



Review Article

Maternal caffeine consumption and childhood behavioural and neurocognitive development: A focused narrative review

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Abstract

Rationale: The majority of pregnant women regularly consume caffeine, a habit-forming substance of no nutritional value for mother or baby.

Objectives: To examine evidence of association between maternal caffeine consumption and childhood behavioural and neurocognitive development, and to consider the soundness of current health guidance concerning the consumption of caffeine during pregnancy.

Methods: Database searches identified a large pool of peer-reviewed articles, which when culled for relevance yielded a modest corpus of animal and human research for inclusion in this focussed narrative review of potential caffeine-related threats to childhood behavioural and neurocognitive development.

Results: High biological plausibility of potential harm from maternal caffeine exposure indicated by early animal research is confirmed by more recent animal studies that sought to mimic human consumption patterns. Reported negative outcomes include increased neuronal network excitability and susceptibility to seizures in offspring, and disruptions to electrophysiological activity, learning, and memory. In contrast, human observational studies have yielded inconsistent findings. Some studies have reported evidence of negative behavioural and neurocognitive outcomes, including hyperkinetic disorder, attention deficit disorder, and intelligence level in preschool- and elementary-aged children. Other studies, however, reported no associations with maternal caffeine consumption for similar parameters.

Conclusions: Current understanding of caffeine-related increased risk of harm for childhood development is limited due to inconsistent findings from human research. However, persistent reports of possible negative outcomes indicate high priority need for further research. In the meantime, the cumulative scientific evidence supports advice to pregnant women and women contemplating pregnancy to avoid caffeine.

Caffeine is the most widely consumed psychoactive substance in history [1]. Its consumption exceeds that of all other common drugs, including alcohol, nicotine, and the spectrum of licit and illicit substances humans ingest. For example, due to the “near universality of use of caffeine-containing beverages and foods” [2], the population consumption of alcohol, caffeine’s likely closest rival as the world’s most popular drug, falls far short of that for caffeine. The consumption of caffeine transcends almost every social barrier, including age, gender, geography, and culture. Whereas general estimates indicate that more than 80% of people worldwide regularly consume caffeine, the proportion of consumers is higher than that in many countries. In Canada, for example, 92 per cent of adults reported daily consumption of coffee or tea or both [3]. In the United States, 98 per cent of children aged five to 18 years were

found to consume caffeine at least weekly, with consumption increasing steadily with age [4]. Indeed, caffeine is unusual among psychoactive compounds in being part of the daily diet of most people worldwide, including the majority of pregnant women [5,6].

The high prevalence of maternal caffeine consumption persists despite decades of reports of potential harm in both animal and human studies [1,7-9]. In particular, evidence of negative clinical outcomes reported in original epidemiological studies and meta-analyses has increased over time in both consistency and volume. For example, among 14 meta-analyses published since the year 2000, maternal caffeine consumption was unanimously reported to be associated with increased risk for low birthweight and/or small for gestational age (5 meta-

analyses), miscarriage (4 meta-analyses), childhood acute leukemia (3 meta-analyses), and stillbirth (2 meta-analyses) [8].

That maternal caffeine consumption remains commonplace is attributable, at least in part, to current health advice to women. The European Food Safety Authority [10], the United Kingdom National Health Service [11], and the American College of Obstetricians and Gynecologists [12] all advise that it is “safe” for pregnant women to consume up to 200 mg caffeine (the approximate equivalent of 2 cups of moderate-strength coffee) per day. Such advice persists despite reports of significant dose-response associations suggestive of causation, including reports of no threshold of consumption below which associations between maternal caffeine consumption and adverse pregnancy outcomes are absent [8].

