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REVIEW OPEN ACCESS

The Physiological, Cognitive, and Developmental Effects of Prenatal Caffeine Consumption on Foetal Pregnancy Outcomes

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Abstract

Introduction: Maternal caffeine consumption during pregnancy may confer developmental risk to the foetus due to caffeine's ability to cross the blood brain barrier (BBB) and blood placental barrier (BPB). This literature review investigated caffeine's properties and mechanism of passage through the BBB and BPB. The subsequent effects of moderate-to-excessive maternal caffeine consumption (≥ 200mg of caffeine daily) on physical development, cognition, and behaviour were further explored.

Methods: The review was conducted using PubMED, NCBI, and Google Scholar, using key terms such as "pregnancy", "caffeine", "prenatal", "adverse effect", "development", and "embryo development". Articles selected were published within the last 15 years (2008-2023) and longitudinal studies, cohort studies, and experimental methods using animal models were included.

Results: It was found prenatal caffeine exposure poses a variety of potential consequences for the infant prior to and after delivery. Notably, physical developmental risks include fetal growth restriction, birth defect(s), and changes in neuronal structure and blood flow. Cognitive and behavioural consequences include possible links to externalizing behaviour problems, decreased intelligence quotient (IQ), attentive deficit and hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) during childhood.

Discussion: This research is primarily restricted to animal models and cohort studies. Moroever, there were several conflicting conclusions surrounding behavioural and cognitive effects of prenatal caffeine exposure. This drives inquiry into how further research can both solidify causal relationships and be conducted ethically to help inform parents about the potential risks of prenatal caffeine exposure.

Conclusion: With a global trend of increasing caffeine consumption, through coffee, black tea, and recently, matcha, this review provided insight into this ever-growing aspect of our lifestyles. It is paramount to understand the effect of caffeine on foetuses to promote safe and healthy pregnancy outcomes.

Keywords: caffeine; pregnancy; maternal outcomes; blood-brain barrier; blood-placental barrier

Introduction

Caffeine is a water- and fat-soluble central nervous system stimulant, found most prevalently in our diets through coffee, energy drinks, chocolate, and tea consumption [1-3]. This amphipathic property of caffeine enables its free passage through biological membranes within the human body, allowing it to elicit various effects including increased alertness and attention, decreased reaction times, and possibly affecting higher order processes such as judgement and decision making [4,5]. These effects can be desirable and even beneficial to consumers in instances of concentration enhancement and physical performance (e.g., gaming, athletics) [6]. However, the effects of caffeine consumption by a mother during pregnancy may pose deleterious effects to the foetus [7]. This may be attributed to decreased caffeine clearance during pregnancy and the ability of caffeine to pass through the placenta, leading to its accumulation in the foetal brain [8]. The blood brain barrier (BBB) and blood placental barrier (BPB) both allow for selective passage of certain molecules, including caffeine, into the brain and placenta through the systemic circulation of blood [7,9]. The BBB and BPB hinders the passage of perceived threats (e.g., virions, bacterial material, and pharmaceuticals) and selectively allows certain molecules through [7,9]. Therefore, the amphipathic nature of caffeine renders its status as a potential 'threat' during pregnancy to be dependent on its ability to cross the BBB and BPB.

Accumulation of caffeine in the biological membranes of the foetus, even at low doses, may cause developmental, cognitive, behavioural, and physical effects.

To mitigate potential risks, expecting mothers are advised to moderate caffeine intake, citing negative consequences to both the mother and foetus. However, there is an immense amount of ambiguity towards what is considered an appropriate and safe amount of caffeine consumption throughout pregnancy. The Swedish National Food Agency recommends less than 300 mg of caffeine per day throughout pregnancy. However, some studies showed that even daily caffeine consumption of 150 mg may increase the risk of miscarriage [10]. To address this notable ambiguity in literature, this paper considered moderate caffeine consumption to be 200 mg of daily caffeine, in accordance with the American College of Obstetricians and Gynaecologists, the UK National Health Service, and the European Food Safety Authority, and excessive dose to be anything higher than 300 mg [11].

This review investigated the mechanism of caffeine's transport across two important biological membranes, the BBB and BPB, as well as potential risk factors for prenatal caffeine consumption. For the purpose of this review, the term "mother" was defined as a non-gender specific term to represent the person carrying the foetus. The review aims to understand the effect of prenatal caffeine consumption by the mother on foetal pregnancy outcomes, and the extent to which caffeine consumption may be safe.

