Systematic review with meta analysis

Potential confounding still clouds the possible association of maternal caffeine intake and low birth weight

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Commentary on: Chen LW, Wu Y, Neelakantan N, *et al*. Maternal caffeine intake during pregnancy is associated with risk of low birth weight: a systematic review and dose-response meta-analysis. *BMC Med* 2014;12:174.

Context

The possible association of maternal caffeine intake to a variety of pregnancy outcomes (eg, low birth weight (LBW), fetal growth restriction, preterm delivery) is important because of widespread exposure to caffeine. If caffeine were causally related to these outcomes, it would be amenable to risk reduction through caffeine reduction or abstention.

Methods

This was a systematic review and meta-analysis of prospective observational studies of maternal caffeine exposure and LBW. The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were followed. Acceptable standards for literature searching, study selection and data extraction were adhered to. Heterogeneity was examined using I^2. No evidence of publication bias was observed. The authors acknowledge the pitfalls of meta-analysing observational studies and were careful not to over interpret their conclusions.

Findings

Thirteen prospective observational studies met inclusion criteria, with birth weight (BW) assessed as a binary outcome (9 studies), a continuous outcome (6 studies) or both (2 studies). The risk ratio (RR) of LBW was 1.13 (95% CI 1.06 to 1.21; I^2 0.0%) for low caffeine intake (50–149 mg/day), 1.38 (95% CI 1.18 to 1.62; I^2 31.9%) for moderate intake (150–349 mg/day) and 1.60 (95% CI 1.24 to 2.08; I^2 65.8%) for high intake (>350 mg/day). In dose–response analysis, each 100 mg/day increment in maternal caffeine intake, equivalent to around one cup of coffee, was associated with a 13% (RR=1.13, 95% CI 1.06 to 1.21) higher risk of LBW.

Commentary

While this is a well conducted systematic review and meta-analysis, its reliability ultimately depends on the validity of the included studies. The two principal sources of bias in the included studies are the measurement of caffeine and residual confounding from maternal smoking. Observational studies are fraught with potential biases, to the extent that entire bodies of epidemiological literature—and the meta-analyses that summarise them—are in error.[1] Caffeine measurement is subject to substantial error depending on cup size (eg, 2–32 oz), type of coffee bean, method of preparation and how much coffee is used.[2] For the meta-analysis, studies that reported coffee consumption in cups had caffeine intake estimated by the method of Bunker. However, it is estimated that 24.8% of individuals classified as consuming >300 mg/day according to Bunker's method, should be in the lower category; 24.6% of the 150–299 mg/day category should also be in a lower category; while 14.4% of the 150–299 mg group should be in the >300 mg/day category.[2] Contrary to widely held belief, this degree of non-random misclassification cannot be assumed to drive risk estimates towards the null.[3]

Smoking is highly correlated with caffeine use. Among Norwegian mothers, total daily caffeine consumption was 54 mg among never-smokers, 109 mg in occasional smokers and 143 mg in daily smokers.[4] The negative influence of maternal smoking on BW is well documented. Moreover, the effects of smoking are substantially larger than caffeine. The risks of LBW are (risk ratio) 1.8, 2.2 and 2.4 for light, moderate and heavy smokers, respectively. Mean BW reductions are −182 g for smokers and −320 g for smokers consuming more than 1 pack a day.[5]

While all studies and the meta-analysis tried to adjust for smoking, adjustment was frequently incomplete owing to crude smoking categorisation. Residual confounding from smoking may have spuriously inflated the caffeine associations. The dose–response of caffeine is also not immune from confounding as heavy caffeine drinkers smoke more. One randomised controlled trial, which corrected for smoking by randomisation, reported a BW reduction owing to caffeine of only −16 g (95% CI −40 to +73 g).[6] More observational data limited to non-smoking mothers would help elucidate this bias.

Implications for practice

Given the small reduction in BW associated with typical caffeine consumption and the possibility that caffeine exposure is biased by misclassification or maternal smoking, there are no implications for public health policy.

Competing interests None.

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