The diversity of adverse clinical outcomes is suggestive of potential disruption to key processes of foetal and child development. Nevertheless, developmental processes associated with potential harm have only recently begun to attract concerted research attention. Accordingly, the main aim of the present focussed review was to examine evidence of association between maternal caffeine consumption and childhood behavioural and neurocognitive development, including potential for long lasting sequelae. A review at this time may help to stimulate further research to clarify inconsistencies in reported findings, elucidate potential causal mechanisms, and identify directions for future research. Notwithstanding the need for further research, a second aim of the present review was to consider the implications of recent empirical findings for current health advice concerning maternal caffeine consumption.

Caffeine pharmacology: Relevant mechanisms of action

Caffeine is readily distributed throughout the body, and achieves peak plasma concentrations within approximately 40–60 minutes [13]. The drug crosses the placenta, exposing the developing fetus to concentrations similar to systemic levels in the mother [14,15]. Metabolism is principally by cytochrome P450 enzymes (monooxygenase and xanthine oxidase) in the liver, involving processes that are undeveloped in newborns and acquired during the first year of life [16,17]. Consequently, whereas adult caffeine elimination half-life is generally about 5 hours, 80 hours is typical of newborns [16].

Caffeine exerts a variety of pharmacological actions at diverse sites, both centrally and peripherally. These actions are due mostly to competitive blockade of the neuromodulator adenosine, with A_1 and A_{2A} receptors appearing to be the primary targets [18]. Effects include maintenance of transmitter release in the CNS (anti-somnolent effect), constriction of cerebral and coronary blood vessels, renal diuresis, respiratory bronchodilation, and gastrointestinal acid secretion [19–21]. A_1 and A_{2A} receptors also interact in functionally important ways with dopamine receptors [22,23], with caffeine serving to stimulate secretion of the catecholamine stress hormones of epinephrine and norepinephrine [24]. In turn, elevated catecholamine levels have the potential to increase placental

vasoconstriction and fetal heart rate [25], leading to impaired fetal oxygenation [26].

Acknowledgment of the high theoretical plausibility of fetal harm due to maternal caffeine consumption was the main impetus for early experimental studies with rodents (mice, rats, rabbits). A range of caffeine-induced gross fetal abnormalities was reported, including cleft palate, ectrodactyly (absent or deformed digits), and skeletal malformations [27–30]. Responding to such reports, the United States Food and Drug Administration issued a warning advising pregnant women to restrict or eliminate coffee consumption [31]. The warning elicited wide discussion, including strenuous representation from caffeine-beverage industries [32]. Much comment focussed on the fact that animal studies frequently used caffeine doses exceeding the levels typical of human dietary intake [33], thereby drawing into question the adequacy of the animal models that had been used to test the human teratogenic potential of caffeine.

Doubts tended to be confirmed by early epidemiologic studies of humans, wherein significant associations between caffeine and/or coffee consumption and birth defects of the kind reported in animal studies were generally reported to be absent [34–38]. Over time, a consensus emerged around the inference that typical patterns of caffeine consumption are an unlikely cause of major physical birth defects in humans. That generally reassuring consensus appears to have encouraged wide acceptance of the reputed safety of “moderate” caffeine consumption during pregnancy. Notwithstanding beliefs about safe levels of intake, it is evident that current recommendations are often breached. For example, in one recent study, 41% of a cohort of pregnant women in Finland reported consuming more than the recommended maximum of 200 mg caffeine per day [39], and in another study 25% of a cohort of pregnant Dutch women reported consuming more than 250 mg caffeine per day [40].

Importantly, of numerous potential adverse pregnancy outcomes, gross morphological abnormality (i.e., “frank” teratogenicity) is but one category, attention to which may have unduly influenced current health guidelines [1,7,9]. As mentioned above, an extensive body of scientific evidence from human observational studies and meta-analyses has emerged independently of early studies of caffeine-related teratogenicity [8]. The more recent evidence of harm appears not to have been fully considered in relation to the framing of current health advice. Against that background, the current focussed review examines recent increased interest in extending the search for potential adverse outcomes of maternal caffeine consumption beyond clinical end states to include subtler, yet potentially no less important, threats in the form of disturbed childhood behavioural and neurocognitive development.

