agregado sobre o peso médio ao nascer mostrou uma redução estatisticamente significativa de 43 gramas entre os recém-nascidos de mães que consumiam maiores quantidades de cafeína. A análise agregada do efeito sobre BPN, RCIU e nascimentos pré-termos apresentou teste de homogeneidade estatisticamente significativo, indicando que uma estimativa combinada não seria confiável. A grande heterogeneidade da literatura disponível quanto ao efeito da cafeína sobre o BPN, RCIU e partos pré-termo não permite o cálculo confiável de estimativas agrupadas através de meta-análise. Torna-se necessária uma avaliação mais cuidadosa do consumo de cafeína durante a gestação em estudos futuros.*

Palavras-chave Cafeína; Baixo Peso ao Nascer; Retardo do Crescimento Fetal; Prematuro

Introduction

The effect of caffeine consumption on birth weight and duration of pregnancy has been the subject of numerous epidemiological studies in recent years. Major sources of caffeine are coffee, black tea, maté, chocolate/cocoa, and cola soft drinks. It has also been estimated that nearly 200 non-prescription drugs contain caffeine, and this may be an important source for a minority of people.

Caffeine (1,3,7-trimethylxanthine) is a plant alkaloid, structurally related to DNA purine bases, the focus of studies with laboratory animals. Caffeine is a pharmacologically active substance with effects on many different organ systems. Interest in the study of caffeine on human pregnancy, however, is based on the fact that its clearance is delayed in pregnant women, mainly in the second and third trimesters, when it is decreased to one half and one third the normal rate, respectively (Aldridge et al., 1979). Caffeine crosses the placental barrier so that maternal and fetal blood levels are virtually the same (Goldstein & Warren, 1962). The enzymes needed for caffeine metabolism are absent both in the fetus and until the eighth month after delivery (Hornung et al., 1985 apud James & Paull, 1985). Concern about the possible harmful effects of caffeine on pregnancy has evolved mainly from studies in animals that have indicated a decrease in intrauterine fetal growth, reduced birth weight, and skeletal abnormalities (Heller, 1987; Dlugosz & Bracken, 1992). Nevertheless, the implications of these findings for human beings are unclear because of differences in the mode of exposure to caffeine, the amounts consumed, and metabolism of the drug. However, despite a proliferation of studies on pregnant women in recent years, the conclusions are controversial. A meta-analytic approach was used here to determine the quantitative summary of these studies.

Material and methods

Study selection

A Medline search from 1966 to 1995 produced twenty-six epidemiological publications on the relationship between caffeine and birth weight and duration of human pregnancy. These studies had investigated the effect of caffeine on low birth weight (LBW – birth weight less than 2,500 grams), intrauterine growth retardation (IUGR – birth weight under the 10th percentile

for gestational age), and preterm delivery (gestational age of less than 37 weeks). A scoring system developed by the UK Nutritional Epidemiology Group for the Nutrition Society (UKNEGNS, 1993) was adapted to rank the overall quality of papers in an objective manner. Based on the system, separate scoring methods were used for case-control and cohort studies. For case-control studies, three areas were scored: quality of caffeine assessment, recruitment of subjects, and analysis of the results. Cohort studies were scored in four areas: caffeine assessment, definition of the cohort, ascertainment of outcome, and analysis of results. This scoring system allowed for a classification of the studies in a range from zero to 10.

Data extraction

When the effect estimate and its standard error for heaviest caffeine consumption as compared to none or lowest consumption were provided, they were simply copied directly from the report. When confidence limits were provided rather than the standard error, the latter was calculated. Considering that the 95% confidence interval for an estimate is equal to (estimate \pm 1.96 standard error) than for a risk estimate with a given 95% confidence interval, the estimated standard error was calculated as follows: *standard error = (log upper limit of the confidence interval - log estimate of risk)/1.96*. When only a p value was given, instead of a standard error or confidence interval, a test-based standard error was estimated as follows: *standard error = log estimate/t or z value or standard error = coefficient estimate/t or z value*; where t or z is the value of the statistic corresponding to the p value (e.g., $Z_p = 1.96$ if $p = 0.05$, two-tailed test). Assuming that the study outcomes were rare in all populations and subgroups under review, relative risks and odds ratios were pooled together.