Methods

To conduct this narrative review, literature searches were completed using PubMED, NCBI, and Google Scholar. It used key MeSH terms such as "pregnancy", "caffeine", "adverse effect", "development", "cognitive", "physical", and "behavioural". Sources were selected using the relevance, authority, date, appearance, and reason (RADAR) framework. Articles must have been published written in the English language and within the previous fifteen years (2008-2023). Articles of longitudinal studies, cohort studies, and experimental studies using animal models were selected.

Results

Mechanism of Caffeine Transport Across the BBB

To discern the effects of caffeine consumption on maternal bodies, it is important to distinguish the chemical properties of the molecule itself and establish whether it can be transported through the BBB. The blood-brain barrier (BBB) is a structural assortment of blood vessels connecting the brain to vascular flow [12,13]. This functional structure and physiological barrier provides nourishment, a pathway for oxygen and ion flow, and a semi-permeable structural defence against large and polar molecules. It is composed of a phospholipid bilayer made of capillary endothelial cells, tight junctions, and astrocytes all acting to maintain a stable microenvironment in the brain (Figure 1) [12,13]. The BBB maintains a high level of restricted permeability against fungi, bacteria, viruses, and parasites that may have been transported through the blood, acting as a passive immunological defence. This is typically due to size-based permeability filtration across the barrier. When crossing the BBB, certain bio-chemical properties are favourable: lipophilicity (fat-solubility), small physical size, a molecular weight below 450 g/mol, and low hydrogen-bonding potential (meaning the molecule exists at a neutral charge at a physiological pH of 7.5). Caffeine falls into the small molecule category, with a molecular weight of 194 g/mol, and demonstrates amphipathicity, allowing it to cross the BBB using passive transport (Figure 1) [14,15].

Once a molecule of caffeine crosses the BBB, it enters the basement membrane and is eventually transported into a pericyte or astrocyte. From this point, the characteristics of the spatial distribution of caffeine in the brain are influenced by age, disease, and development of the individual. For example, various neurocognitive diseases may also influence permeability of the BBB, change tight junction distribution, and cause differences in pumps and transporters. The investigation of caffeine's permeability across other membranes, especially those central to pregnancy, is further warranted to assess the impact which caffeine consumption has on pregnancy outcomes.

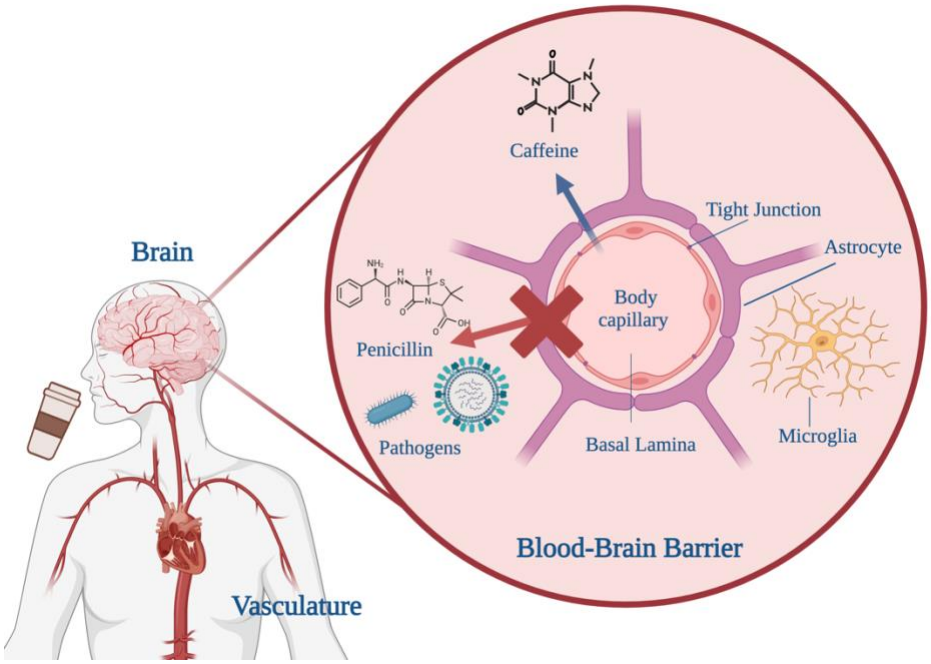

Figure 1. The BBB is a semi-permeable barrier membrane separating the brain environment from the rest of the body. It is comprised of vasculature in which a capillary from the body is surrounded by astrocytes to form tight junctions. These junctions are semi-restrictive, permitting molecules like caffeine to enter the brain. Concurrently, large molecules like penicillin as well as pathogenic species are shielded out. Microglia act as immune cells for the BBB which help counter the pathogenic species. Lastly, the basal lamina acts as a body to the BBB vasculature. Upon passage of caffeine into the brain, it can begin to further exert its effects. Created with BioRender.com.

