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Investigating the Impact of Prenatal Exposure to Hypertensive Disorders of Pregnancy on Adolescent Neurodevelopment and Pubertal Maturation: A Study of Neuroimaging and Salivary Biological Measures.

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Investigating the Impact of Prenatal Exposure to Hypertensive Disorders of Pregnancy on Adolescent Neurodevelopment and Pubertal Maturation: A Study of Neuroimaging and Salivary Biological Measures.

DISSERTATION

submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in Public Health

by

Vida Bobela Fabiola Rebello

Dissertation Committee:
Assistant Professor Dr. Kristina A Uban, Chair
Dean & Professor Dr. Bernadette Boden-Albala
Associate Professor Dr. Andrew O Odegaard

2023

DEDICATION

To

My mother, Maria Sita, and to all the resilient pregnant individuals who have demonstrated unwavering strength in the face of inadequate healthcare systems.

My father, Rosario, and to all the supportive partners who have stood alongside them when these systems fell short

My sisters, Ursula, Tabita, and Wynzel, for teaching me kindness, even on days when being kind is the last thing you want to be.

My Auntie Filu, who always saw the best in me, even during my tumultuous teenage years.

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ABSTRACT OF DISSERTATION

Investigating the Impact of Prenatal Exposure to Hypertensive Disorders of Pregnancy on Adolescent Neurodevelopment and Pubertal Maturation: A Study of Neuroimaging and Salivary Biological Measures.

By

Vida Bobela Fabiola Rebello

Doctor of Philosophy in Public Health

University of California, Irvine, 2023

Dr. Kristina A. Uban, Chair

The increasing prevalence of hypertensive disorders of pregnancy (HDP), including specific types of HDP like pregnancy-related hypertension (PR-HTN), preeclampsia, and eclampsia (P/E), pose significant health risks for pregnant individuals and their offspring. Although, prenatal HDP exposure has been reported to augment children's sensitivity to adverse health outcomes, few studies have examined the long-term associations of prenatal exposure to HDP on neurodevelopment and hormone profiles beyond childhood. Adolescence is a critical period during which both the brain and the endocrine system undergo substantial development, representing a core risk period for when HDP-related differences may become discernable. Previous studies on the impact of HDP on adolescent health have primarily focused on discrete populations (e.g., clinical, low prevalence populations) exposed to a single type of HDP, predominantly preeclampsia. Moreover, these studies have been constrained by the lack of prospective follow-up and insufficient consideration of potential mediators. Elucidating the biophysiological mechanisms that demonstrate long-term postnatal alterations following prenatal exposure to HDP is needed. Therefore, the objective of this dissertation was to identify biological

measures pertinent to psychopathology and metabolic risks influenced by HDP and to examine the role of HDP types in these relationships, utilizing the Developmental Origins of Health and Disease (DOHaD) framework.

Data from the longitudinal Adolescent Brain Cognitive Development (ABCD) Study© was used, including approximately 11,888 adolescents aged 9-10 years at baseline. In Chapter 2, direct and indirect associations between HDP and cortical and subcortical brain structures were examined while accounting for the mediating role of intracranial volume in adolescents, using structural magnetic resonance imaging (sMRI) measures at two timepoints: baseline and year 2 follow-up. In chapter 3, diffusion weighted MRI (dMRI) measures were employed at two time points (baseline and Year 2 follow-up) to assess whether prenatal exposure to HDP contributes to white matter connectivity differences among the adolescents. In chapter 4, the influence of HDP on long-term endocrine development focusing in on androgen hormone profiles were investigated at three timepoints: baseline, year 1 follow-up and year 2 follow-up among the adolescents. HDP exposure was categorized as pregnancy-related hypertension (PR-HTN), preeclampsia/eclampsia (P/E), or unexposed (no HDP). Hierarchical mixed effects models were used to account for the multilevel data structure, and analyses were stratified by biological sex.

In Chapter 1, findings demonstrate direct and indirect impact of prenatal exposure to HDP on the development of cortical and subcortical brain structure, identifying distinct variations in the impact of prenatal HDP exposure on neurodevelopment, with the observed associations being sex-dependent. Specifically, the unique consequences of the two distinct HDP types on brain structures differed between males and females. In chapter 2, further evidence is presented, illustrating that HDP exposure, particularly PR-HTN, is a significant predictor of alterations in white matter

development. This association was observed exclusively among female adolescents, potentially because of the earlier onset of puberty-related initiation of myelination of white matter in females. Chapter 4 revealed distinct androgenic hormonal patterns in both males and female adolescents to the two types of HDP exposures.

Collectively, this dissertation addresses the gap in our understanding of the unique ways in which PR-HTN and P/E influence adolescent neuroendocrine development. It underscores the importance of early monitoring and intervention for neurodevelopment and pubertal maturation to address potential pathological deviations that could lead to neuropsychiatric and metabolic disorders later in life. Additionally, this dissertation emphasizes the need to consider community-level hypertension in preconceptual health, as increased resources could benefit both the pregnant individuals and the child. Furthermore, it highlights the importance of accounting for prenatal HDP exposure when investigating adolescent neurodevelopment and pubertal maturation. Future research is warranted to elucidate the long-term disease outcomes associated with HDP.

CHAPTER 1

INTRODUCTION

Background & Significance

Hypertensive disorders of pregnancy (HDP) have demonstrated a marked increase in prevalence across the United States. Between 2007 and 2019, age-adjusted incidence rates of HDP doubled in both urban and rural areas[1]. During this period, the incidence of HDP per 1000 live births rose from 48.6 to 83.9 in rural areas and from 37 to 77.2 in urban areas[1]. Between 2017-2019, HDP affected approximately one in seven delivery hospitalizations, with pregnancy-related hypertension being the primary driver of this increase[2]. Links between HDP and heightened risks for adverse health outcomes in pregnant individuals during later life have been established. For example, differences in hormonal patterns and structural brain volume, as well as presence of white matter lesions, have been observed that lead to an increased risk of cardiovascular and neurological disorders. White matter lesions act as markers of cerebral vessel diseases and have been implicated in the risk for cognitive impairment and dementia in pregnant individuals[3–8]. Despite established public health significance of experiencing HDP on pregnant individuals, little is known about the presence of similar markers in children exposed to HDP. While numerous studies have reported anthropometric findings in the HDP-exposed child such as low birthweight, fetal growth restriction, and preterm birth, limited literature exists on lasting impact of HDP-exposure on neurodevelopmental and endocrine outcomes [9–12]. The substantial influence of HDP on the pregnant individual's morbidity highlights the importance of understanding its implications on the exposed child who experienced HDP in parallel during critical fetal developmental processes. The long-term impact of HDP on development, particularly during adolescence- a critical and dynamic period for brain and hormonal maturation- warrants further investigation. Therefore, assessing neurodevelopmental and pubertal androgen biological markers in adolescence is crucial for determining the structural brain and hormonal patterns associated with fetal HDP-exposure. These

original research studies will advance understanding of how development adapts physiologically from prenatal HDP exposure. This advanced understanding will illuminate the magnitude of public health significance of rising incidence of fetal HDP-exposure and contribute to a foundation to further study how fetal HDP exposure may contribute to disease later in life.

Hypertensive Disorders of Pregnancy

The primary symptom of HDP is characterized by systolic blood pressure (SBP) exceeding 140 mmHg and diastolic blood pressure surpassing 90 mmHg. HDP encompasses a spectrum of condition (Table 1.1; Figure 1.1), including:

1. Chronic (pre-existing) hypertension: Pregnant individuals with a prior history of elevated blood pressure.
2. Gestational hypertension: De novo hypertension in pregnant individuals after the 20th gestational week.
3. Preeclampsia: A systemic gestational disorder with new-onset hypertension after the 20th gestational week, accompanied by at least one of the following: proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary oedema, and/or cerebral or visual disturbances.
4. Preeclampsia superimposed upon chronic hypertension.
5. HELLP syndrome: A sub-type of preeclampsia predominantly characterized by hemolysis, elevated liver enzymes, and low platelet count. While HELLP syndrome generally occurs with hypertension, it may clinically manifest with masked hypertension, complicating diagnosis.
6. Eclampsia: A preeclampsia complication involving grand mal seizures in a pregnant individuals with no prior history of epilepsy[13].

To investigate the breadth of types of possible fetal HDP exposures, the presented original analyses investigated three types of HDP: 1) pregnancy-related hypertension disorders (PR-HTN; 2) pre-eclampsia and/or eclampsia (P/E).

Pathophysiology And Potential Mechanisms Underlying Adverse Outcomes

The pathogenesis of HDP remain elusive; however, several mechanisms have been proposed (Figure 1.2). During normal pregnancy, hemodynamic adaptations occur, which include increased cardiac output, decreased vascular resistance, upregulation of the renin-angiotensin-aldosterone system (RAAS), and elevated nitric oxide production to facilitate vascular dilation and placentation via the establishment of uteroplacental arteries that form the interface between the maternal and fetal system[14–17]. In HDP, these adaptations may be compromised, leading to pathophysiological consequences.

Three key pathophysiological mechanisms have been hypothesized in the literature to explain the changes observed in HDP. The first and most prevalent mechanism involves alterations in the RAAS: a system that plays a critical role in blood pressure regulation, fluid balance and hormone homeostasis[18]. In early pregnancy, the RAAS is upregulated to increase vasodilation and lower blood pressure[19]. Important RAAS-mediated changes during pregnancy include: a) plasma volume expansion to meet the increased demands of the placenta, b) decreased vascular resistance in the uterine and placental circulation by downregulating angiotensin II receptors, c) increased production of vasodilators like nitric oxide and prostacyclin to accommodate increased blood flow to the placenta, and d) enhanced production of renin and aldosterone to facilitate promoting sodium and water retention, thereby, contributing to maternal plasma volume[20,21]. In HDP, the RAAS is downregulated, causing local RAAS systems to malfunction. Although the precise mechanism of this is not fully understood, studies have reported increased sensitivity to the vasoconstrictive

effects of angiotensin II, despite the downregulation of angiotensin II receptors, leading to elevated blood pressure and diminished blood flow to the placenta. An imbalance between vasoconstrictors such as angiotensin II, and vasodilators, like nitric oxide, has also been observed[22–24]. Some studies have documented low renin and aldosterone levels, resulting in increased sodium and water retention[25,26].

A second biophysiological hypothesis pertains to the overexpression of arginase, an enzyme that catalyzes the conversion of L-arginine, an essential amino acid, into L-ornithine and urea[27]. L-arginine also serves as a substrate for nitric oxide synthase (NOS), which is crucial for generating the vasodilator nitric oxide (NO)[28]. Arginase overexpression depletes the L-arginine pool for NOS, leading to reduced NO production, resulting in compromised vasodilatory effects on placental circulation, and increased reactive oxygen species production, ultimately causing endothelial damage and hypertension[29,30]. The cause of arginase overexpression of arginase is not well understood; however it has been linked to various cardiovascular and renal diseases, as well as immune dysfunctions, including hypertension, arteriosclerosis, sickle cell disease, renal failure and chronic inflammatory diseases[31].

The third prevalent mechanism, posited in the context of HDP pertains to abnormal placentation, which leads to shallow trophoblast invasion and impaired differentiation[32–34]. For successful placentation, the conversion of spiral arteries into uteroplacental arteries is essential[35]. Placentation is contingent upon two sequential waves of endovascular invasion that occur during the initial two trimesters of pregnancy[36]. In cases of HDP, it is postulated that the second wave of trophoblastic invasion into the myometrial segments of the spiral arteries is hindered, resulting in the absence of typical physiological changes[37]. In contrast to normal pregnancies, where uterine spiral arteries undergo remodeling via embryonic cytotrophoblast cell invasion, HDP is

characterized by a lack of such differentiation. This discrepancy initiates a cascade of events associated with constricted and higher-resistance blood vessels, which subsequently leads to reduced placental blood flow and hypoxia, in turn, contributes to endothelial damage in multiple organs in the maternal and fetal system, ultimately manifesting in the systemic features observed in HDP[33,35,38–40].

A general conclusion of the aforementioned mechanisms is that they all induce perturbations in the essential equilibrium of nutrients and oxygen necessary for optimal fetal growth and development. These disturbances trigger an excessive synthesis of soluble fms-like tyrosine kinase (sFlt-1) in HDP[41]. As a regulatory protein, sFlt-1 modulates fetal angiogenesis, and its overproduction exerts antagonistic effects on vascular endothelial growth factors (VEGF) and placental growth factor (PGF), leading to impaired fetal angiogenesis[42]. Angiogenesis, the process of forming new blood vessels, is a critical and tightly regulated aspect of fetal development. It is essential for the establishing and maintaining adequate blood flow to developing organs and tissues[43]. This intricate process is primarily regulated by an interplay of signaling molecules and cellular interactions, with growth factors PGF and VEGFs playing key roles [43]. VEGFs, in particular, are vital for angiogenesis and neurogenesis, as they control brain angiogenesis by mediating cell proliferation and survival, thereby laying the foundation for prenatal and postnatal brain vascularization and development[44]. The embryonic vascular system develops at embryonic day 24. By day 28, coinciding with the closure of the neural tube- the precursor to the central nervous system- the internal carotid artery branches into the cerebral and basilar arteries to supply the developing CNS[45]. The formation of brain- neuronal activity and white matter connectomes is a highly regulated process, significantly influenced by angiogenic factors and hypoxemic conditions[46]. Several studies have demonstrated impaired brain maturation resulting from

inadequate blood supply due to incomplete angiogenesis[47–50]. In addition to its pivotal role in angiogenesis, the placenta also serves as a critical gatekeeper for the production of androgens including dehydroepiandrosterone (DHEA) and testosterone (T), in the developing fetus[51,52]. The production of these hormones is regulated by cholesterol and androgenic precursors that are transferred from the maternal to the fetal system via the placenta. The placenta's capacity to regulate growth factors and androgen production exemplifies the intricate interplay between genetic and environmental factors inherent in pregnancy. As a crucial interface between maternal and fetal systems, disruptions in placental function, such as seen in cases of HDP can have significant implications for long -term health and development, including the 2 main biological outcomes investigated in the presented original analyses: brain and endocrine (puberty) (DHEA and T).

Previous studies on short- and long-term consequences of HDP exposure

The influence of prenatal HDP-exposure on neurodevelopment and endocrine function has been illustrated in numerous human and animal studies. A multitude of animal studies provide evidence on brain differences in offspring exposed to HDP[53]. Research on rats induced with preeclamptic-like syndrome demonstrated decreased brain weight, neurogenesis and lower number of neurons in exposed offspring[54,55]. Similarly, another study reported delayed cerebrovascularization of the brain along with differences in neuroanatomy and neurocognition in mice[56]. Furthermore, white matter hypointensities and lesions have been identified in sheep exposed to preeclampsia[57]: an animal model that better aligns, relative to rodent models, with gestational length and placental properties to those of the human condition.

Comparable differences following HDP-exposure during fetal development have been observed in human studies [58,59]. HDP has been shown to exert a widespread impact on various

organ systems, including the cardiovascular, central nervous, endocrine, renal, immune, and metabolic systems[60]. Heart disorders associated with HDP include neonates exhibiting lower early diastolic filling waves (Ea), late atrial filling waves (Aa) and Ea/Aa ratios in the interventricular septum, indicative of early subclinical signs of cardiac afterload[61]. Neonates exposed to HDP have a higher relative risk for congenital heart disease[62]. Additionally, HDP exposed neonates displayed altered thymic architecture and volume, as well as decreased CD4+ Treg cells, which are essential mechanisms for immune tolerance[63,64] . HDP has been linked to a higher risk of neonatal mortality, neonatal encephalopathy, epilepsy and neonatal stroke[62,65–71]. Preeclampsia exposed neonates exhibit a 3.14 increased odds ratio for developing cerebral palsy[72]. Moreover, evidence suggests that these differences persist into childhood and adolescence. Children and adolescents exposed to HDP have been reported to have higher systolic blood pressure, higher diastolic blood pressure and higher body mass index (BMI) and a 30% higher systolic right ventricular to right atrial pressure gradient, contributing to premature cardiovascular disease[73–75].

Regarding neurodevelopmental outcomes, children, and adolescents with prenatal HDP exposure show an increased risk of developing adverse neurological and neuropsychiatric outcomes. During childhood and adolescence, HDP has been associated with cerebral palsy, autism spectrum disorder, epilepsy and attention deficit hyperactive disorder[71,76–80]. Furthermore, HDP has been linked to an increased risk of mental health disorders and psychiatric disorders[81–84]. In terms of functional outcomes, children exposed to HDP have a higher odds ratio of mild cognitive limitations (2.4 higher than non-exposed children), lower motor competence, motor age, lower motor developmental quotient (MDQ) and mental developmental quotient (MeDQ)[85–88]. As for the immune system, children exposed to HDP have a relative ratio of 1.88 for asthma and an increased odds ratio of 2.2 for allergic rhinoconjunctivities [89,90].

In the context of the endocrine system, children and adolescents exposed to HDP demonstrate increased BMI and waist circumference, with a 2.12 higher odds ratio of developing obesity[91]. Notably, the severity of HDP appears to influence the hormonal profile of exposed adolescents during the early stages of pubertal development. Specifically, an altered androgen hormone pattern has been identified, characterized by elevated testosterone and diminished DHEAS levels[92]. Phenotypic differences have also been documented in HDP-exposed adolescents, with particular emphasis on the onset of pubertal developmental markers. In the general population, breast development typically emerges as the initial sign of pubertal development in females. However, in HDP-exposed female adolescents, pubic hair growth has been reported as the initial sign of puberty[93]. This deviation in the androgen patterns and pubertal maturation highlights potential long-term consequences of HDP-exposure on the endocrine system and overall developmental trajectories. In summary, exposure to HDP has been associated with neuroendocrine phenotypic differences in children and adolescents, atypical markers of adolescence that warrant further research to elucidate the underlying mechanisms and potential long-term implications on health and disease.