Source literature

PubMed and Google Scholar databases were searched by the author using key terms for caffeine exposure, exposure period (namely, pregnancy), and offspring outcomes. The exposure terms were “caffeine” and the main caffeine-



containing beverages of “coffee”, “tea”, “cola”, “energy drink”, and “maté”). The search terms for the exposure period were “maternal” and “pregnancy”. Other sources of caffeine, such as chocolate (including confectionaries, cake, and hot drink), cocoa, and decaffeinated coffee and tea were not included as specific search terms, as they generally represent a negligible fraction of total daily caffeine consumed. Moreover, studies of caffeine beverages frequently include results for the aforementioned “other” sources (sometimes reported for purposes of comparison with the main sources), thereby contributing to the likelihood of information from low-caffeine sources, where relevant, being included as part of the present review. Additionally, it was assumed that the term “caffeine” would capture relevant studies (if any) that had examined a substantial source of caffeine other than those identified by the specific search terms employed here. The search was further refined by inclusion of terms relevant to the key “development”/“developmental” outcomes of interest. These were “behavioural”, “cognitive”, and “neurocognitive” outcomes, and the developmental stages of “neonate”, “neonatal”, “postnatal”, “newborn”, “infant”, “child”, “childhood, and “children”. In turn, articles were hand-searched for additional records.

A total of 1,283 English-language articles published up to and including 31 January 2021 were identified. These were culled to select only those studies that reported empirical findings for the association between caffeine exposure during pregnancy and specific offspring outcomes for postnatal and/or childhood behavioural and/or neurocognitive development. Additionally, whereas earlier literature is discussed to provide background that informs the current state of knowledge, empirical studies published since 2009 were selected as the focus for the current narrative review. The selection process involving the aforementioned criteria yielded a core literature base of 14 articles, comprised of five experimental rodent studies and nine human epidemiological studies (see Table 1).

Experimental studies with rodents

Early experiments with rodents provided strong confirmation of high biological plausibility for harm from maternal caffeine exposure, with consistent reports of disruption to behavioural and neurocognitive development [41-43]. For example, Grimm and Frieder [41] exposed pregnant rat dams to daily doses of 0.15, 0.30 or 0.45 mg/ml caffeine in drinking water for the last 7 days of gestation. Compared to untreated controls, offspring exposed to the low dose (0.15 mg/ml) evidenced hyperactivity in an open-field task, and offspring exposed to the high dose (0.45 mg/ml) evidenced disruption to complex visual and auditory discrimination learning. Foreshadowing later observational research with humans [44-47], Grimm and Frieder [41] reported that the medium (0.30 mg/ml) and high (0.45 mg/ml) doses also led to increased weight observable at 35 days, with weight gains becoming progressively greater as the animals aged.

The salience of the Grimm and Frieder [41] findings can be gauged by comparing the caffeine doses they used to typical human exposures. With the caveat that the translation

of caffeine dosing in animal studies to human consumption patterns is complex and approximate, a dose of 0.30 mg/ml in drinking water was estimated by Silva, et al. [48] to produce plasma concentrations of caffeine in rat dams comparable to that found in the blood of humans drinking 3-4 cups of coffee per day. On the other hand, Li, et al. [49] estimated the same dose (0.30 mg/ml) of caffeine in drinking water to be comparable to the human consumption of about 2 cups of coffee per day. Thus, bearing in mind the approximate nature of such estimates, the Grimm and Frieder [41] “low” dose of 0.15 mg/ml and possibly the “medium” dose of 0.30 mg/ml, could be considered comparable to reputed “moderate” and “safe” levels of exposure during human pregnancy. In that vein, the 0.45 mg/ml dose would be comparable to intake widely considered “high”, but not uncommon, among pregnant women.