Mechanism of Transport of Caffeine Across the BPB

As a highly specialised organ, the placenta plays a critical role in the successful development and growth of the foetus throughout pregnancy [16,17]. It is a multi-layered and membranous organ that mediates the exchange of substances between the mother and foetus [17,18]. This phenomenon requires a large surface area for efficient nutrient and gas exchange to occur, which is achieved by presence of villi. The villi themselves are encompassed by syncytiotrophoblast cells (STCs) in the outer lining of the placenta (Figure 2) [18]. STCs are the main site of nutrient and gas exchange between the mother and foetus and are rich in protein and glucose transporters. STCs therefore provide a transport mechanism during pregnancy for caffeine molecules (Figure 2). As pregnancy is initiated, cytotrophoblast cells begin to fuse into STCs and secrete hormones and proteins [18]. Moreover, the process of caffeine metabolism in non-pregnant versus pregnant individuals is vastly different. Pregnant individuals require 1.5 to 3.5 times longer to metabolise caffeine than those who are not [19]. For example, caffeine may be completely metabolised in 2-8 hours for non-pregnant individuals or 6-16 hours for pregnant individuals. The exact mechanism by which caffeine passes through the BPB is less understood [5]. The passage of caffeine across the placenta is dangerous as the primary enzyme responsible for caffeine metabolism, cytochrome P450 1A2, is completely absent in both the placenta and foetus [9,19]. Therefore, the successful and complete metabolism of caffeine is solely dependent on the pregnant individual, of whom already has a longer metabolism time [19].

Efforts to engineer organ-on-a-chip models of the placenta have been made to represent the true microenvironment of the human placenta. A study by Pemathilaka et al. [19] used a placenta-on-a-chip model to study caffeine transport across the BPB using liquid chromatography mass spectrometry. A caffeine concentration of 0.25 mg/mL, which is equivalent the FDA-specified amount of 300 mg per day, was introduced to the maternal channel of the model for perfusion analysis. Caffeine concentration on the foetal side increased until it began to reach a steady-state concentration of 0.0032 mg/mL at 5 hours and continued maintaining an average of 0.0033 mg/mL steady-state concentration from 5 to 7.5 hours. Caffeine concentration is held relatively constant for a considerable duration of time after initial consumption, in which it can elicit effects on the foetus. This accumulation of caffeine can elicit a myriad of physical, cognitive, and behavioural implications to the foetus.

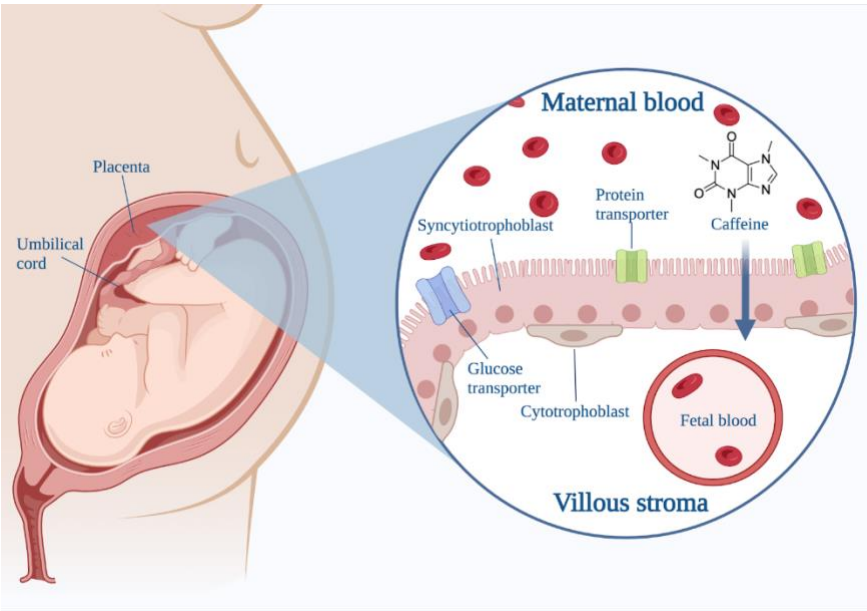

Figure 2. The BPB is a villous membrane composed of STCs which modulate the passage of materials from the maternal blood to the foetus. Cytotrophoblast stem cells line the foetal villous stromal compartment. Glucose transporters, such as GLUT1, and protein transporters allow the passage of molecules across the BPB. Caffeine is depicted passively transporting across the BPB, rendering its access to fetal circulation. Created with BioRender.com.