Typical Neurodevelopment and Hormonal development from fetus to adolescents

Neurodevelopment and hormonal development are two critical processes that shape the growth and maturation of an individual from the fetal stage to adolescence. These processes are interconnected and influence various aspects of an individual's physical, cognitive, and emotional development. A comprehensive understanding of typical neurodevelopment and pubertal maturation is essential for identifying and addressing deviations that may result in developmental disorders or health issues. This process begins during the early stages of fetal development and continues throughout childhood and adolescence. The formation of the neural tube, which

eventually gives rise to the brain and spinal cord, occurs during the first few weeks of embryonic development[94]. Following this, neurogenesis, or the generation of neurons, takes place, with the majority of neurons being formed by the time of birth[95]. The process of neuronal migration, whereby neurons move to their appropriate regions in the developing brain, occurs alongside neurogenesis[96]. Proper neuronal migration is crucial for the establishment of functional neural circuits. Subsequent phases of neurodevelopment include synaptogenesis, the formation of synaptic connections between neurons, and myelination, the development of myelin sheaths around axons to enable efficient nerve impulse conduction[97]. These processes continue throughout childhood and adolescence, with synaptic pruning, the elimination of excess or weak synaptic connections, playing a vital role in refining neural networks during adolescence. During adolescence, the brain undergoes considerable structural changes, such as synaptic pruning and myelination[98] . Synaptic pruning is the process by which weak or redundant synaptic connections are eliminated, allowing for the strengthening and optimization of remaining connections. This process is particularly prominent in the prefrontal cortex, a region involved in higher-order cognitive functions like decision-making, impulse control, and working memory[98]. The pruning of synaptic connections contributes to the fine-tuning of neural networks and is thought to underlie improvements in cognitive efficiency during adolescence. Myelination, the development of myelin sheaths around neuronal axons, is another critical aspect of neurodevelopment in adolescence[98]. Myelin is a fatty substance that insulates axons and enables efficient conduction of nerve impulses[99]. Increased myelination during adolescence contributes to enhanced communication between brain regions and is associated with the maturation of cognitive abilities[100]. Functional changes in brain activity are also observed during adolescence. The balance of activity between the limbic system, which is primarily involved in emotional processing and reward-seeking

behaviors, and the prefrontal cortex, responsible for executive functions and impulse control, undergoes significant shifts[101]. The heightened activity of the limbic system in relation to the prefrontal cortex during adolescence may contribute to the increased propensity for risk-taking and sensation-seeking behaviors observed in this developmental period. The development of neural connectivity is another key aspect of neurodevelopment in adolescence. The brain exhibits increased integration and segregation of functional networks during this period, reflecting the maturation of both local and long-range connections[102]. One example of such maturation is the strengthening of connections within the default mode network (DMN), which is involved in self-referential thinking and social cognition[103]. Enhanced connectivity within the DMN has been associated with improvements in social and emotional processing during adolescence[103].

Concurrent with neurodevelopment, another critical dynamic system shapes various aspects of an adolescent's growth and maturation. Hormonal development begins in utero, with the formation and differentiation of the endocrine glands, which are responsible for producing and secreting hormones[104]. These hormones act as chemical messengers, orchestrating various physiological processes, such as metabolism, growth, and reproduction. Key endocrine glands involved in hormonal development include the hypothalamus, pituitary gland, adrenal glands, gonads (testes in males, ovaries in females), and the thyroid gland[105]. DHEA and testosterone are two important hormones that play critical roles in the development and maturation of adolescents. Both of these hormones belong to the class of androgens, which are primarily responsible for the development of secondary sexual characteristics and the regulation of reproductive function[106]. DHEA is primarily produced by the adrenal glands, with smaller amounts being synthesized in the gonads and the brain[107]. The production of DHEA increases gradually during childhood and peaks around late puberty or early adulthood, a phase known as adrenarche[108]. DHEA serves as a

precursor to the synthesis of other sex hormones, including testosterone and estrogen and is metabolized to DHEA sulfate (DHEAS)[107]. DHEA and DHEAS have been implicated in a variety of physiological processes, including immune function, brain function, bone metabolism, and cardiovascular health[109]. Testosterone is primarily produced by the testes in males and, to a lesser extent, by the ovaries in females[105]. The production of testosterone is regulated by the hypothalamic-pituitary-gonadal (HPG) axis[105]. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH)[110]. LH, in turn, promotes the production of testosterone by acting on Leydig cells in the testes (in males) and theca cells in the ovaries (in females)[105]. During adolescence, the levels of testosterone increase significantly, particularly in males, driving the development of secondary sexual characteristics. In males, these characteristics include the growth of facial and body hair, increased muscle mass, deepening of the voice, and the growth of the external genitalia[111]. In females, testosterone contributes to the growth of pubic and axillary hair, as well as the maintenance of muscle and bone mass[111].

The balance of DHEA and testosterone during adolescence can influence various aspects of growth, maturation, and overall health. Atypical levels of these hormones may lead to a range of developmental issues, such as delayed or precocious puberty, and are associated with various health conditions in adulthood, including polycystic ovary syndrome (PCOS), insulin resistance, asthma, and cardiovascular disease[112–115] . DHEA and testosterone play essential roles in adolescent development by contributing to the maturation of secondary sexual characteristics and regulating various physiological processes.

Both neurodevelopment and the hormonal milieu during adolescence is a dynamic process characterized by significant structural, functional, and hormonal changes. These transformations

contribute to the maturation of cognitive, emotional, and social processes, as well as the emergence of risk-taking and sensation-seeking behaviors. Understanding deviations from typical adolescence growth patterns that may have been caused by an in-utero exposure to HDP, using sensitive biological measures of neurodevelopmental and hormonal adaptations can inform interventions aimed at promoting healthy development and mitigating the impact of potential risk factors that may result in developmental disorders or long-term health consequences.

Conceptual framework

The Developmental Origins of Health and Disease Framework and its Mechanistic Pathways

Previous biomarkers and measures of in-utero health in humans were mainly constrained to anthropometric measures such as low birthweight. With the development of new technologies, comes the ability to uncover biomarkers of *in utero* conditions. This creates the need and opportunity to elucidate more sensitive biological measures to better fit perinatal epidemiological research into biological theories such as the Developmental Origins of Health and Disease (DOHaD). By doing so, I seek to understand the long-term adaptations resulting from *in utero* insults caused by HDP, as conceptualized within the DOHaD framework[116,117]. According to the DOHaD framework, exposure to certain environmental conditions during critical developmental stages, particularly *in utero* life, may increase the risk of disease later in life. Within this context, a developing fetus exposed to *in utero* perturbations, such as hypertensive disorders or prenatal substance or chemical exposure, responds by activating specific adaptive mechanisms to cope with the disrupted environment. These adaptions may be short- term, supporting fetal viability during this critical stage, or long-term, potentially compromising postnatal development[118]. Short-term adaptations, such as the fetal brain-sparing effect, thrifty phenotype effect, involve down-regulation or up-regulations of metabolic functions to prioritize the most vital organ systems

during that developmental window[119,120]. Long-term adaptions, such as the predictive adaptive response (PAR) may manifest as subtle changes in the formation, structure or function of organs that continue to develop postnatally, such as the brain, resulting from alterations in cell differentiation and proliferation[121]. Furthermore, a "mismatch" or "poor" fit may arise if an individual's postnatal environment markedly differs from the prenatal environment, often leading to increased vulnerability to disease. Evolutionary biology offers insights into the DOHaD framework the concept of the Developmental Reaction Norm, which describes how one genotype can be expressed in as various phenotypes depending on environmental exposure[122]. This gene-environment interaction maybe advantageous in one environment and less so in another. From an evolutionary perspective, while immediate transient adaptations may be beneficial in the intrauterine environment, prolonged exposure to a disrupted *in utero* environment may necessitate persistent transient adaptations, leading to deviations from typical developmental trajectory. This concept, known as homeorhesis was introduced by C.H.Waddington, and refers to how dynamic systems, such as development, return to their trajectory by adopting adaptations[123]. If the chosen trajectory provides an immediate adaptive advantage but incurs a long-term cost, a trade- off is created. The concept of biological trade-off is widespread in development, allowing organisms to cope with threats to survival through immediate adaptation that may lead to long-term disadvantages[124,125]. However, this strategy is only successful if the organism survives long enough to reproduce. As viability of longevity in humans is increasing, these adaptations may pose a threat to later life health and disease[126]. The "thrifty phenotype" hypothesis, a concept developed to explain the DOHaD, is based on this trade-off process[127]. It describes a response to maternal undernutrition wherein the fetus grows more slowly, conserving somatic energy for vital organ development, resulting in lower fetal growth measures and insulin resistance, and the increased

risk of developing diseases in later life[127]. The DOHaD framework has been proposed to work mechanistically through a response called the predictive adaptive response (PAR), developed by Gluckman and Hanson[128]. This hypothesis posits that developmental plasticity receives cues from the external *in-utero* environment to adapt to the postnatal environment, with the fetus essentially attempting to "forecast" its future external environment[128]. The PAR hypothesis was developed to explain how early life events could potentially result in long-term disease risks.

Another explanation for the mechanisms underlying the DOHaD framework is the brain-sparing effect. This biophysiological responses posits that when a fetus experiences distress under conditions such as HDP, which cause placental insufficiency, hypoxia or insufficient nutrient supply, resources are allocated to the most critical organ for development- the brain[129,130]. The brain-sparing effect has been demonstrated using *in utero* Doppler ultrasound, with the developing fetus exhibiting cerebral vessel vasodilation to cope with inadequate nutrient supply[131]. However, the relative protective effect on the brain development compared to the development of other organs during fetal growth may not be uniform or guarantee typical long-term development[132]. In an evolutionary context, specific brain regions developing during a particular gestational window, such as those responsible for respiration, vision, and gross motor execution, maybe prioritized[133]. Nevertheless, this protection may come at the expense of brain regions that typically develop during adolescence, such as those involved in emotional regulation, cognitive function, and higher order executive control[134–136]. Epidemiological observations on DOHaD is limited by the reliance on proxy measures of disrupted *in utero* environment such as anthropometric body measures, including low birthweight (LBW), to determine the course of an individual's risk for disease later in life[137–140]. However, it seems to be a trojan horse for later health and disease as recent research has shown that phenotypes can be induced in the child without accompanying LBW[141,142].

Atypical reduction in fetal growth per se do not necessarily lie on the causal pathway to later disease[141]. The statistical relationship may exist because LBW serves as a proxy for a disrupted *in utero* environment. More sensitive markers of fetal adaptive responses are needed. These biophysiological concepts within the DOHaD framework provides a theoretical basis for understanding how HDP could potentially disrupt fetal development through the hypothesized dysregulation of angiogenesis, androgen production and RAAS function (Figure 1.3). Employing neuroimaging and salivary bioscience, I investigate potentially sensitive biological measures that may perhaps be indicative of long-term impact of HDP- exposure in adolescents.

The Present Study

A fundamental question in health research concerns the impact of adverse events experienced during critical developmental periods on an individual's predisposition to diseases. When we apply a structural lens, it widens our interpretative view creating a more nuanced picture of integration that considers several dimensions of influencers of adolescent development. The overall research question of this dissertation seeks to ask does prenatal exposure to HDP lead to long-term physiological adaptations in neurodevelopment and pubertal maturation? I first argue that beyond anthropometric markers of low birthweight and gestational age, predispositions to adverse long-term brain health seen in adolescents exposed to HDP may stem from HDP's impact on cerebral angiogenesis, thereby impacting the architectural framework of the brain resulting in structural and microstructural changes that may manifest during a sensitive period of brain development- adolescence. Moreover, HDP-exposed children are more likely to have atypical hormonal variations, I also examine the hormonal variations in the exposed adolescent to understand if the maternal hormonal fluctuations during HDP further impact the regulation of hormones in the exposed adolescent.

The aim of this dissertation was to understand the long-term adaptations resulting from *in utero* exposure to HDP, as conceptualized within the DOHaD framework and contribute to our understanding of the associations of these prenatal disorders on the exposed child's brain and pubertal maturation, leading to long-term impacts in adolescence, a period characterized by rapid structural brain and endocrine changes.

To that end, my dissertation is arranged by the following chapters reflecting the specific aims. Chapter 2 examines structural changes in brain development among adolescents exposed to HDP. Chapter 3 examines microstructural white matter development among adolescents exposed to HDP and chapter 4 is an investigation of the androgen profile among HDP exposed adolescents. All three empirical studies draw from the same population of typically developing sample of adolescents.

In chapter 2, I examine how HPD i.e., pregnancy-related hypertension and preeclampsia/eclampsia exposure versus non-HDP exposure are associated with age-related changes in subcortical and cortical brain volume among adolescents. I use the brain-sparing mechanism of the DOHaD as the conceptual framework for this paper. Cerebral angiogenesis may be impaired during embryonic stages and may lead to differences in structural development of the brain. I hypothesized that HDP would have differential age -related impact on structural cortical and subcortical volume and that "brain-sparing" maybe preferential depending on the window of exposure and subsequent adaptations i.e., volumetric differences would reflect changes in brain regions that may not be necessary to survive in-utero but are important in later life -adolescence- during social and cognitive development. I further hypothesized that these differences would be meditated by intracranial volume (ICV), in other words, that the effect of volumetric structural changes would vary by ICV, a factor associated with preterm births. I use the baseline and year 2

follow-up data release 4.0 of the Adolescent Brain Cognitive Development (ABCD) study as the primary analytic dataset for this paper. The ABCD is a nationally representative longitudinal cohort of adolescents aged 9-10 years at baseline; this design enables me to use create cohort of community-level exposure to pregnancy-related hypertension and preeclampsia/eclampsia and follow them through their follow-up visit. My analysis included 12 cortical and 8 subcortical regional brain volume outcomes taken at two timepoints and derived using structural magnetic resonance imaging (sMRI).

Chapter 3 examines microstructural white matter tract connectivity among adolescents exposed to pregnancy-related hypertension and preeclampsia/eclampsia from the same dataset. Here also, I consider the brain-sparing mechanism of the DOHaD framework as conceptual basis. I hypothesized that pregnancy-related hypertension and preeclampsia/eclampsia exposed versus non-HDP exposed would have age-related differences reflected in measures of white matter tract morphology and connectivity. When we consider microstructural morphology alongside connectivity, age-related microstructural changes are better understood within the brain-sparing framework. I use baseline and year 2 measures of diffusion weighted imaging (DWI) metrics including fiber volume and fractional anisotropy that is derived from DWI fitted to a tensor. My analysis included four commissural fibers, two projection fibers and four association fibers to encompass the varied functionality of the brain.

Chapter 4 examines the androgen profile trajectory of HDP exposed adolescents from the same dataset. I use the predictive adaptative response (PAR) mechanism of the DOHaD framework as the conceptual basis of this study. Increased hormonal androgen profile in maternal systems have been associated with precocious puberty and dysregulation of the androgen profile in the exposed child. I hypothesized that because of the upregulation of androgens in the maternal system

in HDP, the child exposed to HDP will display a similar pattern of the upregulation of the androgen profile. I use baseline, year 1 and year 2 salivary measures of free testosterone and DHEA from adolescents in the ABCD cohort to estimate the androgen profile in HDP versus non-HDP participants.

Instead of focusing on a single disease outcome in my empirical papers, I used measures of general biophysiological health. These measures align with the definition of the incidence of outcome or disease developed jointly by the United Nations, International Labor Organization, and the International of Chemical Safety (WHO) in which these biological markers are considered "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease"[143]. Because I suggest that biophysiological measures, whether structural or functional, impact risk factors of certain psychiatric and endocrine disease outcomes in later life, my outcomes measures are accordingly broad enough to include a range of possible physiological deviations that may reflect the overall state of adolescent health. I propose 6 measures to assess general biophysiological health: cortical and subcortical volume, white matter fiber volume, white matter fractional anisotropy, DHEA, testosterone, and testosterone: DHEA ratio.

Cortical and Subcortical Volume

Structural cortical and subcortical brain volume is a parameter in the study of neuroanatomy and neuropathology and refers to the quantification of the size or spatial dimensions of brain regions. These measurements encompass gray matter, white matter, ventricles, and cerebrospinal fluid spaces. Assessment of structural brain volume contributes to the understanding of typical brain development and the manifestation of neurodevelopmental, psychiatric, and neurodegenerative disorders. Using Freesurfer, a software that facilitates the processing of MRI

data, and atlases developed from the Pediatric Imaging, Neurocognition, and Genetic (PING) study, ABCD segments and delineates specific brain regions to estimate their volumes. The steps involved include image preprocessing, intensity normalization, skull stripping, segmentation, and surface reconstruction.

Fiber Volume

Fiber volume refers to the size or volume of the white matter tracts in the brain. White matter primarily consists of myelinated axons, extensions of nerve cells responsible for transmitting electrical signals between brain regions. The myelin sheath, a fatty substance that surrounds axons, facilitates efficient signal transmission. White matter fibers play an important role in connecting different brain regions and facilitating communication within the neural network. Fiber volume is estimated using diffusion weighted MRI and assesses the diffusion of water molecules in the brain's white matter. Since water diffusion is more restricted along the direction of axon fibers due to myelinated sheaths, it can reveal organization and orientation of white matter tracts. dMRI in ABCD is derived using multiband echo-planar imaging, 96 diffusion directions, seven b=0 frames, and four b-values and uses eddy current correction for diffusion patterns prediction[144]

White Matter Fractional Anisotropy

Fractional Anisotropy (FA) is a scalar value derived from diffusion tensor imaging (DTI), a specialized form of diffusion MRI. FA quantifies the degree of anisotropy of water molecule diffusion within white matter. In white matter, water diffusion is constrained by the underlying axonal structure, such as the myeline sheath and the arrangement of axons. FA is dimensionless value that ranges from 0-1, with higher values indicating more directionally constrained or organized diffusion, which is typically associated with healthy and intact white matter fibers.