Table 1 summarises key findings from five rodent studies published since 2009 that satisfied the aforementioned selection criteria for inclusion in the current narrative review. In contrast to the Grimm and Frieder [41] study, in which exposure was limited to the latter stages of pregnancy, Soellner, et al. [50] exposed pregnant rat dams to either plain tap water or caffeinated tap water throughout gestation. The level of caffeine exposure was estimated to be the human equivalent of 2 to 3 cups of coffee per day. Adult male and female offspring of dams exposed to caffeine during pregnancy exhibited memory and learning impairments in object recognition and spatial learning tasks. The findings were interpreted as suggesting developmental changes in the expression and/or function of adenosine receptors within the hippocampus and prefrontal cortex leading to long-term alterations in memory and learning. Long-term effects were also reported by Silva et al. [48] who exposed mouse dams to 0.30 mg/ml caffeine in drinking water throughout gestation and lactation. Compared to untreated controls, adult offspring of treated animals showed increased excitability in hippocampal circuits and associated sequelae including increased susceptibility to seizures.

Fazeli, et al. [51] also reported increased seizure susceptibility in a study in which caffeine in drinking water was intended to mimic human consumption of approximately three cups of coffee per day. Compared to control offspring, formation and activity of cortical networks was found to be impaired in offspring of caffeine-exposed mouse dams. In another study that sought to mimic human consumption patterns with the use of 0.30 mg/ml caffeine in drinking water, Zappettini, et al. [52] were careful to parallel human exposure before and during pregnancy until full-term birth, taking account of both the time span of caffeine exposure and amount of caffeine consumed. Electrophysiological recordings of hippocampal CA1 pyramidal cells in vitro revealed caffeine-related changes likely to increase the risk for early onset of dementia-associated pathology. In addition, Li et al. [49] reported that expression of adenosine A₁ and A_{2A} receptors was impaired in fetal and neonatal brain among offspring of rat dams exposed to 20 mg/kg caffeine (compared to saline) administered twice daily via subcutaneous injection. The same study also reported that learning and memory were impaired in adult offspring exposed to caffeine in utero.



Table 1: Summary of original animal and human studies concerning maternal caffeine consumption and childhood behavioural and neurocognitive development, published since year 2009.