Caffeine's Effect on Foetal Development

Caffeine consumption four weeks prior to conception, and continued consumption during weeks 8-12 of pregnancy results in increased risk of fetal growth restriction [20,23]. A study measured this to be correlated directly with amount of mean caffeine consumption, with highest risk also associated in women with a slower caffeine clearance [20]. A slower caffeine clearance results in a higher half-life for caffeine within systemic circulation, which would then increase its bioavailability for uptake in the brain through the BBB, and the placenta through the BPB. Due to increased risk of fetal growth restriction, it is recommended to reduce caffeine consumption before and during pregnancy. Fetal growth restriction is medically defined as the difference in weight between the foetus in question and the normal weight. If this is less than 10th percentile, in which the weights of 90% of foetus with identical gestational age are heavier, then this is a condition which calls for short- and long-term serious implications for the foetus [21,22,24]. The condition is typically due to placental restrictions, as caused by smoking, cocaine usage, and hypertension, in which placental structure and function is compromised [24]. Caffeine is generally regarded to be a vasoconstrictor, leading to acute hypertension. Chronic consumption of caffeine, through coffee, even prior to pregnancy may cause shifts in vasculature contributing to the elasticity of the BBB and BPB and increase risk of hypertension [25]. A 2015 study by researchers in Japan assessed the maternal outcomes for 858 Japanese women who had singleton births and self-reported their diet history throughout pregnancy [26]. Caffeine consumption was predominantly in the forms of Japanese and Chinese tea (73.5% of all caffeine sources), whereas coffee only contributed to 14.3% of consumption - this is notably different than the coffee-predominant Western diet [26]. The study found that higher caffeine consumption, in any form, increased risk of premature birth [26]. Premature birth is defined as birth prior to the completion of 37 weeks of pregnancy, and is well-known to increase risk of mortality and serious physical disability outcomes for the foetus, including cardiovascular and respiratory conditions [27]. Therefore, caffeine has notable physical effects on both the foetus, through foetal growth restriction and high risk of premature birth via the placenta, and the direct consumer (mother) through cardiovascular exertion. Physical effects have further been observed in other non-human *in vivo* studies.

Studies have demonstrated adverse developmental effects with respect to uterine receptivity, placentations, embryo development, and foteal physiological development [28-32]. A study by Gwon et al. [28] observed the effect caffeine has on mouse embryos. Embryos were cultured with caffeine (30, 60, and 120 μg/mL) and/or bisphenol A (BPA), an endocrine disrupter, for 48 hours. Co-exposing embryos to BPA and caffeine showed significant changes such as decreased crown-rump length, abnormal heart development, reduction in the optic system, reduction in hind and fore limbs, and malformed facial development. All combined treatments also showed changes to the structure of the yolk sac such as fewer blood cells, endothelial cells that did not adhere to the visceral endoderm, and an increase in the number of apoptotic cells. This is significant as it demonstrates serious developmental risks in foetal animal models, which could potentially extrapolate risks to human foetuses [19,30-32]. It is

paramount to consider this while discussing moderate caffeine dosages during pregnancy, as well as co-exposure to other harmful chemicals such as BPA. In discussions on caffeine consumption during pregnancy. Further examination of the physical effect that prenatal caffeine exposure has on the brain is warranted.