Statistical meta-analysis

Once the individual studies were analyzed to bring standard errors, statistical meta-analysis was performed using the weighted average of study-specific results (Kleinbaum et al., 1982). Each study result was treated as a dependent variable, with a corresponding weight. When two studies had comparable methodological quality but different sample sizes, the effect reported in the larger one was assumed to be more precise. For these, the statistical component of each study weight was the inverse of the variance of the result, computed from the

estimated standard error as $1/SE^2$ (Greenland, 1987). The pooled summary of the study results was calculated as the exponential of the weighted sum of the results ($S \log estimate^* / variance$) divided by the sum of the weights ($S / variance$). The standard error of this estimate was calculated as the inverse of the square root of the sum of the weights. The 95% confidence interval for the estimate was calculated by ($pool estimate \pm 1.96 standard error$). A test of significance of whether the assumed common value was zero was given by $Z = (pool estimate/standard error)$, which has a standard normal distribution.

However, the adequacy of the pooled estimate as a meta-analytic summary of the effect under study depends on the homogeneity assumption, i.e., that the studies are estimating the same value for the effect and that, apart from bias, the differences observed among them are due to random error. The statistical test of homogeneity used was $chi-squared = S study weight (study estimate-pooled estimate)$, which has a chi-squared distribution with degrees of freedom one less than the number of studies.

Results

Caffeine and birth weight

Twenty-two studies (Mau & Netter, 1974; van den Berg, 1977; Arnandova & Katsulov, 1978; Soika, 1979; Kuzma & Sokol, 1982; Linn et al., 1982; Furuhashi et al., 1985; Watkinson & Fried, 1985; Beaulac-Baillageon & Desrosiers, 1987; Martin & Bracken, 1987; Muñoz et al., 1988; Brooke et al., 1989; Caan & Goldhaber, 1989; Fenster et al., 1991; Olsen et al., 1991; Peacock et al., 1991; McDonald et al., 1992; Godel et al., 1992; Mills et al., 1993; Fortier et al., 1993; Larroque et al., 1993; Shu et al., 1995) focused on birth weight. Most of them showed, in the crude analysis, that coffee or caffeine was related to lower birth weights (Mau & Netter, 1974; van den Berg, 1977; Arnandova & Katsulov, 1978; Soika, 1979; Linn et al., 1982; Furuhashi et al., 1985; Watkinson & Fried, 1985; Martin & Bracken, 1987; Caan & Goldhaber, 1989; Godel et al., 1992; Fortier et al., 1993; Mills et al., 1993), the majority of these differences being statistically significant. Dose-response effects were demonstrated in eight studies (Mau & Netter, 1974; van den Berg, 1977; Martin & Bracken, 1987; Brooke et al., 1989; Fenster et al., 1991; Peacock et al., 1991; McDonald et al., 1992; Fortier et al., 1993). It was also clear

from these studies that drinking coffee was related to smoking (van den Berg, 1977; Arnandova & Katsulov, 1978; Linn et al., 1982; Watkinson & Fried, 1985; Martin & Bracken, 1987; Fenster et al., 1991; Olsen et al., 1991; Godel et al., 1992; Larroque et al., 1993; Mills et al., 1993) and, in some of them, to alcoholic beverage consumption (Arnandova & Katsulov, 1978; Martin & Bracken, 1987; Fenster et al., 1991; Olsen et al., 1991; Mills et al., 1993). After allowing for smoking, twelve of seventeen studies showed that caffeine was still related to LBW (Mau & Netter, 1974; Kuzma & Sokol, 1982; Watkinson & Fried, 1985; Beaulac-Baillageon & Desrosiers, 1987; Martin & Bracken, 1987; Muñoz et al., 1988; Caan & Goldhaber, 1989; Fenster et al., 1991; Olsen et al., 1991; Peacock et al., 1991; McDonald et al., 1992; Fortier et al., 1993). Another study was restricted to non-smokers and the association remained present (Peacock et al., 1991).

Among these studies, only thirteen were used for the pooled estimation (Mau & Netter, 1974; van den Berg, 1977; Kuzma & Sokol, 1982; Linn et al., 1982; Martin & Bracken, 1987; Caan & Goldhaber, 1989; Fenster et al., 1991; Olsen et al., 1991; McDonald et al., 1992; Mills et al., 1993; Fortier et al., 1993; Larroque et al., 1993; Shu et al., 1995). The remaining nine reports neither provided the estimate and its standard error nor permitted extraction of standard errors by publishing relative risks, confidence intervals, or p values. Three studies were on the effect of caffeine on mean birth weight (Kuzma & Sokol, 1982; Larroque et al., 1993; Shu et al., 1995), seven on LBW (Mau & Netter, 1974; van den Berg, 1977; Linn et al., 1982; Martin & Bracken, 1987; Caan & Goldhaber, 1989; Olsen et al., 1991; Fortier et al., 1993), one on IUGR (Mills et al., 1993), and two investigated both, LBW and IUGR (Fenster et al., 1991; McDonald et al., 1992). More detailed information and quality scoring of these studies are shown in Table 1.