Authors	Year	Main aim	Method	Key findings
Experimental Studies with Rodents				
Soellner, et al.	2009	Effects of chronic prenatal exposure to caffeine on cognitive performance in adult male and female offspring.	Pregnant rat dams were exposed via drinking water to the human equivalent of 2 to 3 cups of coffee per day throughout pregnancy, and offspring were compared to the offspring of caffeine-free dams.	Compared to untreated controls, adult male and female offspring of caffeine-exposed dams exhibited impaired cognition, including 24-h memory retention in novel object recognition and spatial learning in a maze task. Findings were suggestive of developmental changes in the adenosine-receptor functioning in the hippocampus and prefrontal cortex, leading to long-term alterations in memory and learning.
Silva, et al.	2013	Effects of maternal exposure to caffeine, as an adenosine modulator, on offspring neural development.	Offspring of mouse dams exposed to 0.30 mg/ml caffeine via drinking water during pregnancy and lactation were compared to offspring of caffeine-free dams.	Compared to untreated controls, caffeine-exposed offspring showed delayed migration and insertion of <i>g</i> -aminobutyric acid (GABA) neurons into the hippocampal circuitry during the first postnatal week, and increased neuronal network excitability and susceptibility to seizures. Adult offspring displayed loss of hippocampal GABA neurons and cognitive deficits.
Fazeli, et al.	2017	The construction and activity of cortical networks in offspring of dams exposed to effects of caffeine during pregnancy and the early postnatal period.	Caffeine was added to the drinking water of female mice to mimic daily consumption of 3 cups of coffee in humans.	Compared to controls, caffeine-exposed offspring showed impaired brain development, including altered construction of GABAergic neuronal networks in the primary visual cortex at postnatal days 6-7; increased synaptic activity <i>in vitro</i> and elevated network activity <i>in vivo</i> in the primary visual cortex; altered <i>in vivo</i> hippocampal network activity from the neonatal period until adulthood; and increased seizure susceptibility.
Li, et al.	2018	Effects of maternal caffeine exposure on neurocognitive functions.	Rat dams received subcutaneous injections of 20 mg/kg caffeine (compared to saline) twice daily throughout pregnancy. Fetal and offspring body and brain weight were measured, learning- and memory-related receptors were measured, and learning and memory were tested in adult offspring.	Compared to untreated controls, caffeine-exposed offspring showed fetal growth restriction, and long-term impairment in learning and memory; intrauterine programming dysfunction of adenosine receptors; and impairment of subunits of down-stream protein-binding systems in fetal, neonatal, and adult brain.
Zappettini, et al.	2019	The long-term consequences of early-life exposure to caffeine for Alzheimer's disease-like pathology.	The study employed a rodent model of Alzheimer's disease (THY-Tau22 transgenic mice). The exposure schedule involved caffeine in drinking water intended to mimic the amount and time span of the human consumption of caffeine before and throughout gestation.	Caffeine-exposed offspring showed deficits in spatial learning and memory earlier than untreated controls; and disordered electrophysiological recordings suggestive of early onset of Alzheimer's disease-like pathology.
Human observational studies				
Linnet, et al.	2009	Associations between maternal coffee exposure and risk of hyperkinetic disorder and attention deficit hyperactivity disorder (ADHD).	A prospective cohort study of 24,068 Danish children, including 88 children aged 3-12 years with hyperkinetic disorder and/or ADHD.	High maternal caffeine consumption (10+ cups of coffee per day) reported at 16 weeks of gestation was associated with a threefold increased risk of hyperkinetic disorder and ADHD. After adjustment for confounders, the risk decreased to RR 2.3 (95% CI 0.9–5.9) and was no longer statistically significant.
Bekkhuis, et al.	2010	Associations between maternal caffeine consumption and inattention/overactivity suggestive of ADHD.	A prospective cohort study of 25,343 Norwegian mothers and their 18-month-old children.	After adjustment for potential confounders, caffeine in the form of soft drinks but not coffee or tea, reported at 17 and 30 weeks of gestation, was found to be associated with inattention/overactivity.
Loomans, et al.	2012	Associations between maternal caffeine consumption and offspring behavioural problems.	A prospective cohort study in The Netherlands of 3,439 children assessed at age 5-6 years for mother- and teacher-reported problem behaviour.	After adjustment for potential confounders, maternal caffeine consumption reported at 16 weeks of gestation was not associated with a higher risk for behaviour problems or with suboptimal prosocial behaviour.



Galéra, et al.	2015	Associations between maternal caffeine consumption and impaired cognitive development in offspring.	A prospective cohort study of 1,083 French mother-child pairs followed from pregnancy to when the children were aged 5.5 years.	After adjustment for potential confounders, there was a significant caffeine-related association with reduced childhood IQ of nearly one full IQ point per additional 100 mg/day of maternal caffeine intake assessed before pregnancy and after delivery.
Klebanoff and Keim	2015	Associations between maternal serum paraxanthine (the primary metabolite of caffeine) and offspring IQ and problem behaviour.	A prospective cohort study in the United States of 2,197 children assessed at ages 4 and 7 years.	After adjustment for potential confounders, no statistically significant associations were reported between maternal serum paraxanthine, measured at "early pregnancy" (<20 weeks) and "third trimester" (>26 weeks), and either IQ or problem behaviour.
Del-Ponte, et al.	2016	Associations between maternal consumption of caffeine during pregnancy and childhood ADHD.	A prospective cohort study of 3,485 Brazilian children assessed at age 11 years.	After adjustment for potential confounders, maternal caffeine consumption, assessed by interview after delivery, was not associated with ADHD.
Mikkelsen, et al.	2017	Associations between maternal caffeine consumption and offspring behavioural and psychiatric disorders.	A prospective cohort study of 47,491 Danish mother-child pairs.	After adjustment for potential confounders, maternal caffeine consumption reported at 15 weeks gestation was reported to be associated with increased risk of a range of behavioural and psychiatric disorders.
Berglundh, et al.	2021	Associations between maternal caffeine consumption and childhood neurodevelopment.	A prospective cohort study of 64,189 Norwegian children assessed at ages 6 and 18 months, and 3, 5 and 8 years.	After adjustment for potential confounders, maternal caffeine consumption reported at 22 weeks of gestation yielded no consistent associations with childhood neurodevelopment at any age.
Christensen, et al.	2021	Associations between maternal caffeine consumption and childhood neurodevelopment.	A prospective cohort study in the United States of 9,157 children assessed at 9-10 years using magnetic resonance imaging (MRI).	After adjustment for potential confounders, MRI revealed caffeine-related alterations in brain microstructures associated with maternal caffeine consumption reported "throughout gestation".