Lower FA values suggest less organized or more isotropic diffusion, which can be indicative of damaged or disrupted white matter structures.

A reliable quantification of these brain measures is important in public health research for several reasons. By examining structural brain volume in relation to various genetic, environmental and lifestyle factors, we can identify potential risk factors and biomarkers for neurodevelopment and psychiatric disorders. These findings can contribute to early detection, prevention, and intervention strategies, ultimately improving public health outcomes. Furthermore, studying the relationship between structural brain volume and individual or population-level differences in exposomic risk factors can contribute to the development individualized clinical approaches, thereby reducing the disparities gap and promoting equitable, efficient healthcare.

Salivary Dehydroepiandrosterone (DHEA)

Salivary dehydroepiandrosterone (DHEA) is a non-invasive measure of the unbound (or free) DHEA present in saliva. DHEA is a steroid hormone produced primarily by the adrenal glands, but it can also be synthesized in the brain and gonads. It serves as a precursor to produce other hormones, such as androgens (testosterone) and estrogens. Salivary DHEA reflects biologically active, unbound fraction of DHEA in the body, providing a useful indicator of hormonal activity. DHEA has been implicated in various physiological processes, such as immune function, metabolism, and cognitive function. DHEA levels have been linked to a range of conditions including cardiovascular and immune disorders.

Salivary Testosterone

Salivary testosterone is a measure of the unbound testosterone present in the saliva. Testosterone is a steroid hormone primarily produced in the testes in males and, to a lesser extent,

in the ovaries in females. It is also produced in small amounts by the adrenal glands in both sexes. Testosterone plays a crucial role in the development of reproductive tissues, the maintenance of secondary sexual characteristics, and the regulation of sexual function, as well as influencing muscle mass, bone density, and the distribution of body fat. Salivary testosterone measurements are used in various health-related contexts, including the study of hormonal changes across the lifespan, the evaluation of androgen-related conditions, and the assessment of the relationship between testosterone levels and various behavioral, cognitive, and physiological outcomes.

Salivary Testosterone: DHEA ratio

The testosterone-DHEA ratio is a measure that represents the balance between the levels of the levels of these two steroid hormones in circulating form. Testosterone is an androgen hormone that plays a significant role in pubertal development, muscle mass, bone density and other physiological processes. DHEA, on the other hand, is a precursor hormone produced mainly by the adrenal glands and can be converted into other hormones, including testosterone and estrogen. The ratio is used to assess hormonal balance that occur during pubertal changes. Imbalances in these hormones may be associated with various health conditions or symptoms.

Besides being non-invasive salivary measures of hormone, the unbound (free) fraction of a hormone is considered biologically active because it can interact with target cells and tissues more easily, representing the hormone's functional availability, which is an indicator of hormonal activity and is often used in research and clinical assessments.

Together, my three dissertation papers narrate a story about the biophysiological influences of prenatal exposure to HDP on adolescent health. In doing so I hope to demonstrate how health can be influenced by insidious community-level exposures such as HDP at critical windows *in utero* that are not typically associated with having a long-term impact on biophysiological health

in adolescents. This will expand our understanding of the cumulative effects of risk factors and their complex interplay that influences sensitive periods of later life health and disease trajectories.

FIGURES

Figure 1.1. The spectrum of hypertensive disorders of pregnancy and their prevalence[145]. The figure presents the prevalence of the type of HDP, including pregnancy-related hypertension, preeclampsia, HELLP syndrome, and eclampsia, all of which initiate after the 20th week of gestation. Chronic hypertension increases the risk of superimposed preeclampsia occurring after the 20th week of gestation. The disorders are presented in descending order of clinical severity.

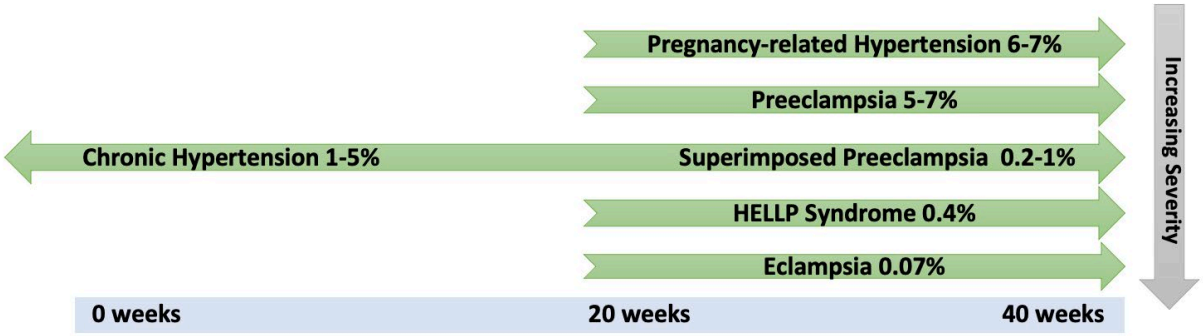


Figure 1.2. Hypothesized pathophysiological mechanisms of hypertensive disorders of pregnancy. The figure demonstrates the three hypothesized mechanisms for the pathogenesis of HDP outlined in this figure are (1) Downregulation of maternal renin-angiotensin-aldosterone system (RAAS) (2) Overexpression of arginase (3) Abnormal placentation. These mechanisms lead to vicious cycle of imbalanced levels of angiogenic factors, vasoconstrictors and vasodilators, an excess of sFlt-1 and androgenic precursors, resulting disrupted placental blood flow and endothelial damage.

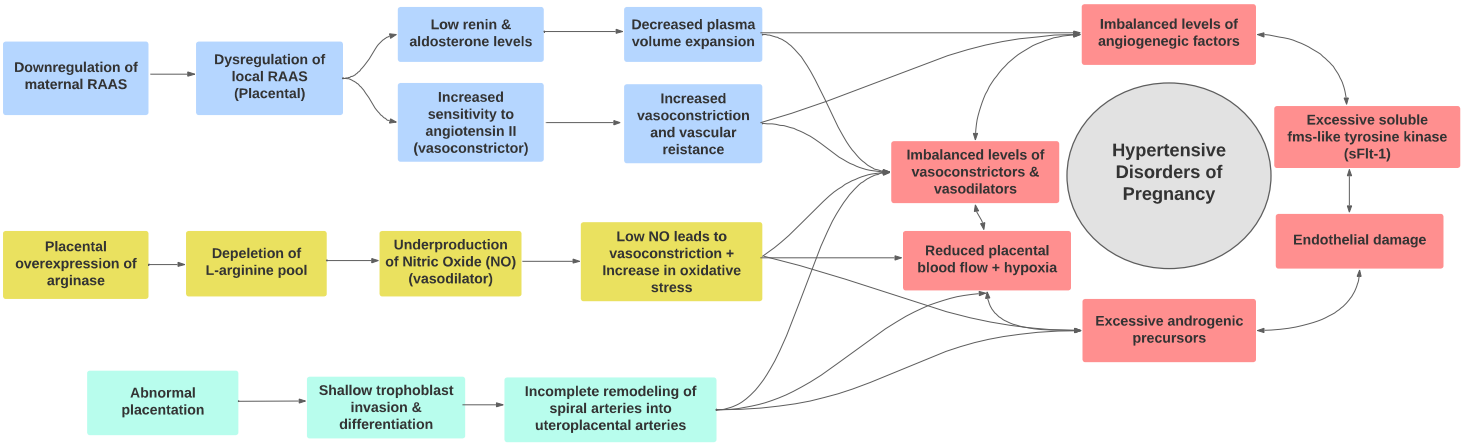
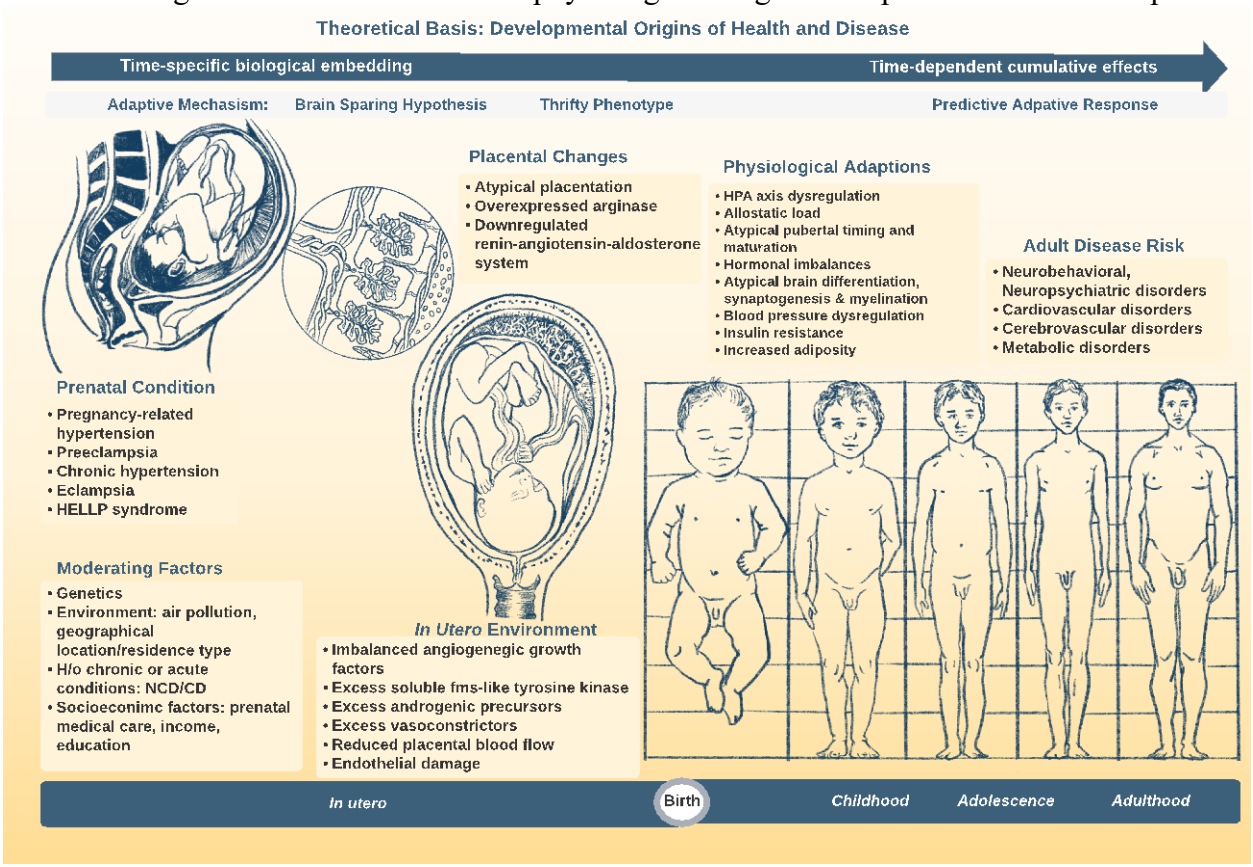


Figure 1.3. Conceptual model of the Developmental Origins of Health and Disease (DOHaD) mechanisms in fetal short-term and adolescent/adult long-term adaptation of hypertension disorders of pregnancy. This figure demonstrates an integrative model of the brain-sparing hypothesis, the thrifty phenotype hypothesis and predictive adaptive responses with the contributing factors involved in the biophysiological long-term implications of HDP exposure.



TABLES

Table 1.1. Classification of Hypertensive Disorders of Pregnancy[146]. The table presents the description of each HDP disorder as per the International Classification of Diseases code 010-016.

Disorders	**Clinical Definition**
Chronic Hypertension	Elevated BP (>140/90 mm Hg) before the 20th week of gestation or persisting beyond 12-weeks postpartum.
Pregnancy-related Hypertension	De novo BP elevation (>140/90 mm Hg) after 20th week of gestation without other organ system dysfunction.
Preeclampsia	De novo BP elevation after the 20th week of gestation coupled with at least one of the following: - Proteinuria (>300mg/day) - Thrombocytopenia (platelets<105/microL) - Renal Insufficiency (serum creatinine >1.1. mg/dL) - Impaired liver function (blood liver transaminases two times normal value)
Preeclampsia superimposed on chronic hypertension	Increased BP and new-onset proteinuria or other end-organ dysfunction in addition to preexisting hypertension.
HELLP syndrome	Subtype of preeclampsia with or without hypertension characterized by hemolysis, elevated liver enzymes, and low platelet predominantly.
Eclampsia	Occurrence of a grand mal seizure in a woman with preeclampsia in the absence of other neurologic conditions that could account for the seizures.

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CHAPTER 2

Associations between Prenatal Hypertensive Disorders and Structural Brain Volume in Adolescence: Disentangling Direct and Indirect Effects of Intracranial Volume

ABSTRACT

BACKGROUND: Structural neuroimaging studies have demonstrated differences in regional gray matter volume among children exposed to prenatal hypertensive disorders of pregnancy (HDP). With the escalating prevalence of HDP including pregnancy-related hypertension (PR-HTN) and preeclampsia/eclampsia (P/E), and its consequences on neurodevelopment, there is limited research investigating the persistence of these cerebral differences beyond childhood. Furthermore, prior studies predominantly employed cross-sectional designs and inadequately accounted for potential mediators. In this study, we examined both direct and indirect associations between prenatal HDP exposure and adolescent neurodevelopment by assessing the mediating role of intracranial volume (ICV).

METHODS: This study utilized longitudinal data from the Adolescent Brain Cognitive Development (ABCD) cohort, collected at two timepoints: adolescents aged 9-10 years at baseline and 11-12 years at the year-2 follow-up scan. HDP was retrospectively obtained from caregiver reports. sMRI volume data for 12 cortical and 8 subcortical regions of interest were analyzed using hierarchical mixed-effects models. Corrections for multiple comparisons were performed. Subsequently, a mediation analysis was conducted using the Baron and Kenny mediation approach.

RESULTS: In females, direct associations were observed between P/E exposure and bilateral putamen. Indirect associations were found between PR-HTN and bilateral insular, bilateral putamen, and bilateral accumbens area. In males, direct associations were observed between PR-HTN and bilateral superior frontal gyri, bilateral caudate, right isthmus cingulate, right lateral orbitofrontal, and right insula. Indirect associations were identified between P/E exposure and

bilateral pars orbitalis, bilateral caudate, left insula, right caudal anterior cingulate, and right rostral middle frontal.

CONCLUSIONS: Adolescents exposed to HDP displayed significantly lower volumes in cortical and subcortical regions. While some associations were dependent on ICV, P/E exposure in females were directly associated with bilateral putamen volumes, a structure susceptible to neonatal stroke. In males, cerebral lateralization biased towards the right structures was observed in the direct association of PR-HTN exposure with cortical regions. These findings emphasize the significant role of the *in utero* environment in shaping fetal cerebrovascularization and adolescent neurodevelopment.

Introduction

Adolescence is a sensitive period of brain development, marked by dynamic changes in brain structure and function. During this period, the brain undergoes extensive remodeling including synaptic pruning, myelination and the associated cortical thinning[1] , to adapt to the demands of adulthood, including increased cognitive complexity, heightened emotional regulation and social maturation. While several factors contribute to adolescent neurodevelopment, it is widely acknowledged that the structural foundation of the brain, laid out during the prenatal period, sets the stage for the developmental trajectory of the adolescent brain[2–6]. Fetal neurodevelopment is shaped by complex interactions between genetic and environmental factors, and disturbances in this environment can lead to long-lasting changes in brain structure and function that can persist into adolescence. Hypertensive disorders of pregnancy (HDP) including pregnancy-related hypertension, preeclampsia and eclampsia have been found to impact fetal neurodevelopment in numerous ways, including long-term differences in postnatal brain structure. Studies have reported enlarged regional brain volumes in the caudate nucleus, cerebellum, temporal lobe, brain stem and the amygdala in offspring exposed to preeclampsia[7,8]. The underlying pathophysiological mechanisms of fetal HDP-exposure on brain structure remain unclear. It is hypothesized that the imbalance between vasogenic growth factors may trigger incomplete cerebrovascularization of the brain. In particular, placental growth factor (PGF), and vascular endothelium growth factors (VEGFs), which are essential for angiogenesis and neurogenesis, are commonly implicated in the pathogenesis of HDP-exposure on fetal brain development[9,10]. Furthermore, children with prenatal preeclampsia exposure display a reduced radius of the cerebral vessels located in the occipital and parietal lobes, indicating altered cerebrovascular function that may precede structural brain differences[7]. The adaptive mechanisms that occur in the intrauterine environment to counteract

decreased nutrient and oxygen supply may have long-term consequences for neurodevelopment. Therefore, the identification of more sensitive biomarkers is necessary to better integrate perinatal epidemiological research with biological theories such as the Developmental Origins of Health and Disease (DOHaD) framework, which posits that intrauterine conditions may increase susceptibility for chronic disease later in life[11].

It is important to note that prenatal HDP exposure can have significant effects on the physical development of the offspring, including changes in intracranial volume (ICV) resulting, in part, from preterm birth[12,13]. These changes can, in turn, exert a considerable influence on regional reductions in brain volume[14]. The prevalence of HDP is a significant public health concern, complicating approximately 10-15% of pregnancies in the United States, with incidence rates increasing[15]. This highlights the need for further research to better understand the impact of prenatal HDP exposure on neurodevelopment[16]. However, to date, limited research has investigated the association between HDP and brain volume in adolescents, and none of these studies have explored the possibility of this association being mediated by ICV, which often lies on the causal pathway. Investigating potential mediating factors such as ICV may help elucidate the underlying mechanisms through which HDP affects brain development in adolescents.