Caffeine's Physical Effects on the Brain

Caffeine ability to compromise BBB integrity, neuroinflammation, and change neural activity may have significant effects on the mother and foetus [33-35]. The effect caffeine has on the brain is primarily facilitated through its role as an adenosine antagonist [12,36]. It readily binds to the A_1, A_{2A} , and A_{2B} adenosine receptors on neurons. This increases neural activity and alertness as well as elicits tachycardia and diuresis through blocking the inhibitory effect adenosine has on synaptic vesicle release [12]. A study by Xu et al. [37] looked at the effects of caffeine consumption on brain metabolism through examining cerebral blood flow. They found that cerebral blood flow decreased by 16.4% in young adults who consumed 200 mg of caffeine. Fazeli et al. [34] observed changes in the construction of neuronal networks, which operate based on gamma-amino butyric acid (GABA), of the visual cortex after mice offspring were exposed to caffeine throughout gestation. GABA receptors respond to and control the major inhibitory neurotransmitters in the central nervous system. Fazeli et al. [34] found that mice experienced increased neuronal network activity and increased seizure rates in a hyperthermia-induced seizure experiment. The physical changes associated with caffeine consumption in animal models informs a deeper understanding of the resulting effects caffeine may have on foetuses' cognition and behaviour later in life.

Caffeine's Effect on Cognition and Behaviour

Caffeine exposure during pregnancy has serious cognitive and behavioural implications for the foetus, which may be caused by physical changes in the brain. The effects of caffeine on the aforementioned A_1, A_{2A} , and A_{2B} adenosine receptors may suppress the neural plasticity within the hippocampus and neighbouring brain regions, thereby reducing neural functions. These changes have been studied in various *in vivo* animal model experiments. For example, the negative effects of prenatal caffeine exposure on learning and memory in rat offspring have been studied [38,39]. Li et al. [38] found offspring not prenatally exposed to caffeine (control group) and offspring prenatally exposed to 20 mg/kg of caffeine twice daily (CAF group) were examined. Effects were assessed using performance of the groups on the Morris water maze, which show spatial learning and memory capacity. It was found that the CAF group had a longer escape time and longer path length than the control group, indicating damaged spatial learning ability. It was found that A_1 and A_{2A} receptors were significantly increased in the foetuses of the CAF group, which eventually decreased in expression as the CAF group matured into young adults. This study indicates structural changes to the rat brain with prenatal caffeine exposure resulting in neurocognitive effects such as decreased spatial learning ability. This may be extrapolated to the effects on human foetal brains and the resultant risk for neurocognitive effects with human prenatal caffeine exposure. Although experimental studies in human models may be unethical, impairments relating to memory, learning, and social development of children who were prenatally exposed to caffeine have been suggested in other studies methodologies [40-42].

A cohort study by Zhang et al. [43] examined 11,875 children between the ages of 9 and 11 who were prenatally exposed to caffeine. These children showed increased rates of externalizing behaviour problems, depression, anxiety, and oppositional defiant behaviours. This study, among others, showed links between prenatal caffeine exposure and attention-deficit hyperactivity disorder (ADHD) for mothers who consumed at least 8 cups of coffee per day [43,44]. However, other studies showed that prenatal caffeine exposure has no correlation with rates of ADHD diagnosis in children [3,45]. This discrepancy speaks tremendously to the difficulty in precisely characterising the risks of prenatal caffeine exposure [46]. Other studies have shown prenatal caffeine exposure alters reward sensitivity and correlates with preference for sugar intake [47]. This can subsequently explain the high body mass index (BMI) value that children who were prenatally exposed to caffeine tend to have [48-50].

Another neurological disorder that hosts discrepancies between caffeine's influence on its incidence is autism spectrum disorder (ASD). ASD is a neurodevelopmental disorder that is characterised by communication deficits, social deficits, and restrictive or repetitive stereotypical behaviours [51]. Investigations on caffeine's role in behavioural traits related to ASD have been completed on two pregnancy cohorts by Patti et al. [51]. In this study, pregnant mothers self-reported caffeine intake and caregivers ranked child behaviour relating to ASD on the social responsiveness scale. In one cohort, caffeine intake through pregnancy was associated with higher scores on the Social Responsiveness Scale, thereby associated with traits relating to ASD. The other cohort had a slight correlation. Other studies, however, contradict this finding. A cohort study by Havdahl et al. [4] reported no causal relationship between prenatal caffeine exposure and ASD. In all cases, correlation does not imply causation; it does, however, act as preliminary evidence for increased risk of neurological disorders such as ADHD and ASD.

Other cohort studies, such as one by Galéra et al. [8], showed that children's intelligence quotient (IQ), often used as a metric for intelligence and critical reasoning ability, at 5 years old was significantly decreased with mothers who consumed more than 200 mg/day of caffeine during pregnancies compared to no caffeine consumption or 100 mg/day of caffeine consumption. Table 1 summarizes how prenatal caffeine exposure may have damaging effects to foetal developmental, cognition, and behaviour.