In summary, recent animal studies confirm the decades-long inference of high biological plausibility for potential harm from maternal caffeine exposure. The studies summarised in Table 1 report a wide range of caffeine-related disruption to brain function and structure, and associated developmental impairment in behaviour and cognition. Whereas there may have been a tendency to discount earlier similar findings due to pregnant animals being exposed to levels of caffeine in excess of those typical of human consumption patterns, the studies summarised in Table 1 were careful to use regimens of caffeine intake intended to mimic typical human exposure. As such, recent animal findings are important in raising awareness of potential negative effects for child development due to maternal caffeine consumption.

Human observational studies

Table 1 summarises key findings from nine recent prospective cohort studies of potential caffeine-related harm to childhood behavioural and neurocognitive development. It is evident from the table that diversity of investigatory approach and inconsistency in reported findings represent major challenges to interpreting the evidence. In an early study of caffeine and attention deficit hyperactivity disorder (ADHD), Linnet et al. [53] reported that high maternal caffeine consumption (defined as 10+ cups of coffee per day) was associated with a three-fold increased risk of ADHD-related behaviour among 24,068 Danish children aged between 3 and 12 years. However, adjustment for confounders reduced the estimated risk to RR 2.3 (95% CI 0.9–5.9), which no longer represented a statistically significant difference.

Bekkhuis, et al. [54] also reported a significant association for ADHD-related behaviour among 25,343 Norwegian children aged 18 months. In this instance, however, increased risk was observed for maternal consumption of soft drinks but not coffee and tea, leading the authors to suggest that caffeine was unlikely to be responsible for the reported effect. At the same time, the authors cautioned that the children may have been "too young" for caffeine-related effects to be reliably observed. In a study of 3,439 Dutch children, Loomans et al. [40] reported that maternal caffeine consumption was unrelated to mother and teacher ratings of ADHD-related behaviour among children aged 5 to 6 years. Absence of association was also reported by Klebanoff and Keim [55] in the United States for 2,197 children aged 4 and 7 years, and by Del-Ponte et al. [56] for 3,458 Brazilian children aged 11 years. Conversely, in a larger study of 47,491 Danish children aged 11 years, Mikkelsen et al. [57] reported that high maternal caffeine consumption (defined as 8+ cups of coffee per day) assessed at 15 weeks of pregnancy was associated with increased risk for a range of behavioural and psychiatric disorders including ADHD-related behaviour.

In the same study that reported no association for ADHD-related behaviour, Klebanoff and Keim [55] found no association between maternal caffeine consumption and intelligence quotient (IQ) in children aged 4 and 7 years. Conversely, Galéra et al. [6] reported a significant association between maternal caffeine consumption and lower IQ among 1,083 French children aged 5.5 years. Reasons for the discrepant findings were debated in an exchange of letters without the respective groups [58,59] reaching agreement. Bernard, et al. [58] reasoned that a combination of the two sets of results



supported the conclusion that a causal link exists between high caffeine exposure and lower childhood IQ. In reply, Klebanoff and Keim [59] reiterated their belief “that the amount of caffeine consumed by most pregnant women . . . is not likely to be associated with reduced child cognition” (p. 873).