Investigating whether prenatal HDP exposure is associated with brain volume in a community-based cohort of adolescents will provide novel epidemiological health information and help identify potential risk factors for adverse neurodevelopmental outcomes. Moreover, it is possible that the emergence of adolescent age-related changes is a consequence of overall and sustained ICV reductions associated with HDP, and thus potentially restraining regional brain volumes in a generalized and global manner. Determining whether prenatal HDP exposure impacts

regional brain volumes via the mediating role of ICV will provide valuable insight into the underlying mechanisms of HDP's impact on neurodevelopment.

In this study, associations between prenatal HDP exposure, including pregnancy-related hypertension (PR-HTN) and preeclampsia and/or eclampsia (P/E), and subsequent adolescent brain development were examined. Longitudinal brain structure data were leveraged from the Adolescent Brain Cognitive Development (ABCD) Study©: an epidemiologically informed pediatric cohort aged 9-10 years at baseline and 11-12 years at year 2 follow-up. The impact of prenatal HDP exposure on structural cortical and subcortical brain volumes were assessed. This study aimed to determine if volumetric differences observed in structural cortical and subcortical regions following prenatal HDP exposure were entirely dependent (i.e., mediated) upon ICV. To address this question, hierarchical mediation analyses were employed, allowing for exploration of the direct and indirect effects of prenatal HDP exposure on brain structure as well as the potential mediating role of ICV.

Methods

Participants

Longitudinal data from the ABCD study release 4.0 were utilized, comprising baseline and year 2 follow-up timepoints. The ABCD study is a nationally representative longitudinal cohort of approximately 11,878 participants aged 9-10 years at baseline from 21 sites across the United States[17]. Exclusion criteria for the ABCD study included non-English fluency, MRI contraindication (e.g., irremovable ferromagnetic implants or dental appliances, claustrophobia, pregnancy), major neurological disorder, gestational age below 28 weeks or birthweight under 1,200 grams, history of traumatic brain injury, or current diagnoses of schizophrenia, autism

spectrum disorder (moderate, severe), intellectual disability, or alcohol/substance use disorder[18–20].

Current analyses focused on neuroimaging data that met the quality imaging criteria for cortical, subcortical, and intracranial volume, collected at baseline and year 2 follow up, in addition to obstetric data obtained at baseline visit. Participants that were excluded in current analyses include those from site 22 (n= 32), twins and triplets (n= 4,124), and participants with missing or substandard sMRI scans (n= 2,369). Further, one sibling was selected at random per family. The final sample comprised 6,571 females and 7,489 males. The baseline sample size included 3,999 females and 4,435 males, with a year 2 follow-up sample of 2,572 females and 3,054 males (Figure 2.1). Data collection for the baseline assessment transpired between 2016 and 2018. This investigation adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline[21].

Prenatal Exposure to Hypertensive Disorders of Pregnancy

Prenatal hypertensive disorders of pregnancy (HDP) were classified into three categories: Pregnancy-related hypertension (PR-HTN), Preeclampsia and/or Eclampsia (P/E) and no HDP. Participants' parent/caregiver who reported "Yes" to both PR-HTN, and P/E were solely included in the P/E group. Categorization was based on retrospective caregiver report collected during the baseline visit. Definitions, in accordance with the NDA ABCD data dictionary are provided in Table 2.1.

Outcome measures: sMRI cortical and subcortical regional volume

Neuroimaging data were obtained using three MRI scanners - 3T Siemens Prisma, General Electric 750 or Philips- across the 21 ABCD study sites. A harmonized standardized protocol for acquisition of images was employed across sites and utilized multi-channel adult-size coils capable

of multiband echo planar imaging (EPI)[22]. Prior to scanning, participants underwent MR screening for contraindications including braces, pacemakers, metallic objects such as piercings, medical screws, pins. MRI processing and quality control were centrally performed by the ABCD study's Data Analytics, Informatic and Resource Center (DAIC). Briefly, DAIC employed Multi-Modal Processing Stream (MMPS), an in-house software package developed by the Center for Multimodal Imaging and Genetics (CMIG) at the University of California, San Diego and utilized neuroimaging packages like FreeSurfer[23]. The processing and analysis pipeline comprised of five general stages: (1) Unpacking and conversion of Digital Imaging and Communications in Medicine (DICOM) into compressed volume files (2) Distortion and motion correction alongside cross-modality registrations (3) Modality-specific, single-subject level analyses carried out and imaging-derived measures extracted (4) Region of interest (ROI) analysis compiled across subjects[23]. sMRI preprocessing involved correction and standardizing T1-weighted and T2-weighted structural images by addressing gradient nonlinearity distortions, aligning images, and applying intensity inhomogeneity correction using B1-bias fields[23]. Images were normalized, registered to an averaged reference brain. Subcortical volume measures were calculated using segmentation via FreeSurfer and labeled through an automated, atlas-based segmentation (ASEG) procedure[23]. Cortical volume measures were estimated by multiplying cortical thickness and cortical surface area, calculated by averaging each cortical parcel via standard FreeSurfer Desikan-Killiany atlas[23].

Quality checks recommended by DAIC were checked before including scan data in the analyses. Inclusion criteria for the sMRI scans included T1w and T3w recommendations for inclusion provided by ABCD (Table 2.2). Baseline and Year 2 follow-up measures of volume were procured for key regions of interest (ROI) for the left and right hemispheres separately. Cortical

ROIs included caudal anterior cingulate (CACg), caudal middle frontal (CMF), isthmus cingulate (IstCg), lateral orbitofrontal (LOrF), medial orbitofrontal (MOrF), pars orbitalis (Or), rostral anterior cingulate (RoACg), rostral middle frontal gyrus (RoMF), superior frontal gyrus (SFG), frontal pole (FPol), temporal pole (TPol), and insula (INS). Subcortical ROIs encompassed the thalamus proper (THALp), caudate nucleus (CAU), putamen (PUT), pallidum (PAL), hippocampus (HIP), amygdala (AMYG), nucleus accumbens area (NAc), and the ventral diencephalon (vDC).

Mediator measure: Intracranial volume

Intracranial volume (ICV) represents the estimated volume of the cranial cavity, delineated by the supratentorial dura matter or cerebral contour when the dura is not visible[24]. ICV data were acquired using the same imaging processing as the outcome measures as described above, executed through FreeSurfer[23]. ICV calculation involves initial segmentation of the brain from surrounding tissues, a process termed brain masking of MRI data, followed by estimation of target image data boundaries[25].

Covariates

Covariates for the current study were selected based on previous literature and considering the multilevel structure of the data[26–36]. The selection of the variables was guided by a directed acyclic graph (DAG) (Figure 2.2). For instance, prenatal exposure to tobacco (PTE) and prenatal exposure to alcohol (PAE) were selected as covariates because they are known teratogens posing significant risk factors for brain development and are associated with the occurrence of HDP (Rebello et al., in preparation). Addition covariates include participant's age (months), household income categorized as < \$50k, ≥ \$50k - <\$100k and ≥ \$100k USD, maternal age (years), PTE (yes/no), and PAE (yes/no) as fixed effects. Additionally, to account for site-specific and

individual variability, subject ID and study site ID were included as random effects in the models. Descriptions of the variables per the ABCD NDA data dictionary are presented in Table 2.3.

Statistical Analyses

All analyses were conducted using R version 4.1.3 (R Foundation for Statistical Computing)[37]. The analytic approach consisted of 4 steps, employing Baron and Kenny's method for mediation[38] (Figure 2.3): Step 1) Investigate the association between HDP and cortical/subcortical volume, while correcting for multiple comparisons, Step 2) Ascertain if HDP significantly influences the mediator: ICV, Step 3) Determine whether ICV mediates the association between HDP and cortical/subcortical volume, Step 4) Assess if the mediation effects, whether complete or partial mediation, are statistically significant. For each step, longitudinal hierarchical mixed-effects models were employed to test the associations in hemispheric-stratified models (equation 2.1). Fixed and random parameters were obtained through maximum likelihood estimation, fitting the models using the lmer package, which combines Newton-Raphson and EM algorithms[39]. For models with convergence issues, we set the optimizer to the BOBYQA optimization algorithm, a derivative-free optimization for high-dimensionality[40]. Estimated parameters and their standard errors were checked for optimizer accuracy. Significance was determined using the lmerTest package[41] , which applies Satterthwaite's method to estimate degrees of freedom and generate p-values for mixed models. Residual diagnostics at each level were conducted using the HLMdiag package[42]. The false discovery rate (FDR) approach was employed to correct for multiple comparisons with p-value threshold of <0.05. FDR correction was chosen because it controls the expected proportion of falsely rejected null hypotheses among all rejections, making it more powerful than traditional multiple comparison correction methods[43].

Utilizing the associated standard errors, Sobel test was used to derive z-scores and estimate the significance of the mediation (indirect) effects[44].

Equation 2.1:

$$y_{ijk} = \gamma_{00k} + \gamma_{10k}t_{ij} + b_{1j}X_{1j} + b_{2j}X_{2j} + b_{3j}X_{3j} + b_{4j}X_{4j} + b_{5j}X_{5j} + b_{6ij}X_{6ij} + U_{[j]k} + \varepsilon_{ijk}$$

where:

- y_{ijk} is the measured outcome for timepoint i (0 = baseline, 1 = Year 2 follow-up), participant j, from study site k.
- γ_{00k} is the overall intercept for study site k.
- $\gamma_{10k}t_{ij}$ represents the overall time effect for study site k.
- $b_{1j}X_{1j}$, $b_{2j}X_{2j,}$ $b_{3j}X_{3j,}$ and $b_{4j}X_{4j}$ are the time-invariant covariates (HDP, PAE, PTE, maternal age) for participant j, with b_{1j}, $b_{2j,}$ $b_{3j,}$ and b_{4j} being their corresponding coefficients.
- $B_{5ij}X_{5ij}$ and $b_{6ij}X_{6ij}$ are the time-varying covariates (Age, Household income) for participant j at time point i, with b_{5ij} and b_{6ij} being their corresponding coefficients.
- $U_{[j]k}$ is the random intercept term for participant j nested within study site k.
- ε_{ijk} is the error term for participant j at time point i, from study site k.

Results

We examined the distribution of PR-HTN, P/E and No HDP in relation to sample characteristics in females and males. Participants were divided into three groups: no HDP, PR-HTN and P/E. Table 2.4 presents the descriptive statistics for biological females in the study. The total sample size at baseline (B) was 3,844 (mean age [SD]= 118 [7.7] months; No HDP = 3,415, PR-HTN= 207, P/E= 222). In year 2 (Y2), the sample size was of 2,490 (mean age [SD]= 142 [7] months; No HDP= 2,210, PR-HTN = 134, P/E= 146. There were significant differences in birthweight and gestational term between the groups. For participants at baseline and year 2, the average birthweight in the P/E group was the lowest (mean [SD]: B = 2962 [756], Y2 = 3009 [741]) and the proportion of preterm births was the highest compared to the other groups (mean [SD]: B= 78 [35.8%], Y2= 50 [34.5%]); note: this finding is contextualized within participants all born after 28 weeks' gestation, as those with very preterm births were excluded from participation

in the parent cohort). There were nonsignificant differences in PAE between groups at baseline and year 2. However, there were significant differences in PTE between groups at both baseline and year 2. Regarding the CBCL ADHD scores at baseline, there was significant differences between the groups, with the P/E group having the highest proportion of clinical ADHD scores (9.5%). However, the differences in the ADHD scores were not significant in year 2.

Table 2.5 shows the descriptive statistics for biological males. At baseline, there were 3,814 males in the no HDP group, 207 in the PR-HTN group, and 235 in the P/E group. The total number of males at baseline was 4,256. In year 2, there were 2,625 males in the no HDP group, 141 in the PR-HTN only group and 175 in the P/E group. The total number of males in year 2 was 2941. The mean age at baseline was 119 months (SD= 7.5). The mean age in year 2 was 143 (SD= 7.7). Relative to the other groups, birthweight significantly differed between the groups with the P/E group having the lower birthweight at baseline [3147 (SD=742)] and at year 2 [3139 (SD= 736)]. The percentage of preterm and term births was significantly different among groups, and this persisted in year 2. There was a significant difference in household income, race/ethnicity, and prenatal visits among the groups at both baseline and year 2. CBCL ADHD scores were significantly different among groups at baseline only. There were no significant differences in PAE among the groups at baseline and year 2. However, there was a significant difference in PTE among groups at both baseline and year 2.

Pregnancy-Related Hypertension

Females

Cortical structures

In Step 1 of the mediation model, the regression of cortical volume of bilateral insular cortex on pregnancy-related hypertension ignoring the mediator, were significant, LH insula: *b* =

-233, p = .00002 and RH insula: b= -184, p= .0004. Step 2 showed that the regression of the HDP on the mediator, intracranial volume (ICV) was also significant for the pregnancy-related hypertension group only (b = -23819, p =.003). Step 3 of the mediation process showed that the mediator (ICV), controlling for HDP (PR=HTN), was significant, for bilateral insular cortex, LH insula: b = -149, p =.0007 & RH insula: b = -108, p = 0.009. Sobel test indicated significant partial mediation of ICV between PR-HTN and bilateral insular cortex volume (LH Insula: z = -2.89, p = .003; RH Insula: z = -2.89, p =.003). [Figure 2.4 & Figure 2.5]

Subcortical structures

In Step 1 of the mediation model, the regression of subcortical volume of bilateral caudate nuclei (Caud), putamen (Putam), nucleus Accumbens area (NAc), ventral diencephalon (vDC), Left thalamus proper (TP) and right amygdala (Amyg), on preeclampsia/eclampsia, ignoring the mediator, were significant (LH Caud: b = -90, p =.005 ; RH Caud: b = -79, p =.01 ; LH Putam: b = -138, p =.0002; RH Putam: b = -131, p =.0003; LH NAc: b = -22, p =.001; RH Nac: b = -25, p =.00009; LH vDC: b = -52, p =.03; RH vDC: b = -69, p =.004; LH TP: b = -52, p =.03; RH Amyg: b = -38, p =.005).

Step 2 showed that the regression of the HDP on the mediator ICV, was also significant for the pregnancy-related hypertension group only (b = -23819, p =.003). Step 3 of the mediation process showed that the mediator (ICV), controlling for HDP (PR=HTN), was significant, for bilateral nucleus Accumbens area, putamen, left TP, left caudate (LH Putam: b = -95, p =.003; RH Putam: b = -88, p=.005; LH NAc: b = -13, p =.03; RH NAc: b = -17, p =.002; LH Caud: b = -57, p =.04; LH TP: b= -148, p= .002). ICV fully mediates the relationship between PR-HTN & bilateral vDC (LH vDC: z = -2.89, p = .003; RH vDC: z = -2.89, p = .003), the left TP (z = -2.89, p =.003), RH Caud (z = -2.9, p = .003), RH Amygdala (z = -2.89, p = .003) and was found to

partially meditate PR-HTN's association on bilateral putamen (LH Putam: z = -2.9, p = .003; RH Putam: z = - 2.9, p = .003), Accumbens (LH NAc: z = -2.9, p = .003; RH NAc: z = -2.9, p =.003), LH Caud (z = -2.9, p =. 003). [Figure 2.6 & Figure 2.7]

Males

Cortical structures

In Step 1 of the mediation model, the regression of cortical volume of bilateral superior frontal gyri (SFG), right insular cortex, right caudal middle frontal (cMF), right isthmus cingulate (IHC), right lateral orbitofrontal (LOF) and medial orbitofrontal (MOF) on HDP ignoring the mediator, were significant (SFG: b = -564, p = .02; RH SFG: b= -472, p= .05; RH cMF: b = -242, p = .02; RH insula: b = -127, p = .02; RH IHC: b = -88, p = .01; RH LOF: b = -173, p = .03 ; RH MOF: b = -122, p = .02.) [Figure 2.8]

Step 2 showed that the regression of the HDP on the mediator, ICV was not significant for the pregnancy-related hypertension group. Failure of step 2 means that there is no mediation by ICV on pregnancy-related hypertension in males.

Subcortical structures

In Step 1 of the mediation model, the regression of subcortical volumes of bilateral caudate on PR-HTN ignoring the mediator, were significant, LH Caud: b = -104 p = .003; RH Caud: b = -100, p = .004. Step 2 showed that the regression of the HDP on the mediator, ICV was not significant for the pregnancy-related hypertension group. Failure of step 2 means that there is no mediation by ICV on pregnancy-related hypertension in males. [Figure 2.9]

Preeclampsia

Females

Cortical Structures

In Step 1 of the mediation model, the regression of cortical volume of all ROIs were not significant.

Subcortical Structures

In Step 1 of the mediation model, the regression of subcortical volumes of bilateral putamen on PE ignoring the mediator, were significant, LH Putam: b = -81 p = .03; RH Putam: b = -87, p = .01. Step 2 showed that the regression of the HDP on the mediator, ICV was not significant for the preeclampsia/eclampsia group. Failure of step 2 means that there is no mediation by ICV on preeclampsia/eclampsia in females. [Figure 2.10].

Post-hoc Analysis

The effects of PE on bilateral putamen volume were consistent across all ranges of systolic and diastolic blood pressure, maternal age, and levels of preterm birth among females.

Males

Cortical structures

In Step 1 of the mediation model, the regression of cortical volume of bilateral pars orbitalis (POR), superior fronton gyri (SFG), insular cortex, right caudal anterior cingulate (cAC), isthmus cingulate (IHC), lateral orbitofrontal (LOF) and rostral middle frontal (rMF) on preeclampsia/eclampsia, ignoring the mediator, were significant, LH POR: b = -233, p = .0001; RH POR: b= -184, p= .0004; LH SFG: b= -184, p= .04; RH SFG: b= -184, p= .03; LH insula: b=

-184, *p*= .001; RH insula: *b*= -184, *p*= .02; RH cAC: *b*= -184, *p*= .004; RH IHC: *b*= -184, *p*= .02; RH LOF: *b*= -184, *p*= .03; RH rMF: *b*= -184, *p*= .007.