Table 1. The effects of prenatal caffeine exposure, as per the studies investigated in this review, on foetal development, cognition, and behaviour

Author	Year	Study Type	Population and Number	Assessment	Significant Results
Pemathilaka et al. [19]	2019	Experimental study	Engineered placenta-on-a-chip model.	• Analysis of caffeine transport across a placental-on-a-chip model using liquid chromatography mass spectrometry	• Caffeine is able to cross the BPB and accumulate on the foetal side, allowing it to elicit effects • A steady caffeine concentration of 0.003mg/mL is achieved on foetal side after 5 hours • A steady caffeine concentration of 0.1513 was achieved on the maternal side after 7.5 hours
Okubo et al. [26]	2015	Cohort study	858 Japanese women.	• Questionaires assessing lifestyle behaviours, dietary habits, and neonatal anthropometric measurements	• Maternal caffeine consumption was correlated to increased risk of premature birth • No evidence for caffeine's correlation to low birth weight or small for gestational age babies
Crump et al. [27]	2020	Systematic review	8 studies conducted in Norway, Sweden, and Australia.	• Systematic literature review identified 1281 studies, 30 were selected for in depth analysis, and 8 met final selection criteria	• Premature birth demonstrated increase risk of mortality and chronic diseases • Physical disabilities for the foetus and later into adulthood
Gwon et al. [28]	2020	Experimental study	Mouse embryos.	• Histalogical analysis • Embryonic anomaly analysis using the morphological scoring index • Target gene analysis using real time PCR	• Co-exposing mouse embryos to BPA and caffeine caused a decreased crown-rump length, abnormal heart development, malformed facial development, and reduction in the optic system, hind and fore limbs • Increase in the number of apoptotic cells • Fewer blood cells in the yolk sac
Xu et al. [37]	2015	Experimental study	Study 1 included 10 subjects (5 female). Study 2 included 10 subjects (6 female).	• MRI to examine time dependent changes to cerebral metabolic rate of oxygen	• Caffeine consumption affected the brain of young adults by decreasing cerebral blood flow • Caffeine affect on vasaculture and neurons is region dependent • Posterior regions have a slower blood flow rate compared to anterior regions with caffeine consumption

Author	Year	Study Type	Population and Number	Assessment	Significant Results
Fazeli et al., [34]	2017	Experimental study	Mice offspring.	• *in vitro* and *in vivo* electrophysiological studies • Morphometric analysis of dendritic trees to support 3D reconstruction of neurons	• Caffeine consumption in early life affected the brain of mice through disrupted development of cortical networks • Reduction of interneurons in V1 cortex • Increased susceptibility to seizures with caffeine exposure
Li et al. [38]	2018	Experimental study	Rat offspring.	• Morris water maze test to assess learning and memory • Body and brain weight	• Rats prenatally exposed to caffeine demonstrated damaged spatial learning ability, increased escape latency, and increased path length in navigation testing • Increased caffeine receptors in the brain (A_1 and A_{2A})
Zhang et al. [43]	2022	Cohort study	9,978 American children aged 9-11.	• Developmental history questionnaire • Sleep disturbance scale for children • Child behaviour checklist	• Children prenatally exposed to caffeine experience increased rates of externalizing behaviour problems, depression, anxiety, and opposition defiant behaviours • Links to ADHD with excessive prenatal caffeine consumption
Hvolgaard Mikkelsen et al. [44]	2017	Cohort study	47,491 Danish children aged 11.	• Strengths and Difficulties questionnaire filled out by the child, parent, and teacher	• Children prenatally exposed to caffeine experience increased risk of ADHD • Increased risks of conduct-oppositional disorder, anxiety-depressive disorder, and any psychiatric disorder
Del-Ponte et al. [3]	2016	Cohort study	3,485 Brazilian children aged 11.	• Development and Well-Being Assessment completed by mothers	• Children prenatally exposed to caffeine have no links to ADHD
Patti et al. [51]	2021	Cohort study	Data harmonized from two pregnancy cohorts from the United States for a total of 389 participants.	• Questionnaire completed by mothers that assessed autism spectrum disorder using the Social Responsiveness Scale	• Prenatal caffeine exposure may be a marker of risk for childhood ASD or ASD-related behaviours