Table 2 presents the results of reanalyses of the studies. The studies by Kuzma & Sokol (1982), Larroque et al. (1993) and Shu et al. (1995) presented results in terms of mean birth weight according to caffeine consumption. The weighted mean of these results was -42.99 (95% CI: -32.04 to -53.94; $p < 0.001$), indicating that, among heavy consumers, newborns were about 43g lighter as compared to newborns of mothers who consumed lower amounts or no caffeine. The homogeneity test was not significant ($p > 0.05$).

Among the nine studies reporting LBW, the pooled effect of greatest caffeine intake com-

Table 1

Summary of the epidemiologic studies on the effect of caffeine on birth weight and duration of pregnancy used in the meta-analysis

Study	Design	Sample size	Caffeine source	Main result	Quality scoring
Mau & Netter, 1974	cohort	5,220	coffee	association with LBW but not prematurity	6
Weathersbee et al., 1977	cohort	489	coffee, tea, cola drinks	association with prematurity	6
van den Berg, 1977	cohort	15,000	coffee	association with LBW and preterm delivery	7
Kuzma & Sokol, 1982	cohort	5,093	not presented	association with decreased mean birth weight	7
Berkowitz et al., 1982	case-control	175/313	coffee, tea	no association with prematurity	8
Linn et al., 1982	cohort	12,205	coffee, tea	no association with LBW or preterm delivery	7
Martin & Bracken, 1987	cohort	3,891	coffee, tea, cola drinks, medicines	association with LBW but not prematurity	7
Caan & Goldhaber, 1989	case-control	131/136	coffee, tea, cola drinks	association with LBW	8
Olsen et al., 1991	cohort	11,858	coffee, tea	association with LBW but not with preterm delivery	7
Fenster et al., 1991	case-control	87/1,143	coffee, tea, cola drinks	association with IUGR and LBW but not preterm delivery	6
Williams et al., 1992	case-control	795/2,252	coffee, tea	association with preterm delivery	8
McDonald et al., 1992	cohort	40,445	coffee	association with preterm delivery	7
Mills et al., 1993	cohort	431	coffee, tea, cola drinks, cocoa, medicines	no association with IUGR	6
Fortier et al., 1993	cohort	7,025	coffee, tea, chocolate, cola drinks	association with IUGR but not LBW or preterm delivery	6
Larroque et al., 1993	cohort	628	coffee, tea, cocoa, cola drinks	association with decreased mean birth weight	6
Pastore & Savitz, 1995	case-control	408/490	coffee, tea, cola drinks, other caffeinated soft drinks	no association with preterm delivery	7
Shu et al., 1995	cohort	712	coffee, tea, cola drinks	no association with mean birth weight	6

LBW: low birth weight

IUGR: intrauterine growth retardation

pared to none or lower amounts was 1.33 (95% CI: 1.22-1.44; $p < 0.001$) (Figure 1). This pooled estimate suggests that there is a 33% increase in risk of LBW among mothers who consumed the largest amounts of caffeine throughout pregnancy. The homogeneity test, however, showed a significant result, indicating that the studies were highly heterogeneous and should thus not be summarized in a single estimate

($p < 0.001$). Later calculations excluding the two outlier studies (Martin & Bracken, 1987; Caan & Goldhaber, 1989) produced a summary relative risk of 1.29 (95% CI: 1.18-1.41) and a homogeneity test with a p value greater than 0.10.