Step 2 showed that the regression of the HDP on the mediator, ICV was also significant for the preeclampsia/eclampsia group only (*b* = -17005, *p* =.03). Step 3 of the mediation process showed that the mediator (ICV), controlling for HDP (P/E), was significant, for bilateral POR, left insular cortex, right cAC and rMF (LH POR: *b*= -85, *p*= .007; RH POR: *b*= -93, *p*= .001; LH insula: *b*= -120, *p*= .007; RH cAC: *b*= -99, *p*= .01; RH rMF: *b*= -329, *p*= .03). Sobel test was conducted and found complete mediation of ICV between P/E and bilateral superior frontal (LH SFG: *z* = -2.05, *p* =.03; RH SFG: *z* = -2.05, *p* =.03), RH Isthmus cingulate (*z* = -2.05, *p* = .03), RH lateral orbitofrontal (*z* = -2.05, *p* = .03), and RH insular cortex (*z* = -2.05, *p* = .03). We found significant partial mediation of ICV between P/E and bilateral pars orbitalis (LH POR: *z* = -2.05, *p* = .03; RH POR: *z* = -2.05, *p* = .03), LH insula (*z* = - 2.05, *p* = .03), RH cAC (*z* = - 2.06, *p* = 0.03), RH rostral middle frontal (*z* = -2.05, *p* = .03). [Figure 2.11 & Figure 2.12]

Subcortical structures

In Step 1 of the mediation model, the regression of subcortical volume of bilateral caudate on preeclampsia/eclampsia, ignoring the mediator, were significant, LH Caud: *b*= -128, *p*= .0001; RH Caud: *b*= -121, *p*= .0002.

Step 2 showed that the regression of the HDP on the mediator, ICV was also significant for the preeclampsia/eclampsia group only (*b* = -17005, *p* =.03). Step 3 of the mediation process showed that the mediator (ICV), controlling for HDP (P/E), was significant, for bilateral caudate, LH Caud: *b*= -103, *p*= .0003; RH Caud: *b*= -95, *p*= .0007. Sobel test for significance revealed partial mediation of ICV on the association between P/E on bilateral caudate volume (LH Caud: *z* = -2.05, *p* = .03, RH Caud: *z* = -2.05, *p* = .03). [Figure 2.13 & Figure 2.14

Discussion

In the present study, associations between prenatal exposure to hypertensive disorders of pregnancy (HDP) and postnatal brain structural volumes were observed within a longitudinal pediatric cohort (aged 9-10 years at baseline and 11-12 years at 2-year follow-up): representative of population-level incidence rates of HDP in the United States. Observed HDP and brain associations were dependent upon HDP type (PR-HTN or P/E), whether brain differences were a direct effect of HDP or indirect, in part, due to lower intracranial volumes (ICVs), and patterns of findings were dependent upon biological sex. Among females, P/E was associated with direct effects on sustained lower putamen volumes bilaterally. PR-HTN exposure among females was associated primarily with sustained lower subcortical volumes bilaterally (e.g., insula cortex, caudate, putamen, accumbens area, ventral diencephalon, thalamus proper, amygdala) as indirect effects mediated, in part, by sustained lower ICVs. Among males, prenatal PR-HTN exposure was associated with direct effects on sustained lower volumes within a mixture of cortical and subcortical regions primarily (e.g., superior frontal, caudal middle frontal, isthmus cingulate, lateral orbito-frontal, medial orbitofrontal, insula cortex, caudate), with the right hemisphere more impacted relative to left hemisphere. P/E exposure among males was associated primarily with sustained lower volumes within a mixture of cortical and subcortical regions (e.g., pars orbitalis, insula, caudate, caudal anterior cingulate, rostral middle frontal, superior frontal, isthmus cingulate, lateral orbito-frontal) as indirect effects mediated, in part, by sustained lower ICVs. Again, the right hemisphere was more impacted relative to left hemisphere by P/E among males. These results indicate the existence of robust differences among two types of prenatal HDP exposures and subsequent sustained lower cortical/subcortical volumes, some of which are direct effects, while others are indirect effects mediated by ICV. Given the substantial public health

burden of HDP in the United States, these findings underscore the importance of considering the differential impact of the ways in which the placenta responds to HDP pathophysiology across sexes to inform proximal and on-going interventions. The findings underline the importance of considering HDP type and biological sex when investigating public health significance of prenatal HDP exposures.

Pregnancy-related hypertension and preeclampsia/eclampsia are associated with lower cortical and subcortical volume

The present study raises concerns regarding the direct impact of P/E on bilateral putamen volume in females. The putamen, a component of the dorsal striatum along with the caudate nucleus, plays a significantly role in goal-directed learning and behavior, including action selection and initiation, and has been implicated in mood and addiction disorders[45,46]. Importantly, the putamen is the most common site for hypertensive spontaneous intracerebral hemorrhage in neonates, which is the prevalent form of stroke observed in children exposed to HDP[47]. The lower volumes in this specific region, as reported in this study for female P/E exposed, may reflect a heightened sensitivity, supporting the hypothesis that HDP could interfere with fetal cerebral vascular changes induced by imbalanced angiogenic factors that precede structural development[48]. Another intriguing finding of the study is the direct impact of PR-HTN in males, which is primarily localized to the right hemisphere, particularly in the superior frontal, caudal middle frontal, isthmus cingulate, lateral orbito-frontal, medial orbitofrontal, insula cortex, caudate. According to Geschwind and Galabureda's right-hemisphere conservatism theory, in typical development, the right side of the brain develops earlier in gestation as compared with the left hemisphere, and is thus less susceptible to postnatal influences[49]. Existing literature has corroborated this theory, highlighting the dominance of right hemispheric sensory and visuospatial functional connectivity

during fetal neurodevelopment, functions essential for survival adaptability[50]. This is consistent with the lateral difference in cerebrovascular in typically developing neonates, with the right hemisphere exhibiting larger arteries than the left[51]. Moreover, some studies on adolescents born very preterm without evidence of previous neonatal cerebral lesions or severe brain injury have reported a protective strategy of cerebral lateralization, displaying decreased right hemispheric lateralization in the right parietal and temporal lobes[52]. *In utero* exposure to PR-HTN during this sensitive period of fetal development may impede the lateralization of cerebral development, as evidenced by the lower volumes observed predominantly in the right hemisphere. This observation further reinforces the hypothesis that vascular neurogenesis may be altered in utero in HDP, preceding structural changes[48,53]. These findings underscore the significant role of the *in utero* environment in shaping fetal cerebrovascularization and adolescent neurodevelopment. Although functional connectivity is partially influenced by structural development, functional plasticity remains a possibility, therefore further research on functional connectivity is necessary to estimate its impact on development and disorders.

While prior literature has demonstrated that children exposed to P/E exhibit differences in brain volume[54], contrary to these prior studies that reported increased volume in five brain regions including the amygdala, caudate nucleus, and temporal lobe, in P/E exposed children, an opposite trend was observed, characterized by consistently lower volume measures in cortical and subcortical regions. This discrepancy might be attributable to heterogeneity of HDP subtype developmental timing and maturation rates, study population or methodological approaches in the previous studies. For instance, while prior research focused on children exposed solely to preeclampsia, our study considered both PR-HTN and P/E cases, the presence of these distinct subtypes of HDP or the inclusion of eclampsia within our P/E group might have driven these

results. Furthermore, our study's sample size was substantially larger than that of previous investigations. Additionally, developmental time and maturation rates could have contributed to these divergent findings, as our study involved children aged 9-10 years at baseline and 11-12 years at year 2 follow-up, whereas earlier studies examined children aged 9 years at a single timepoint. Considering the dynamic nature of brain development, the age at which measurements are taken could significantly influence the interpretations of observed findings across sexes. Sex differences were observed in the findings, with females exhibiting a greater proportion of affected cortical regions, while males demonstrated a tendency towards subcortical regions. Perhaps, these observations reflect age and sex differences influencing brain maturation during puberty. The cortex undergoes substantial differentiation with age, and previous research has established that sex and age moderate cortical and subcortical development. Throughout adolescence, regions of the cortex undergo significant cortical thinning, particularly in the insula and prefrontal cortex. However, when adjusting for age, males exhibit increased cortical thickness compared to females[55]. Cortical surface area, on the other hand, exhibits varied changes with age, demonstrating age-related expansion only in the cingulate region and decreases in the temporal and parietal cortices[55]. With regard to sex, males exhibit greater cortical surface area expansion than females in multiple brain regions. Nevertheless, surface area, particularly of the superior frontal gyri, decreases with age in both sexes. Subcortical structures, including the thalamus, putamen, pallidum and amygdala, display surface area expansion with age in both males and females[55,56]. Understanding structural brain development is challenging due to its dynamic nature and the influence of factors such as pubertal development and environmental conditions. It is possible that the study's findings related to lower cortical measures merely indicate typical cortical development coinciding with puberty. However, atypical decreases in volume within subcortical structures in

the HDP groups suggest a differential impact on brain development related to HDP. The lower cortical volumes may indicate an acceleration of growth ahead of the typical growth curve in adolescents exposed to HDP, a pattern commonly observed in children exposed prenatal preeclampsia[57,58]. This accelerated growth might have implications for future health risks, as studies have associated rapid height gain during puberty with hypertension and cardiovascular disease later in life[59]. Whether exposure to HDP serves as a precursor to accelerated growth remains unclear. Our results generally align with the DOHaD framework. One of the mechanisms underpinning this framework is the fetal brain sparing hypothesis, which postulates that, during adverse growth restrictions *in utero,* the fetus adapts by redistributing nutrients and oxygen supply to the brain to maintain proper function and development[60]. While this may be the case, it is more plausible that the brain sparing effect operates in the short-term (i.e., sparing crucial areas of the brain during specific developmental phases, such as breathing centers in the pons, motor cortex and the motor network) at the expense of the other structures that develop later during adolescences, structures that may be responsible for emotional, higher-order cognitive processes and executive functioning[61,62]. Consequently, the findings of this study might reflect the possibility that the brain sparing effect, while a beneficial adaptive mechanism during adverse *in utero* conditions, may not adequately protect regions that develop during adolescence.

Intracranial volume mediates the association between HDP and regional brain volume

The complete or partial mediation of ICV is consistent with previous literature indicating that adverse *in utero* conditions are associated with changes in ICV in adulthood[63]. ICV was significantly influenced by HDP, with decreases in ICV observed in females exposed to PR-HTN and males exposed to P/E. The differential impact of HDP subtypes on ICV across sexes may suggest sex differences in strategies employed by the fetus *in utero*. When exposed to placental

stress, male pregnancies tend to have a greater risk of term preeclampsia, whereas female pregnancies tend to have a greater risk of preterm preeclampsia. This is hypothesized to be because female fetuses can induce hypertension in mothers for better perfusion and exhibit increased placental transcriptome and human chorionic gonadotrophin (hCG) levels[64,65]. These observations suggest that PR-HTN and P/E may induce distinct coping mechanism dependent on sex. Although, sex differences in HDP manifestation may have a greater significance in brain development than previously stated, the underlying mechanisms remain unclear. These findings emphasize that much work remains in our effort to better understand the factors contributing to the observed differences in HDP-exposed adolescents. While the findings could indicate typical age-related ICV changes consistent with previous literature, the general trend in ICV is an increase during adolescence[66–68]. Differences in cortical and subcortical regions are a result of a constellation of multiple moderating and mediating biological, socioeconomic, and environmental factors that exert varying degrees of risk and resilience over time. The relationship between other multimodal neuroimaging metrics and HDP exposure in adolescence remains understudied. It is possible that certain brain region, such as the left ventral diencephalon in females, may be especially vulnerable to P/E during specific stages of adolescence but not at other timepoints or in all females exposed to P/E. Furthermore, ICV might mediate this association in later adolescence for females exposed to P/E but not in all cases. Future iterations of the data with more longitudinal timepoints might provide a better assessment of the mechanisms involved in this association.

Limitations and future directions

While the findings of this study benefits from a large longitudinal sample size, mediation analysis, and distinct categories of HDP, there are important limitations to consider. HDP exposure was retrospectively collected from self-questionnaire at the baseline visit and therefore, is prone

to recall bias. However, research validating self-report of PR-HTN and P/E has been shown to be captured accurately[69]. While the specificity of self-reported HDP is >90%, the sensitivity is less, affecting the report of PR-HTN more than that of preeclampsia or eclampsia, which may be a potential source of misclassification error. Additionally, preeclampsia and eclampsia, which have different clinical manifestations were captured in the same question, preventing us from disentangling their impacts. Future studies may benefit from investigating these disorders separately. Despite the longitudinal nature and temporal distance between HDP, ICV and cortical/subcortical volume measures being a strength of the study, accurately capturing individual differences in development requires more than two timepoint. Furthermore, while cortical and subcortical volume differences are important biomarkers to consider when examining responses to different exposures, they do not directly correlate with psycho-behavioral functioning. A knowledge gap exists in our understanding of typical global brain development, as most neuroimaging studies thus far have had small samples and were primarily cross-sectional. With the ABCD study, we are just beginning to gain insight into brain development in a large representative sample of adolescents. Therefore, caution must be exercised not as to confuse individual differences in typical age-related changes in cortical/subcortical volume. Future research with completed timepoint data within the ABCD study will help provide insight into these occurrences and enhance our understanding of the complex relationship between HDP, ICV, and brain development in adolescence. Finally, prenatal alcohol exposure (PAE) and prenatal tobacco exposure (PTE) were included as covariates given that PAE has been recently implicated as a mechanism for increased congenital abnormalities relating to cardiovascular health[70], and PTE occurred at higher rates among PR-HTN exposed pregnancies; however prenatal substance exposure warrants further investigation to more comprehensively disentangle the complex

interplay between teratogens, pregnancy complications and implications for postnatal brain development and well-being.

Conclusion

The current study provides evidence that common pregnancy-related complications within the category of hypertensive disorders of pregnancy (HDP) result in direct effects on lower brain volumes in both females and males. Additionally, several indirect effects on brain volumes following prenatal HDP exposure were observed mediated by lower ICVs. Together, these findings emphasize that the complexities in cerebral lateralization and sensitivity of subcortical structures may occur due to disruptions during critical time periods of fetal neurodevelopment and these differences can be seen at least up to adolescence. This report should elevate the importance of prenatal HDP exposures for public health priorities.

FIGURES

Figure 2.1. Analytical Sample Inclusion and Exclusion Flowchart

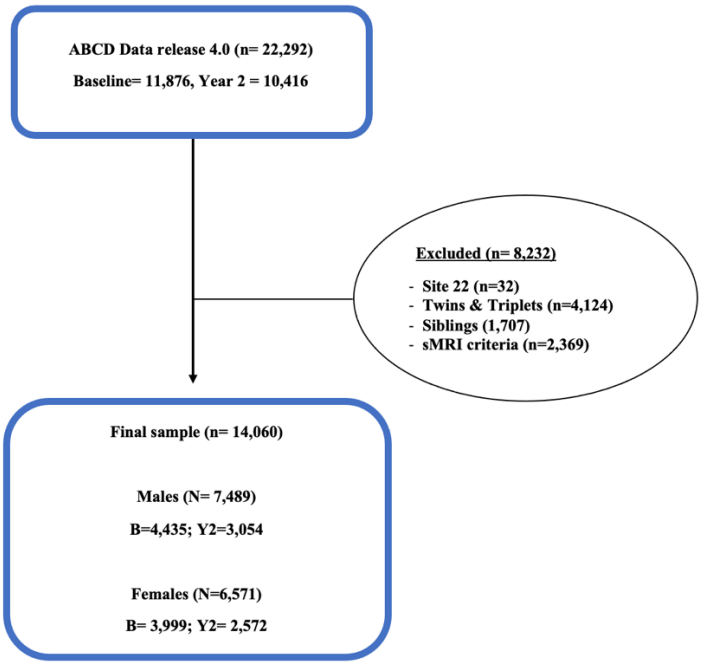


Figure 2.2. Directed Acyclic Graph (DAG). Hypertensive disorders of pregnancy (the exposure) acts on cortical and subcortical brain volume (outcome) directly, and indirectly through the mediating role of intracranial volume.

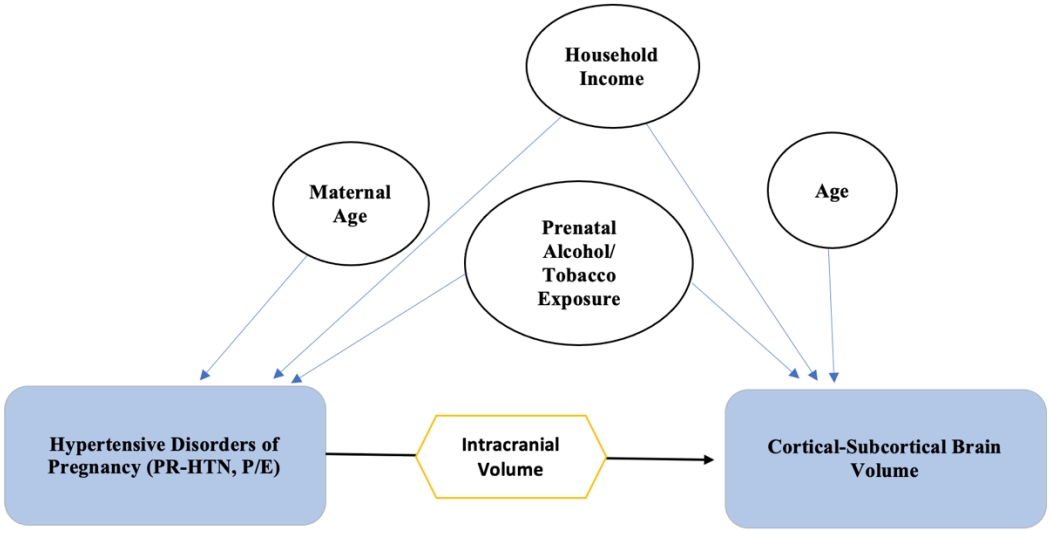


Figure 2.3. Analytical process flowchart. Y = cortical or subcortical ROI volume, X= HDP, M = ICV.