Unfortunately, inconsistencies in findings continue to characterise the most recent research. Berglundh, et al. [60] examined the association between maternal caffeine consumption and impaired neurodevelopment, including motor development, behaviour problems, and language difficulties, among 64,189 Norwegian children aged 6 and 18 months, and 3, 5 and 8 years, and found no consistent associations. Conversely, Christensen, et al. [61] in the United States, examined maternal caffeine consumption and regional brain microstructure among 9,157 children aged 9 to 10 years. Maternal exposure to caffeine was measured dichotomously to create an exposed group of women who reported consuming caffeine more than once a week throughout pregnancy and a group comprised of women who reported consuming caffeine less than once a week. Magnetic resonance imaging (MRI) indicated microstructure alterations of “critical fibre tracts” among children of the exposed group of mothers compared with children of control mothers,

Limitations and inconsistencies among human observational studies

No one set of factors can explain all the inconsistencies in the reported findings from human observational studies of maternal caffeine consumption and childhood development. Notably, studies to date have been few in number and have involved participants in different countries with varying patterns of caffeine consumption. In addition, apart from being prospective in nature, studies have employed widely differing investigatory approaches. In particular, there has been little consistency in the measurement of maternal caffeine exposure, the population samples examined have differed greatly in size, children have been assessed at different ages, and different behavioural and neurocognitive developmental outcomes have been examined.

In addition to those inconsistencies, studies share a limitation common to much human observational research, namely, the challenge of controlling for potentially confounding variables. In this respect, it would be fair to say that studies have generally been carefully conducted. Among a wide range of potential confounders, including marital status, ethnicity, employment status, and education level of one or both parents, maternal smoking and alcohol consumption have received particular attention. Of the nine human observational studies summarised in Table 1, all adjusted for cigarette smoking, and all but one [61] adjusted for alcohol consumption.

Recall bias in relation to amount of caffeine consumed during pregnancy has long been offered as a possible source of confounding, especially by commentators with caffeine-industry affiliations [62–66]. However, as with many recent studies concerning clinical outcomes associated with maternal caffeine consumption [8], all of the observational

studies summarised in Table 1 employed prospective designs. Consequently, recall bias is an unlikely source of confounding in those studies, since caffeine consumption was assessed in advance of assessment of indicators of childhood behavioural and neurocognitive development. For example, Linnet, et al. [53] assessed maternal caffeine consumption at 16 weeks of pregnancy, and developmental outcomes were assessed when the children were aged between 3 and 12 years. Similarly, Mikkelsen, et al. [57] assessed maternal caffeine consumption at 15 and 30 weeks of pregnancy, and developmental outcomes were measured when the children were aged 11 years. Likewise, Berglundh, et al. [60] assessed caffeine consumption at 22 weeks of pregnancy, and developmental outcomes were measured when the children were aged 6 and 18 months, and 3, 5 and 8 years.

Notwithstanding likely absence of recall bias, lack of consistency in the specific methods used to measure caffeine consumption during pregnancy could account for inconsistencies in the findings. In most studies, caffeine intake during pregnancy was assessed by means of self-report questionnaire, administered in person or by mail. Typically, participants were asked to report the number of servings (e.g., cups, mugs, glasses, or bottles) of caffeine beverages (e.g., coffee, tea, or caffeinated soft drinks). In some, but not all studies, participants reported information concerning method of preparation (e.g., instant, espresso, percolated, or filtered coffee), and responses were aggregated to derive estimates of milligrams of caffeine consumed per day. Typically, studies provided little or no information concerning the reliability and validity of the measurements used. Only one study, that of Klebanoff and Keim [55], used an objective biomarker of caffeine exposure in the form of serum paraxanthine, the primary metabolite of caffeine.