When IUGR was the outcome of interest, the pooled effect of the three studies which satisfied inclusion criteria was 1.24 (95% CI: 1.05-1.43; $p < 0.01$), suggesting that heavy consumers

Table 2

Summary of reanalyses of studies of caffeine and birth weight and duration of pregnancy

Study	Log estimate	Standard error	Weight
Mean birth weight			
Kuzma & Sokol, 1982	3.76120	1.190253	0.031746
Larroque et al., 1993	3.68879	65	0.000236
Shu et al., 1995	3.89182	117.346938	0.000072
Low Birth Weight			
Mau & Netter, 1974	0.457424	0.154015	42.15735
van den Berg, 1977	0.216722	0.082403	147.2670
Linn et al., 1982	0.182321	0.146777	46.41801
Martin & Bracken, 1987	1.526056	0.421081	5.639862
Caan & Goldhaber, 1989	1.078409	0.606402	2.719433
Olsen et al., 1991	0.182321	0.206870	23.36711
Fenster et al., 1991	0.693147	0.457188	4.784216
McDonald et al., 1992	0.357674	0.176236	32.19655
Fortier et al., 1993	-0.01005	0.324484	9.497586
Intrauterine Growth Retardation			
Fenster et al., 1991	1.064710	0.442250	5.112856
McDonald et al., 1992	0.329303	0.180507	30.69116
Mills et al., 1993	0.104360	0.118425	71.30436
Preterm delivery			
Weathersbee et al., 1977	2.120263	0.855556	1.366165
Berkowitz et al., 1982	-0.69314	0.402274	6.179533
Linn et al., 1982	0.173953	0.166746	35.96579
Olsen et al., 1991	0.182321	0.177707	31.66565
Williams et al., 1992	0.788457	0.206870	23.36711
McDonald et al., 1992	0.215111	0.187298	28.50580
Fortier et al., 1993	-0.17435	0.309253	10.45616
Pastore & Savitz, 1995	-0.51082	0.432295	5.351061

have a 24% increase in risk of delivering a small-for-gestational-age child. However, the homogeneity test was also significant, indicating that deriving a pooled estimate would not be adequate ($p < 0.001$).

Caffeine and preterm delivery

Eleven studies focused on gestational age (van den Berg, 1977; Weathersbee et al., 1977; Berkowitz et al., 1982; Linn et al., 1982; Watkinson & Fried, 1985; Martin & Bracken, 1987; Olsen et al., 1991; Williams et al., 1992; McDonald et al., 1992; Fortier et al., 1993; Pastore & Savitz, 1995) and only three found significant association (Weathersbee et al., 1977; van den Berg, 1977; Williams et al., 1992) (Table 1). The eight remaining studies, including two specifically designed to measure this outcome

(Berkowitz et al., 1982; Pastore & Savitz, 1995) did not detect any association. Under the assumption of homogeneity among the studies, the weighted analysis of the effect of caffeine on gestational age showed a 24% increase in risk (combined estimate: 1.24; 95% CI: 1.11-1.38; $p < 0.001$) among heavy consumers (Figure 2). This result was obtained from estimates reported by eight studies (Weathersbee et al., 1977; Berkowitz et al., 1982; Linn et al., 1982; Olsen et al., 1991; Williams et al., 1992; McDonald et al., 1992; Fortier et al., 1993; Pastore & Savitz, 1995). However, the homogeneity test result was statistically significant ($p < 0.001$), indicating that a pooled estimate should not be valid. The exclusion of the outlier study of Weathersbee et al (1977) did not enhance homogeneity among the remaining studies ($p < 0.001$).

Figure 1

Relative risk of LBW (estimate and 95% confidence interval) in high caffeine consumers compared to non or low consumers.