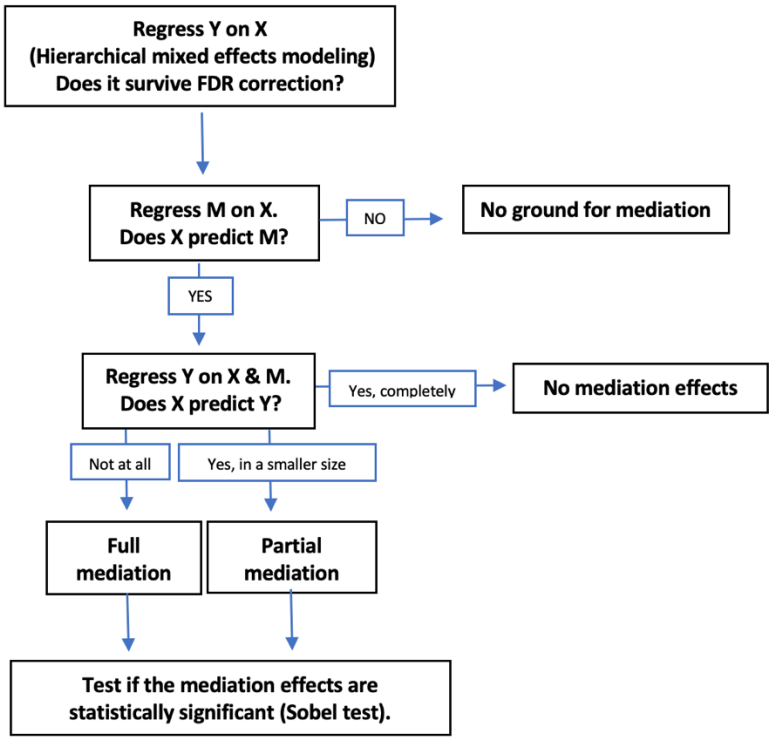


Figure 2.4 Regression coefficients for the relationship between HDP (PR-HTN) and left and right hemispheric insular cortex volume as mediated by ICV, among females. The regression coefficients between PR-HTN and insula volume, controlling for ICV are presented by c'. **p < 0.01, *** p < 0.001.

Figure 2.5. Analysis of cortical volume among females exposed to pregnancy-related hypertension. The figure is a graphical depiction showing the association between PR-HTN and left and right hemispheric insular cortex volume as mediated by ICV, among females. Figures are created using the Desikan-Killiany atlas used in the ABCD processing pipeline via Freesurfer. Lateral views are shown for left and right hemispheres. The panel depicts the p-value change for the relationship between PR-HTN and bilateral insular cortex post-FDR correction (q-value) and the indirect effect of the association working through partial mediation of mediator, ICV.

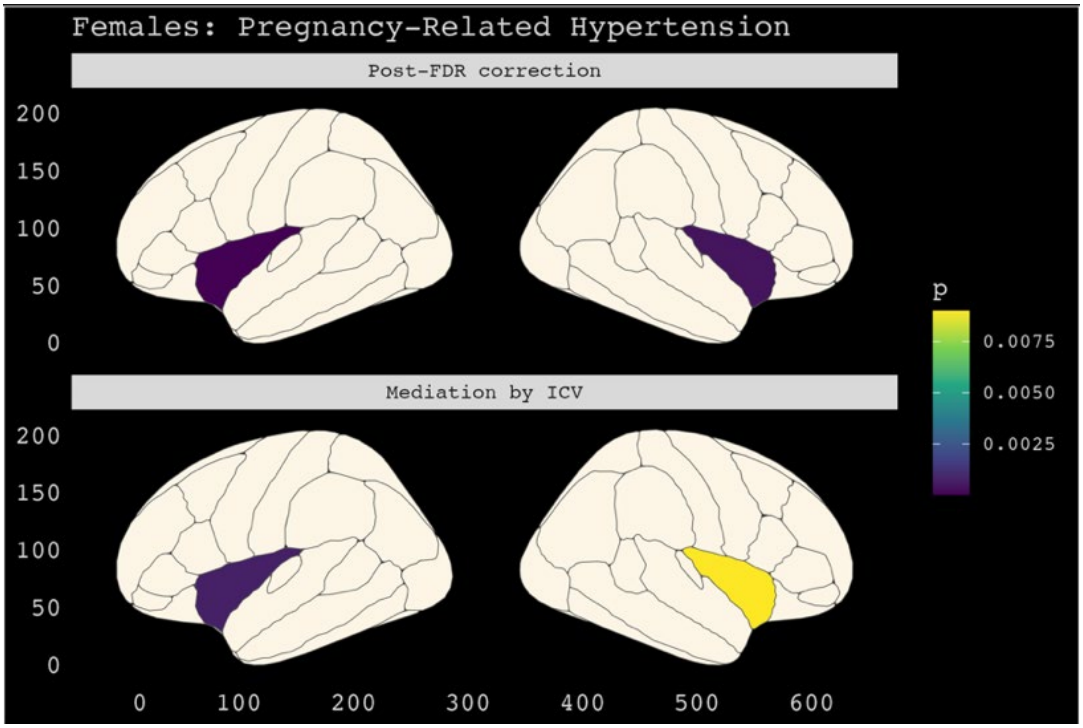


Figure 2.6. Regression coefficients for the relationship between HDP (PR-HTN) and volume of left and right hemispheric ventral diencephalon, Accumbens area, putamen, caudate, left hemispheric thalamic proper and right hemispheric amygdala, as mediated by ICV, among females. The regression coefficients between PR-HTN and subcortical structure volumes, controlling for ICV are presented by c'. n.s.= non-significant, *p < 0.05, **p < 0.01, *** p < 0.001.

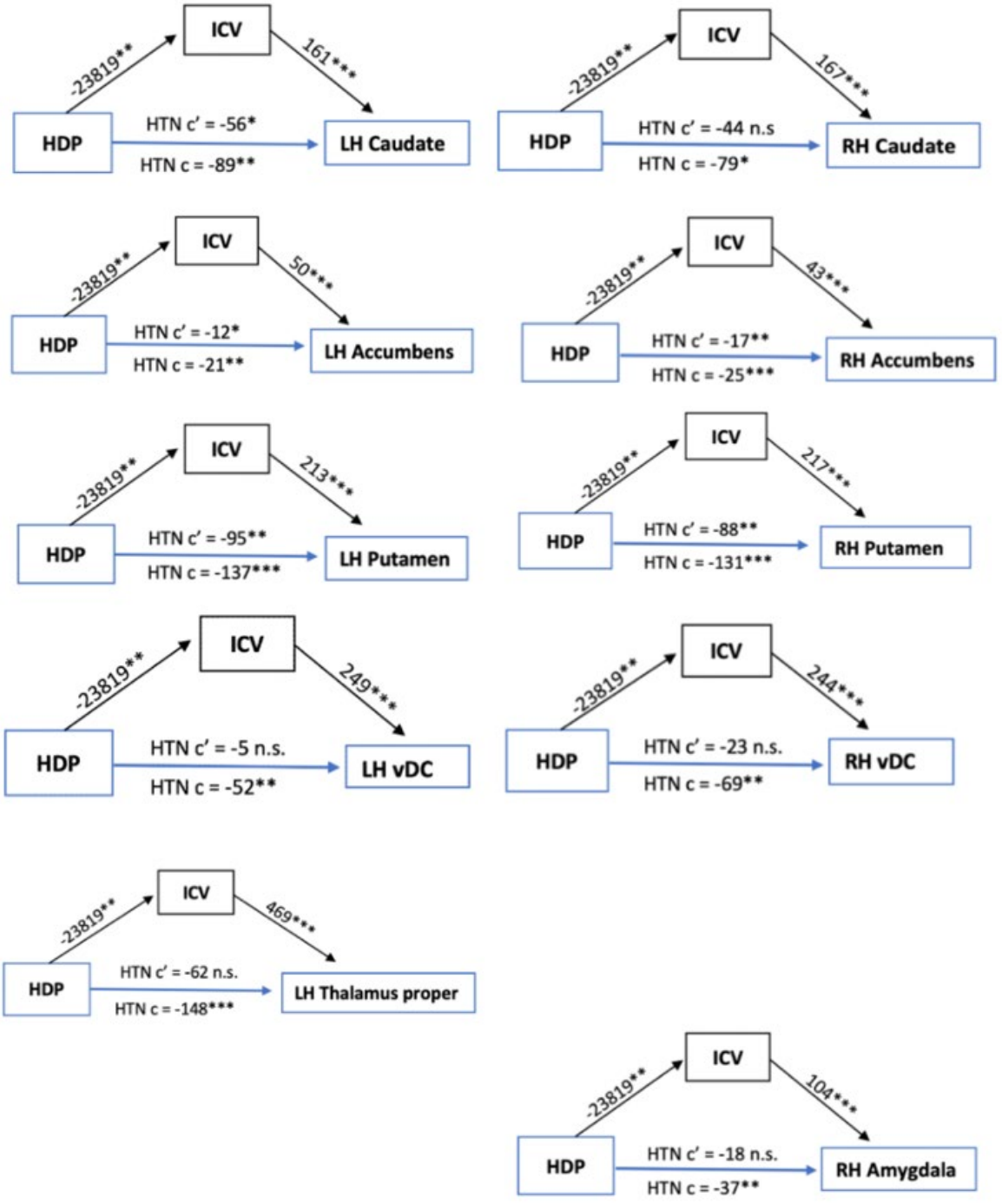


Figure 2.7. Analysis of subcortical volume among females exposed to pregnancy-related hypertension. The figure depicts the p-value change for the association between PR-HTN and left and right hemispheric caudate nucleus, Nucleus Accumbens, ventral diencephalon, putamen, left thalamus proper and right amygdala, as mediated by ICV, among females. Figures are created using the automatic subcortical segmentation (ASEG) atlas used in the ABCD processing pipeline via Freesurfer. Coronal views are shown for left and right hemispheres. The left panel depicts the q-value for relationship between PR-HTN and subcortical volume post-FDR correction (q-value) and right panel depicts the indirect effect of the association working through partial mediation on bilateral putamen, Accumbens and left caudate, and ICV completely mediates the association in subcortical volume of bilateral ventral diencephalon, left thalamus proper, right caudate, and right amygdala.

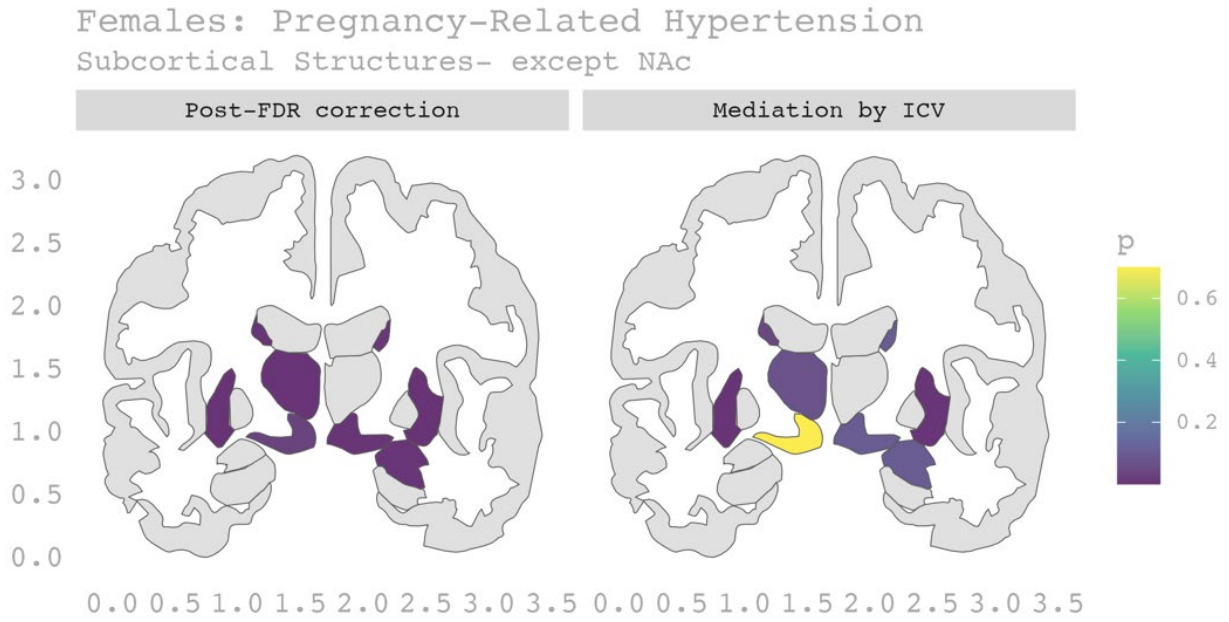


Figure 2.8. Analysis of cortical volume among males exposed to pregnancy-related hypertension. The figure is a graphical depiction showing the association between PR-HTN and left and right hemispheric superior frontal gyri, right hemispheric insular cortex, caudal middle frontal, right isthmus cingulate, lateral orbitofrontal and medial orbitofrontal cortex volume post-FDR correction and not mediated by ICV. Figures are created using the Desikan-Killiany atlas used in the ABCD processing pipeline via Freesurfer. Lateral and medial views are shown for left and right hemispheres.

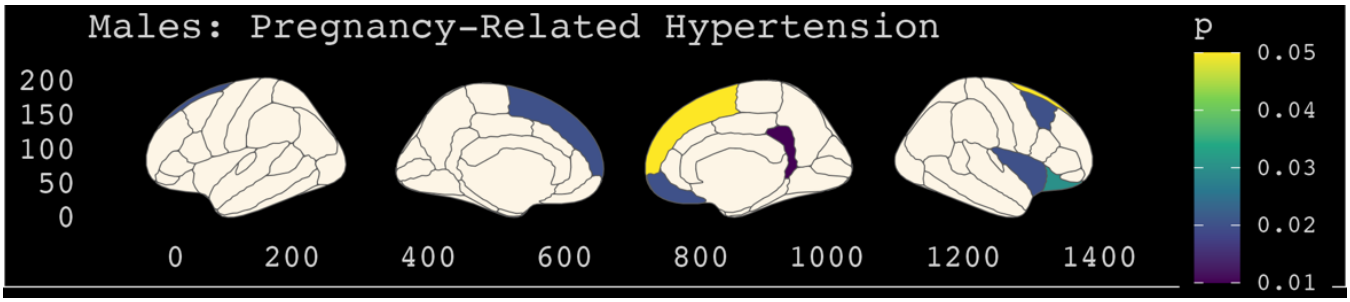


Figure 2.9. Analysis of subcortical volume among males exposed to pregnancy-related hypertension. The figure shows the p-value change for the relationship between PR-HTN and left and right hemispheric caudate nucleus, post-FDR correction and not mediated by ICV. Figures are created using the ASEG atlas used in the ABCD processing pipeline via Freesurfer. Coronal views are shown for left and right hemispheres.

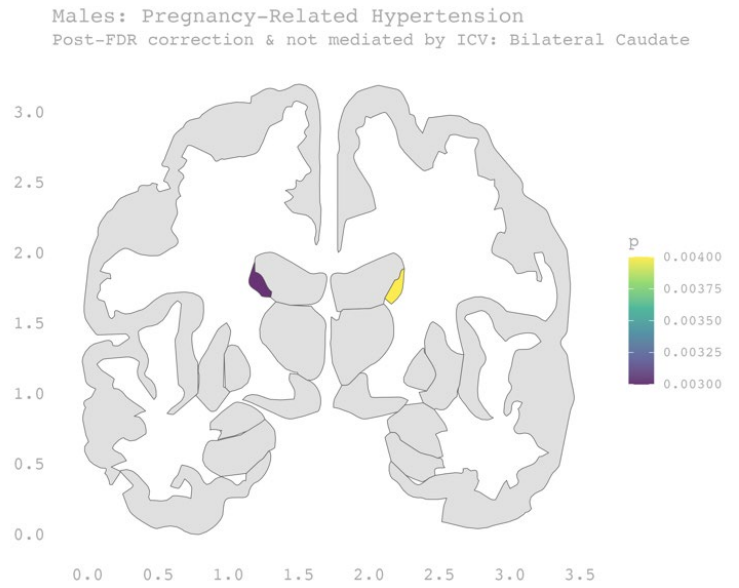


Figure 2.10. Analysis of subcortical volume among females exposed to preeclampsia/eclampsia. The figure shows the p-value for the relationship between P/E and left and right hemispheric putamen post-FDR correction and not mediated by ICV. Figures are created using the ASEG atlas used in the ABCD processing pipeline via Freesurfer. Coronal views are shown for left and right hemispheres.

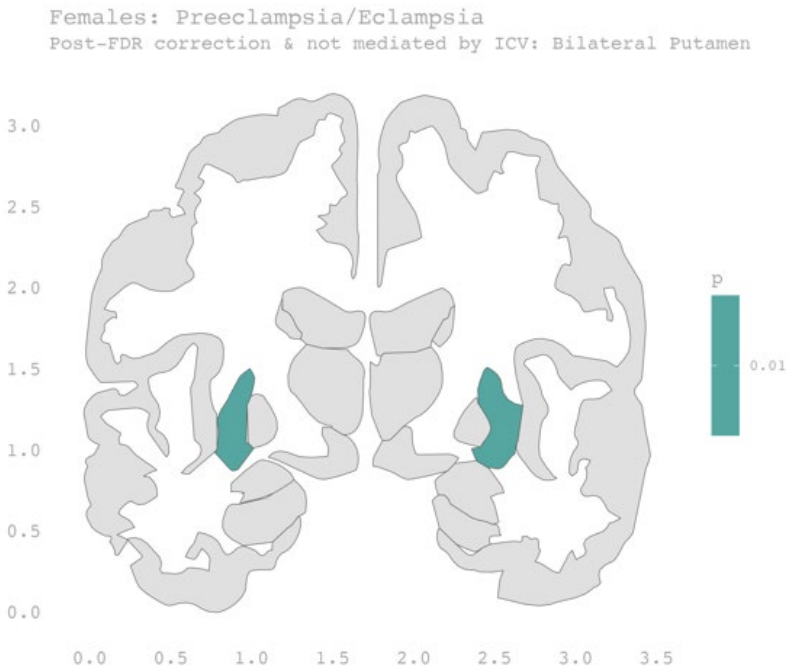


Figure 2.11. Regression coefficients for the relationship between HDP (PE) and volume of left and right hemispheric superior frontal gyri, insular cortex, pars orbitalis, right hemispheric rostral middle frontal, lateral orbitofrontal, caudal anterior cingulate, and isthmus cingulate, as mediated by ICV, among males. The regression coefficients between PR-HTN and cortical structure volumes, controlling for ICV are presented by c'. n.s.= non-significant, *p < 0.05, **p < 0.01, *** p < 0.001.