Author	Year	Study Type	Population and Number	Assessment	Significant Results
Galéra et al. [8]	2016	Cohort study	1083 mother-child pairs from France. Children aged 5.5 years.	• Wechsler Prescholl and Primary Scale of Intelligence Third Edition was administered to children to assess their IQ	• Prenatal caffeine exposure was negatively associated with children's IQ • High caffeine intake was associated with a two-fold risk for borderline or low intellectual functioning
Agarwal et al. [47]	2022	Cohort study	5,534 American children from the Adolescent Brain Cognitive Development Study.	• Developmental History Questionnaire to assess prenatal caffeine exposure • Block kids food screener questionnaire and child BMI calculations • Monetary incentive delay task MRI	• Prenatal caffeine exposure is positively correlated with high BMI • Elevated total sugar intake, increased insular thickness, altered reward sensitivity to food • Elevated risk of obesity

Abbreviations: BPB: blood placental barrier; PCR: polymerase chain reaction; BPA: bisphenol A; MRI: magnetic resonance imaging; ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorder; IQ: intelligence quotient; BMI: body mass index.

Discussion

This review determined prenatal caffeine exposure to have considerable adverse effects on the foetus, as explored through experimental animal models and various cohort studies. It explored caffeine's mechanisms of transport across the blood brain barrier and blood placental barrier to better understand the implications of caffeine consumption throughout pregnancy. Various developmental, cognitive, and behavioural foetal effects were explored and described. However, this review is limited to the gestational studies. Primary research is generally restricted to animal models and cohort studies for ethical reasons. Although animal models provide excellent analogues, human placental and foetal development is ultimately different. This may limit the applicability of animal models to the human foetus. Moreover, there are conflicting reports surrounding cognitive and behavioural outcomes in prenatal caffeine exposure with cohort studies. Many cohort studies debate between causation or correlation, as seen in the various reports on rates of ASD in children prenatally exposed to caffeine. This drives inquiry into how scientists can draw more concrete solutions while maintaining ethical practice. Ultimately, this review explored a great breadth of potential outcomes to prenatal caffeine exposure. This review had strengths in defining caffeine consumption from a multitude of sources and factored in the cultural differences in pregnant populations through a diverse study inclusion criteria. The methodology was also constructed to enable critical evaluation of source authenticity and applicability, which proved instrumental in the selection of appropriate and studies.

Conclusion

Overall, this review provides insights on health effects and outcomes of prenatal caffeine consumption. Exposing the foetus to caffeine has serious effects spanning from developmental impairments, anatomical alterations, impaired learning and memory, increased rates of mental health disorders, development of conditions such as ADHD and ASD, and lower IQ status. This research warrants further understanding of how better research models can be constructed and optimised, as well as how caffeine from different sources (e.g., matcha, cultural teas, coffee) can differentially impact both the mother and the foetus. Understanding implication of caffeine consumption during pregnancy may help parents make informed health decisions for their child during early development. Ultimately promoting healthy and safe pregnancies for both the mother and child.

List of Abbreviations Used
BBB: blood-brain barrier
BPB: blood-placental barrier
STCs: syncytiotrophoblast cells
BPA: bisphenol A
CAF: caffeine twice daily
GABA: gamma-amino butyric acid
ADHD: attention-deficit hyperactivity disorder
BMI: body mass index
IQ: intelligence quotient
ASD: autism spectrum disorder

Conflicts of Interest
The author(s) declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent
This literature review did not require ethics approval nor participant consent due to its nature of writing. All information consulted was previously published in public journals.

Authors' Contributions
PHP: Drafted the manuscript, revised the manuscript critically for intellectual content, and gave final approval of the version to be published.
CAB: Drafted the manuscript, revised the manuscript critically for intellectual content, and gave final approval of the version to be published.

Acknowledgements
The authors of this paper would like to thank Sonya Kouthouridis, PhD Candidate in Chemical Engineering, McMaster University for her mentorship throughout the writing and publication process. Her insight has been much appreciated.

Funding
This study was not funded.

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Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Sonya Kouthouridis, Patricia Acosta
Article Dates: Received Apr 02 23; Accepted Jun 27 23; Published Jul 31 23

Citation
Please cite this article as follows:
Patel PH, Burow CA. The physiological, cognitive, and developmental effects of prenatal caffeine consumption on foetal pregnancy outcomes. URNCST Journal. 2023 Jul 31: 7(7). https://urncst.com/index.php/urncst/article/view/480
DOI Link: https://doi.org/10.26685/urncst.480

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