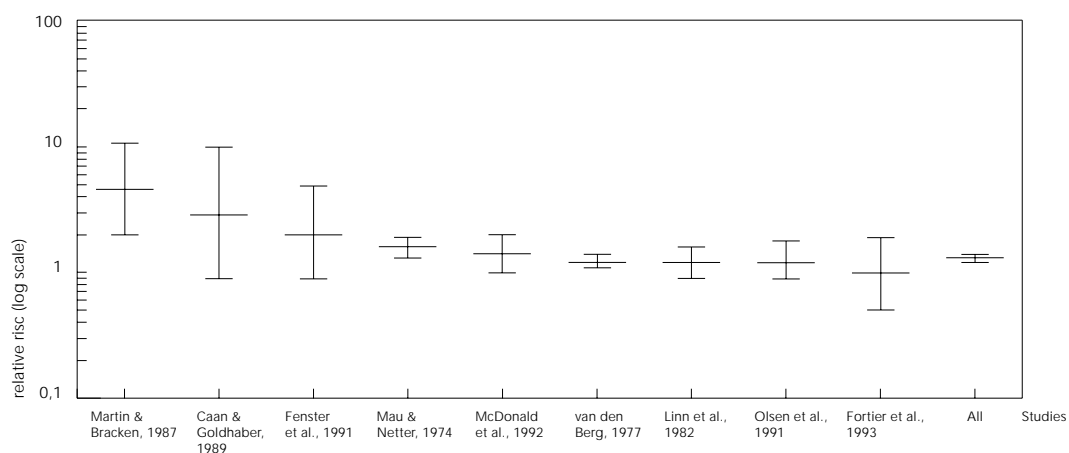
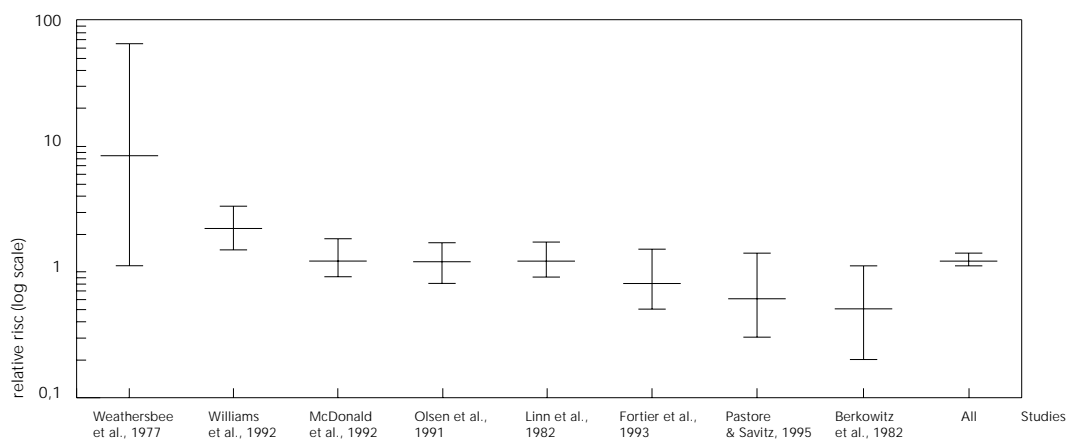


Figure 2

Relative risk of preterm delivery (estimate and 95% confidence interval) in high caffeine consumers compared to non or low consumers.



Discussion

Meta-analysis was used for contrasting and combining results of different studies on the effect of caffeine on human pregnancy outcomes, particularly birth weight and gestational age at birth. Apart from providing a combined effect, meta-analysis is useful for investigating whether the pooled studies are quantitatively consistent. Taken together, in a purely descriptive analysis, these studies suggested a probable effect of caffeine on birth weight,

while gestational age did not seem to be affected. However, weighted analyses showed that it was not possible to derive a summary estimate based on the majority of available published studies, since heterogeneity among the studies was highly significant. The significant results of the homogeneity tests are direct evidence of the inconsistency of the studies on the effect of caffeine in human pregnancy.

Association between an exposure and a disease observed in a single study may depend on the population sampled, level of exposure in

the study population, definition of outcome, and the study's various methodological characteristics (Greenland, 1987; Spector & Simon, 1991; Dickersin & Berlin, 1992; Hasselblad et al., 1995). The scoring system provided suitable evidence that the reported studies were not highly discrepant in terms of methodological quality. Definition of outcomes was also well-established and in agreement with the current literature. However, prior qualitative reviews had already suggested the need for more careful measurement of caffeine consumption (Heller, 1987; Narod et al., 1991; Shiono & Klebonoff, 1993). Some studies evaluated only coffee (Mau & Netter, 1974; van den Berg, 1977; McDonald et al., 1992), while others included a variety of caffeine sources. In most populations, coffee accounts for most of the caffeine consumed, but other sources may be equally important, including mate (a caffeine-containing infusion widely used in South America), black tea, cola drinks, chocolate, cocoa, and medicines. Moreover, caffeine content in

coffee varies with the strength and method of preparation. It is thus possible that observed differences in effect magnitudes in different studies result from inadvertent misclassification due to different levels of exposure in the distinct populations.

The possibility of bias induced by the exclusion of some studies is another explanation. Unfortunately, these studies failed to provide direct information on, or measures from which to infer, needed parameters for the pooled analyses.

In summary, this meta-analysis showed that the effects of caffeine consumption during pregnancy on birth weight and gestational age at birth are quantitatively too inconsistent for a valid summary estimate to be derived. From the above results, it is evident that available information on the effect of caffeine on pregnancy outcomes is incomplete and remains controversial. Measurement of exposure to caffeine is an issue requiring a more in-depth approach in future research.

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