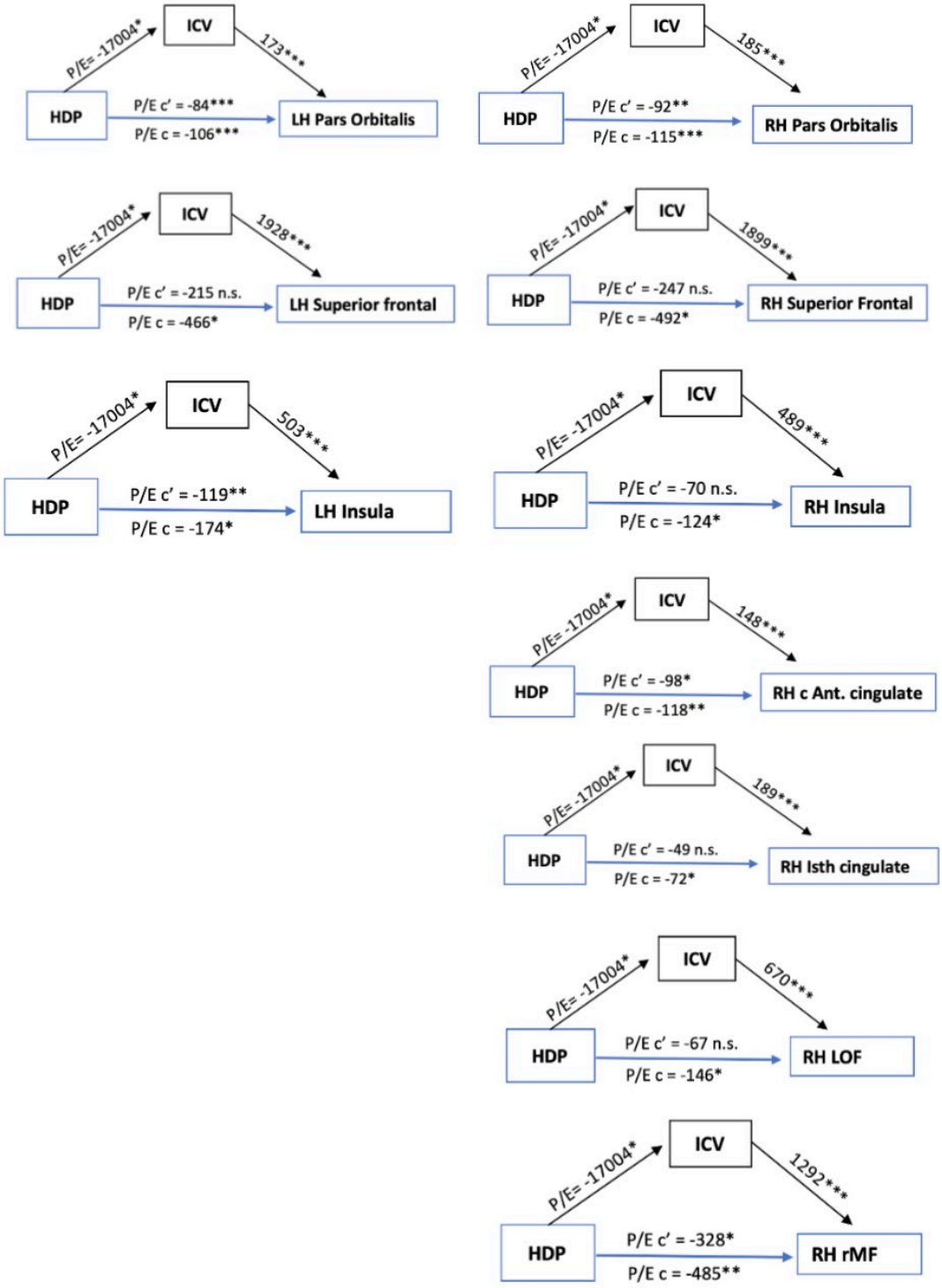


Figure 2.12. Analysis of cortical volume among males exposed to preeclampsia/eclampsia. The figure shows the association between P/E and left and right hemispheric superior frontal gyri, insular cortex, pars orbitalis, right hemispheric rostral middle frontal, lateral orbitofrontal, caudal anterior cingulate, and isthmus cingulate cortex volume, as mediated by ICV, among males. Figures are created using the Desikan-Killiany atlas used in the ABCD processing pipeline via Freesurfer. Lateral and medial views are shown for left and right hemispheres. The panel depicts the p-value change for the relationship between P/E and cortical volume post-FDR correction (q-value) and the indirect effect of the association on bilateral pars orbitalis, left insula, right caudal anterior cingulate and right rostral middle frontal through partial mediation of mediator, ICV and complete mediation by ICV on bilateral superior frontal, right isthmus cingulate, right lateral orbitofrontal and right insular cortex.

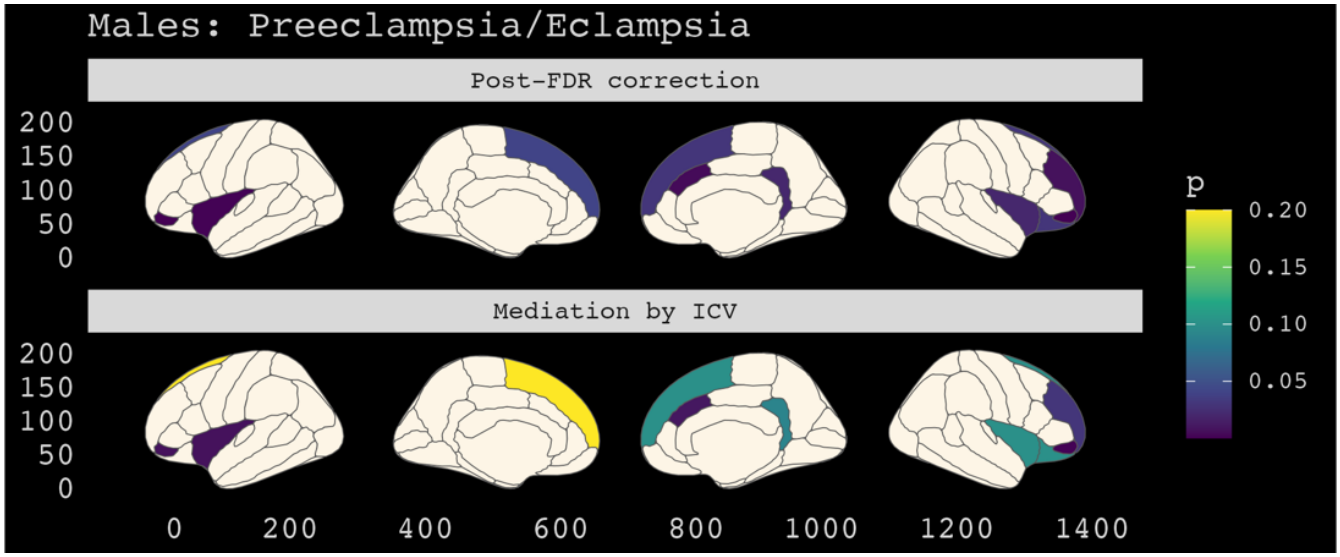
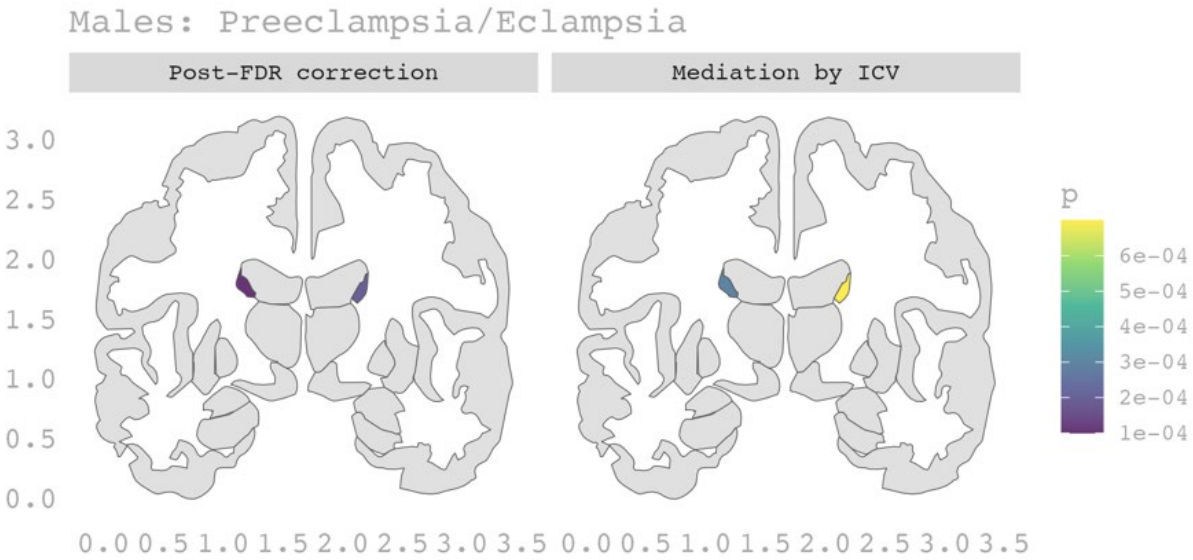


Figure 2.13. Regression coefficients for the relationship between HDP (PE) and volume of left and right hemispheric caudate, as mediated by ICV, among males. The regression coefficients between PR-HTN and cortical structure volumes, controlling for ICV are presented by c'. n.s.= non-significant, * $p < 0.05$, *** $p < 0.001$.

Figure 2.14 Analysis of subcortical volume among males exposed to preeclampsia/Eclampsia. The figure depicts the p-value change for the association between P/E and left and right hemispheric caudate nucleus, as mediated by ICV, among males. Figures are created using the automatic subcortical segmentation (ASEG) atlas used in the ABCD processing pipeline via Freesurfer. Coronal views are shown for left and right hemispheres. The left panel depicts the q-value for relationship between P/E and subcortical volume post-FDR correction (q-value) and right panel depicts the indirect effect of the association working through partial mediation of ICV on bilateral caudate.



TABLES

Table 2.1. Exposure to HDP data. The category HDP was created based on the following questions:

ABCD variable Name	Variable Description	Variable Value
devhx_10c3_p	During the pregnancy with this child, did you/biological mother have any of the following conditions? Pre-eclampsia, eclampsia, or toxemia	1 = Yes; 0 = No; 999 = Don't know
devhx_10j3_p	During the pregnancy with this child, did you/biological mother have any of the following conditions? Pregnancy-related high blood pressure	1 = Yes; 0 = No; 999 = Don't know

Table 2.2. ABCD Recommended Imaging Inclusion for T1 and T2w scans.

T1w and T2w Criteria	Variable
T1 series passed rawQC	mriqcrp103
FreeSurfer QC not failed	abcd_fsurfqc01
Derived results exist	abcd_smrip202
T2 series passed rawQC	mriqcrp103
T1 series passed rawQC	mriqcrp103
FreeSurfer QC not failed	abcd_fsurfqc01
T2w manual post-processing QC not failed	abcd_t2wqc01
T2w registration to T1w	abcd_auto_postqc01
Derived results exist	abcd_smrip302

Table 2.3. ABCD Description of Covariates used in the study.

ABCD variable Name	Variable Description	Variable Value/Scale/Definition
devhx_3_p	How old were you/biological mother when the child was born?	Continuous- in years
demo_comb_income_v2_1	Which of these categories best describes your TOTAL COMBINED FAMILY INCOME for the past 12 months? This should include income (before taxes and deductions) from all sources, wages, rent from properties, social security, disability and/or veteran's benefits, unemployment benefits, workman's compensation, help from relative	1 = Less than $5,000. 2 = $5,000 - $11,999. 3 = $12,000 - $15,999. 4 = $16,000 - $24,999. 5 = $25,000 - $34,999. 6 = $35,000 - $49,999. 7 = $50,000 - $74,999. 8 = $75,000 - $99,999. 9 = $100,000 - $199,999. 10 = $200,000 and greater. 999= Don't know.

	(include child payments and alimony), and so on. ?	777= Refuse to answer
devhx_9_alcohol	Once you /biomom knew you/she were pregnant, were you/biomom using any of the following? Alcohol	1 = Yes, 0 = No, 999 = Don't know.
devhx_9_tobacco	Once you /biomom knew you/she were pregnant, were you/biomom using any of the following? Tobacco	1 = Yes, 0 = No, 999 = Don't know.
interview_age	Age in months at the time of the interview/test/sampling/imaging.	Age is rounded to chronological month. If the research participant is 15 days old at time of interview, the appropriate value would be 0 months. If the participant is 16-days-old, the value would be 1 month.
demo_sex_v2	What sex was the child assigned at birth, on the original birth certificate?	1 = Male; 2 = Female; 3 = Intersex-Male; 4 = Intersex-Female; 999 = Don't know
Random Effects		
src_subject_id	Subject ID how it's defined in ABCD	
site_id_l	Anonymized site name for the participant and visit.	1-21

Table 2.4. Descriptive Statistics for Biological Females

		No HDP	HTN only	P/E	Total	p- value*
		n(baseline)= 3415 n (Year 2) = 2210	n(baseline)=207 n (Year 2) =134	n(baseline)=222 n (Year 2) =146	N(baseline)=3844 N (Year 2) =2490	
Age (months) mean (SD)	*Baseline*	118 (7.4)	118 (7.7)	118 (6.8)	118 (7.7)	0.3
	Year 2	142 (7.7)	142 (7.8)	142 (7)	142 (7.0)	0.7
Birthweight (g) mean (SD)	*Baseline*	3312 (532)	3191 (597)	2962 (756)	3285 (557)	<.001
	Year 2	3322 (532)	3248 (581)	3009 (741)	3299(553)	<.001
Gestational term Preterm Term	*Baseline*	276 (8.1%) 3136 (91.9%)	27 (13.2%) 177 (86.8%)	78 (35.8%) 140 (64.2%)	381(9.9%) 3453 (90.1%)	<.001
	Year 2	170 (7.7%) 2038 (92.3%)	13 (9.9%) 118 (90.1%)	50 (34.5%) 95 (65.5%)	233 (9.4%) 2251 (90.6%)	<.001
Race/Ethnicity Asian Black Hispanic Other/Multiple White	*Baseline*	85 (2.5%) 482 (14.1%) 800 (23.4%) 352 (10.3%) 1696 (49.7%)	1 (0.5%) 58 (28%) 38 (18.4%) 26 (12.6%) 84 (40.6%)	2 (0.9%) 53 (23.9%) 52 (23.4%) 26 (11.7%) 89 (40.1%)	88 (2.3%) 593 (15.4%) 890 (23.2%) 404 (10.5%) 1869 (48.6%)	<.001
	Year 2	50 (2.3%) 283 (12.8%) 485 (21.9%) 249 (11.3%) 1143 (51.7%)	1 (0.7%) 23 (17.2%) 29 (21.6%) 21 (15.7%) 60 (44.8%)	1 (0.7%) 27 (18.5%) 34 (23.3%) 21 (14.4%) 63 (43.2%)	52 (2.1%) 333 (13.4%) 548 (22.0%) 291 (11.7%) 1266 (50.8%)	0.08
CBCL ADHD score (t-score) Non-clinical range (≤ 59) At risk ((60 ≥ t-score ≥ 64) Clinical (≥ 65)	*Baseline* *Year 2*	3016 (88.3%) 222 (6.5%) 176 (5.1%) 1686 (89.4%) 110 (5.8%) 89 (4.7%)	162 (78.3%) 27 (13.0%) 18 (8.7%) 97 (82.2%) 12 (10.2%) 9 (7.6%)	181 (81.5%) 20 (9.0%) 21 (9.5%) 108 (87.8%) 8 (6.5%) 7 (5.7%)	3359 (87.4%) 269 (7.0%) 215 (5.6%) 1891 (88.9%) 130 (6.1%) 105 (4.9%)	<.0.01 0.1
Systolic Blood Pressure (mmHg)	*Year 2*	101.6 (10.3)	102 (10)	104 (10.5)	101.7 (10.3)	0.1
Diastolic Blood Pressure (mmHg)	*Year 2*	60.7 (8.2)	60.8 (8.6)	62.6 (10.3)	60.8 (8.4)	0.1
Prenatal Alcohol Exposure No PAE Yes PAE	*Baseline*	3301 (97.2%) 96 (2.8%)	195 (95.6%) 9 (4.4%)	213 (98.2%) 4 (1.8 %)	3709 (97%) 109 (2.9%)	0.2
	Year 2	2061 (97%) 63 (3%)	124 (96.1%) 5 (3.9%)	130 (97%) 4 (3%)	2315 (97%) 72 (3%)	0.8
Prenatal Tobacco Exposure No PTE Yes PTE	*Baseline*	3246 (95.4%) 155 (4.6%)	185 (90.7%) 19 (9.3%)	202 (92.2%) 17 (7.8%)	3633 (95.0%) 191 (5.0%)	0.002
	Year 2	2037 (95.9%) 87 (4.1%)	118 (91.5%) 11 (8.5%)	121 (89%) 15 (11%)	2276 (95.3%) 113 (4.7%)	<.001
Household Income < $50k ≥ $50k - $100k ≥ $100k	*Baseline* *Year 2*	987 (31.7%) 858 (27.6%) 1267 (40.7%) 535 (26.2%) 573 (28.1%) 933 (45.7%)	87 (45.1%) 58 (30.1%) 48 (24.9%) 45 (35.4%) 40 (31.5%) 42 (33.1%)	79 (39.5%) 57 (28.5%) 64 (32.0%) 42 (32.1%) 43 (32.8%) 46 (35.1%)	1153 (32.9%) 973 (27.8%) 1379 (39.3%) 622 (27.1%) 656 (28.5%) 1021 (44.4%)	<.001 0.009
Maternal Age (years) Mean (SD)	*Baseline*	29 (6.4)	29 (6.4)	28 (6.1)	29 (6.4)	0.09
	Year 2	29 (6.2)	30 (6.3)	29 (6.1)	29 (6.3)	0.2
Prenatal Vitamin Intake No Pre-Vitamin Yes Pre-Vitamin	*Baseline*	156 (4.6%) 3206 (95.4%)	11 (5.5%) 190 (94.5%)	12 (5.6%) 204 (94.4%)	179 (4.7%) 3600 (95.3%)	0.7
	Year 2	91 (4.2%) 2091 (95.8%)	7 (5.4%) 123 (94.6%)	7 (5%) 133 (95%)	105 (4.3%) 2347 (95.7%)	0.7

Prenatal Visits Mean (SD)	*Baseline*	14.5 (5.4)	15.7 (5.8)	16.6 (9.9)	14.7 (5.8)	<.001
	Year 2	14.5 (4.9)	15.2 (5.3)	16.2 (6.8)	14.6 (5)	<.001

*p-values derived from ANOVA test (continuous variables) and Pearson's Chi Squared test (categorical variables).