Public-health advice

Even in the absence of other information, the status of caffeine as a common habit-forming substance of no nutritional value to either mother or baby is a clear indicator of the need to adopt a cautionary approach when framing public-health advice about consuming the drug during pregnancy. In respect of potential harm to childhood behavioural and neurocognitive development, findings from animal studies add substantial additional grounds for concern. On the other hand, the relative paucity of human observational studies, and especially the many contradictory results among the few that have been conducted, preclude definitive conclusions. However, whereas contradictory findings may incline some commentators to be dismissive, precisely the opposite inclination is warranted. The core empirical fact concerning potential caffeine-related developmental harm is that some studies have reported null results whereas others have not. Therefore, unless and until maternal caffeine consumption is consistently shown to be without risk to childhood development, persistent intermittent empirical findings of harm should figure prominently in health advice for mothers and mothers-to-be.

Recent guideline revisions hint at possible growing circumspection among relevant health authorities. Specifically,



in keeping with the hitherto broad consensus, the *Dietary Guidelines for Americans Committee, 2015* (DGAC) [67] advised women of the reputed safety of consuming 200 mg caffeine per day during pregnancy. However, that advice is absent from the recently-revised *Dietary Guidelines for Americans, 2020-2025* [68]. Instead of continuing to condone the consumption of reputedly “safe” amounts of caffeine during pregnancy, the new *Guidelines* state that women “who could be or who are pregnant should consult their healthcare providers for advice concerning caffeine consumption” (p. 118).

We may guess that this revised advice is an attempt at compromise, reflecting growing awareness of the many and increasing reports of harm associated with maternal caffeine consumption. However, the revised DGAC [68] guidance is disappointing at least, and even shocking in its prevarication. Following a protracted process of review of scientific literature, open public consultation, and extensive stakeholder (including industry) consultation, all under the guidance of a select group of experts, the DGAC [68] aims to deliver dietary advice that is clear and direct. However, in this instance, on a subject of relevance to the majority of women, the DGAC has effectively said that it has no opinion. In so doing, the DGAC has opted to transfer responsibility for advice about maternal caffeine consumption to an amorphous and countless number of individual “healthcare providers”, the large majority of whom may be assumed to possess neither the required expertise nor any clear means for mustering an informed opinion.

Future research

Whereas current knowledge is limited concerning caffeine-related risks to childhood behavioural and neurocognitive development, there are many facts about maternal caffeine consumption that are far from uncertain. As discussed above, there is high biological plausibility for potential harm; there is consistent evidence from animal research of harm to behavioural and neurocognitive development among offspring (summarised in Table 1); and extensive evidence from human observational research and meta-analyses of harm for diverse clinical pregnancy outcomes [8]. The inconsistent findings described herein (and summarised in Table 1) from human observational studies of childhood behavioural and neurocognitive development serve, at the very least, to indicate the high-priority need for more and better-controlled studies in this area.

For the present, it is not possible to be highly prescriptive as to what constitutes better-controlled studies in this relatively undeveloped field. Animal experimentation offers the substantial advantage of permitting controlled manipulations of caffeine exposure and should be pursued so as inform researchers about potentially important human sites of caffeine-related harm (e.g., impaired development of critical brain structures). Alas, comparable levels of experimental control, such as may be achieved in randomised controlled trials, although theoretically possible, are unlikely to be conducted in practice due to the questionable ethicality of conducting such trials with pregnant women [8,69].

Consequently, advances in the field are likely to depend on continued epidemiological investigation. Here, much benefit would accrue were greater standardisation achieved in relation to the use of reliable and validated measurement protocols for assessing caffeine exposure, such as has been in use for some time in the Norwegian Mother and Child Cohort Study [70,71]. Similarly, continued attention to the control of potential confounders is strongly advised, including where possible the use of biological indicators of exposure, not only for caffeine, but also for nicotine and alcohol.

Conclusion

There are strong grounds for eschewing the complacency that may be said to characterise much current public-health advice about maternal caffeine consumption. Taken as a whole, the cumulative scientific evidence supports advice to pregnant women and women contemplating pregnancy to avoid caffeine.

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