Table 2.5. Descriptive Statistics for Biological Males

		No HDP	**HTN only**	**P/E**	**Total**	**p- value***
		n(baseline)= 3814 n (Year 2) = 2625	n(baseline)=207 n (Year 2) =141	n(baseline)=235 n (Year 2) =175	N(baseline)=4256 N (Year 2) =2941	
Age (months) mean (SD)	*Baseline*	119 (7.5)	118 (7.4)	118 (7.6)	119 (7.5)	0.06
	Year 2	143 (7.7)	142 (7)	142 (8)	143 (7.7)	0.04
Birthweight (g) mean (SD)	*Baseline*	3437 (551)	3395 (606)	3147 (742)	3418 (570)	<.001
	Year 2	3447 (547)	3371 (605)	3139 (736)	3425 (567)	<.001
Gestational term Preterm Term	*Baseline*	361 (9.5%) 3444 (90.5%)	31 (15.2%) 173 (84.8%)	63 (26.9%) 171 (73.1%)	455 (10.7%) 3788 (89.3%)	<.001
	Year 2	241 (9.2%) 2381 (90.8%)	20 (14.5%) 118 (85.5%)	48 (27.6%) 126 (72.4%)	309 (10.5%) 2625 (89.5%)	<.001
Race/Ethnicity Asian Black Hispanic Other/Multiple White	*Baseline*	82 (2.1%) 492 (12.9%) 874 (22.9%) 375 (9.8%) 1991 (52.2%)	5 (2.4%) 48 (23.2%) 43 (20.8%) 25 (12.1%) 86 (41.5%)	3 (1.3%) 58 (24.7%) 52 (22.1%) 27 (11.5%) 95 (40.4%)	90 (2.1%) 598 (14.1%) 969 (22.8%) 427 (10.0%) 2172 (51.0%)	<.001
	Year 2	51 (1.9%) 293 (11.2%) 571 (21.8%) 240 (9.1%) 1470 (56 %)	4 (2.8%) 28 (19.9%) 26 (18.4%) 21 (14.9%) 62 (44%)	3 (1.7%) 42 (24%) 31 (17.7%) 17 (9.7%) 82 (46.9%)	58 (2%) 363 (12.3%) 628 (21.4%) 278 (9.5%) 1614 (54.9%)	<.001
CBCL ADHD score (t-score) Non-clinical range (≤ 59) At risk ((60 ≥ t-score ≥ 64) Clinical (≥ 65)	*Baseline*	 3242 (85%) 289 (7.6%) 282 (7.4%)	 160 (77.3%) 20 (9.7%) 27 (13.0%)	 194 (82.6%) 18 (7.7%) 23 (9.8%)	 3596 (84.5%) 327 (7.7%) 332 (7.8%)	0.01
	Year 2	1976 (87.7%) 161 (7.1%) 89 (4.7%)	104 (84.6%) 8 (6.5%) 11 (8.9%)	124 (82.1%) 13 (8.6%) 14 (9.3%)	2204 (87.2%) 137 (5.4%) 186 (7.4%)	0.2
Systolic Blood Pressure (mmHg)	*Year 2*	102.8 (10.7)	103.8 (11.4)	104.9 (10.7)	103 (10.8)	0.1
Diastolic Blood Pressure (mmHg)	*Year 2*	60.1 (8.9)	61.1 (9.1)	62.5 (9.3)	60.3 (9)	0.02
Prenatal Alcohol Exposure No PAE Yes PAE	*Baseline*	3696 (97.5%) 96 (2.5%)	199 (96.6%) 7 (3.4%)	226 (97.4%) 6 (2.6 %)	4121 (97.4%) 109 (2.6%)	0.7
	Year 2	2449 (97.4%) 65 (2.6%)	130 (95.6%) 6 (4.4%)	160 (96.4%) 6 (3.6%)	2739 (97.3%) 77 (2.7%)	0.3
Prenatal Tobacco Exposure No PTE Yes PTE	*Baseline*	3627 (95.4%) 173 (4.6%)	185 (90.2%) 20 (9.8%)	221 (94.4%) 13 (5.6%)	4033 (95.1%) 206 (4.9%)	0.003
	Year 2	2415 (95.9%) 104 (4.1%)	120 (89.6%) 14 (10.4%)	159 (94.6%) 9 (5.4%)	2694 (95.5%) 127 (4.5%)	0.002
Household Income < $50k ≥ $50k - $100k ≥ $100k	*Baseline*	1041 (30.1%) 977 (28.2%) 1441 (41.7%)	79 (40.9%) 53 (27.5%) 61 (31.6%)	91 (41.6%) 55 (25.1%) 73 (33.3%)	1211 (31.3%) 1085 (28.0%) 1575 (40.7%)	<.001
	Year 2	620 (25.7%) 646 (26.8%) 1142 (47.4%)	46 (34.8%) 41 (31.1%) 45 (34.1%)	53 (32.9%) 39 (24.2%) 69 (42.9%)	719 (26.6%) 726 (26.9%) 1256 (46.5%)	0.01

Maternal Age (years) Mean (SD)	*Baseline*	29 (6.2)	29 (6)	29 (6.7)	29 (6.2)	0.4
	Year 2	29 (6.2)	29 (6)	29 (6.7)	29 (6.2)	0.8
Prenatal Vitamin Intake						0.3
No Pre-Vitamin	*Baseline*	191 (5.1%)	13 (6.5%)	8 (3.4%)	212 (5.1%)	
Yes Pre-Vitamin		3544 (95.9%)	188 (93.5%)	224 (96.6%)	3956 (94.9%)	
	Year 2	123 (4.8%)	10 (7.2%)	4 (5%)	137 (4.8%)	0.1
		2443 (95.2%)	128 (92.8%)	169 (97.7%)	2740 (95.2%)	
Prenatal Visits Mean (SD)	*Baseline*	14.4 (4.2)	15.1 (5.3)	17.5 (10.7)	14.6 (4.9)	<.001
	Year 2	14.4 (4.2)	15.1 (5.5)	18 (9.2)	14.6 (5)	<.001

*p-values derived from ANOVA test (continuous variables) and Pearson's Chi Squared test (categorical variables).

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CHAPTER 3

Associations Between Prenatal Exposure to Hypertensive Disorders and White Matter Microstructural Development in Adolescents

ABSTRACT

Importance: Incidence of Hypertensive disorders of pregnancy (HDP) in the United States is increasing, yet little is known about lasting impacts of prenatal HDP-exposure on offspring neurodevelopment.

Objective: To examine neurodevelopment following prenatal HDP-exposure via white matter (WM) connectivity in adolescence, a period of rapid WM myelination, in a large, US-based pediatric neuroimaging cohort.

Design, Setting, and Participants: Longitudinal diffusion weighted imaging data from the Adolescent Brain Cognitive Development (ABCD) study© were leveraged to examine WM metrics at 2 timepoints: Baseline: 9-1; 2-year follow-up: 11-12 years old. Data analysis was performed between November,1, 2021 to October,15,2022.

Exposure: Prenatal HDP-exposure via parental self-report included: No HDP, Pregnancy-related hypertension (PR-HTN), and Preeclampsia/Eclampsia (P/E).

Main Outcome and Measures: Using hierarchical mixed-effects models, longitudinal measures of fiber volume (FV) and fractional anisotropy (FA) from 13 WM tracts were examined separately among 5,903 females (baseline = 3,538, mean [SD] age, 118 [7.4] months; Year 2= 2,365, mean [SD] age, 142 [7] months) and 6,668 males (baseline= 3851, mean [SD] age, 119 [7.5] months; Year 2 = 2817, mean [SD] age, 143 [7.2]).

Results: Females with PR-HTN-exposure, relative to No HDP, exhibited decreased FV and FA among 3 midline WM tracts. CIs computed at 95% confidence level. (corpus callosum: FV= -2656 [-4173, -1139], FA= -0.005 [-0.008, -0.002]; forceps major: FV= -637 [-945, -329], FA= -0.006 [-

0.01, -0.002], forceps minor: FV= -600 [-1035, -165], FA= -0.005 [-0.009, -0.0009]) and decreased FV among 6 bilateral WM tracts (fornix: right= -125 [-203, -48], left= -126 [-205, -45]; cingulum: right= -102 [-178, -25], left= -85 [-165, -5]; anterior-thalamic-radiation: right= -236 [-428, -44], left= -319 [-521,-118]; uncinate: right= -19 [-321, -61], left= -187 [-286, -89]; inferior-longitudinal-fasciculus: right= -372 [-591, -152], left= -328 [-554, -101]; inferior-fronto-occipital-fasciculus: right= -428 [-646, -210], left= -454 [-654,-254]). No WM alterations were observed following P/E nor among males.

Conclusions and Relevance: We observe that PR-HTN is associated with WM differences during early adolescence in females suggesting that distinct biophysiological and lifestyle factors related to PR-HTN, compared to P/E may lead to neurodevelopmental alterations. Interventions promoting healthy cardiovascular health during pregnancy may have long-term implications for offspring brain WM development.

Introduction

Fetal neurodevelopment involves complex biophysiological processes that transpire as the brain develops concurrently with, and in response to, the hemodynamic alterations within the intrauterine environment. The microstructural organization of *in utero* white matter (WM) tracts is critical for facilitating efficient long-term neural signal transmission[1,2]. The Developmental Origins of Health and Disease (DOHaD) framework posits that *in-utero* conditions may have long-term health implications, and has been implicated in influencing WM connectivity[3,4]. Intrauterine hemodynamic perturbations, such as those experienced in hypertensive disorders of pregnancy (HDP), can disrupt the *in-utero* milieu, thereby impacting fetal neurodevelopment. Exposure to HDP during gestation may affect the microstructural organization of WM by disrupting angiogenic processes[5]. As these processes play a pivotal role in neurodevelopment, their dysregulation may be a mechanism for continued impact on postnatal neurodevelopment[6–11]. Consequently, an understanding of these complex interactions is crucial for elucidating the enduring impact of intrauterine conditions on an individual's neurodevelopment and function.

HDP, a spectrum of disorders encompassing pregnancy-related hypertension (PR-HTN) , preeclampsia (P), HELLP syndrome and eclampsia (E), constitute a substantial and escalating public health concern[12]. From 2007 to 2019, the incidence of HDP per 1000 births witnessed a marked increase, rising from 48.6 to 83.9 in rural areas and from 37 to 77.2 in urban areas in the US[12]. Previous studies have established associations between HDP and WM alterations in pregnant individuals[13–15]. However, less is known about the effects of prenatal HDP-exposure on WM development in human offspring.

Adolescence represents a critical period characterized by rapid myelination, axonal pruning, and synaptogenesis of WM[16]. Sparse literature has demonstrated WM alterations in HDP-

exposed adolescents using magnetic resonance imaging (MRI). Xing et al.[17] reported lower fractional anisotropy (FA) values, a metric generally indicative of increasing myelination during pubertal WM maturation, in specific WM tracts, including the corpus callosum (CC). Figueiró-Filho et al.[6] observed larger fiber volumes (FV) in the superior longitudinal fasciculus (SLF) and elevated FA in the caudate nucleus in children exposed to preeclampsia. Nonetheless, these studies were constrained by limitations in sample size, design, and selection bias for clinical/high-risk sample, which impede generalizability and preclude the examination of distinct WM outcomes in relation to various types of HDP exposure[11,18]. To understand the public health implication of HDP exposures on public health, it is imperative to investigate community-level manifestation of HDP within a larger sample that accounts for the epidemiologically trends of HDP (PR-HTN, P, E) seen in the US. Therefore, the present study's aim was to examine the associations between prenatal exposure of PR-HTN and P/E, and key white matter tracts using FV and FA to measure WM connectivity in US adolescents aged 9-10 at baseline and 11-12 years at year 2 follow-up. Longitudinal diffusion weighted imaging (DWI) data were analyzed within a large pediatric cohort, the Adolescent Brain Cognitive Development (ABCD) study©. The *a priori* hypothesis posited was that HDP exposure would be associated with decreased FV and FA, and that more widespread alterations throughout the brain would be observed in cases of P/E-exposure, given the heightened severity of clinical symptomology associated with these conditions. Moreover, considering that biological sex has been shown to moderate WM maturation, with earlier onset of puberty-related myelination observed in females, the analyses were stratified by biological sex[19].

Methods

Data and Participants

The present study used data from the ABCD study, a nationwide cohort of 11880 children aged 9-10 years enrolled through 21 sites across the U.S. using school-based enrollment[20]. The ABCD study is a longitudinal study that aims to understand psychological and neurobiological development from pre-adolescence to young adulthood. The study involved recruitment of a baseline cohort of approximately 11,500 child aged 9-10 years with the aim of following them for ten years with annual lab-based assessments, including biennial MRI and yearly salivary collections[21]. The extensive questionnaire and test batteries aims to provide a comprehensive understanding of change across critical periods of human development. The large sample size provides statistical power to identify precursors of the range of developmental outcomes that emerge over the adolescent years, allowing for stratification of individual differences. The study design offers the advantage of providing baseline assessments that precede many clinically relevant behaviors and outcomes that emerge during adolescence.

The primary recruitment approach for the ABCD study is through elementary schools, both public and private[21]. Probability sampling of U.S. schools within 21 catchment areas was the primary method for contacting and recruiting eligible children and their parents. The catchment areas intended to include a large, geographically distributed, demographically and socio-economically diverse, and was meant to cover over 1 in 5 of all eligible U.S. 9 and 10-year-olds[21]. The study aimed to minimize systematic biases in the sampling, but self-selection by families is likely a major source of sampling bias. The participating sites are listed below, and the list of study investigators and research associates can be found at https://abcdstudy.org/principal-investigators.html.

Children's Hospital Los Angeles

Florida International University

Laureate Institute for Brain Research

Medical University of South Carolina

Oregon Health & Science University

SRI International

University of California Los Angeles

University of California San Diego

University of Colorado Boulder

University of Florida

University of Maryland at Baltimore

University of Michigan

University of Minnesota

University of Pittsburgh

University of Rochester

University of Utah

University of Wisconsin-Milwaukee

University of Vermont Virginia Commonwealth

University Washington University, St. Louis

Yale University

The ABCD study was approved centrally and locally by the institutional review board (IRB) at the University of California, San Diego and by each study site. With the present analyses approved by IRB at the University of California, Irvine. Exclusion criteria included lack of English proficiency, severe neurological, medical, or intellectual limitations, gestational age less than 28 weeks, and inability to complete an MRI scan at baseline. Participants were excluded for the

following reasons: child not fluent in English, MRI contraindication (e.g., irremovable ferromagnetic implants or dental appliances, claustrophobia, pregnant), major neurological disorder, gestational age less than 28 weeks or birthweight less than 1,200 grams, history of traumatic brain injury, or had a current diagnosis of schizophrenia, autism spectrum disorder (moderate, severe), mental retardation/intellectual disability, or alcohol/substance use disorder [22–24]. All participants provided assent, while the parent/caregiver provided written informed consent.

In the present study, data from ABCD data release 4.0 were analyzed. Baseline measures included 11876 participants aged 107-132 months (8.9-11 years), and Year 2 follow-up measures included 10416 participants aged 127-166 months (10.5-13.8 years). Participants excluded from the analyses were from site 22 (n=32), twins, and triplets (n=2168), participants with missing or subpar DTI scans (n=3370) and one sibling per family was randomly selected through sampling to address the issue of non-independence within families. The final analytical sample included 5903 biological females and 6668 biological males (Figure 3.1). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline[25].

Exposure to Hypertensive Disorders of Pregnancy (HDP)

Prenatal HDP information was collected via self-report questionnaire at baseline and categorized into three categories: 'No HDP', 'Hypertension only', and 'Preeclampsia/Eclampsia' (Table 3.1).

Diffusion Weighted Imaging (DWI): White Matter Fractional Anisotropy and Fiber Volume

The ABCD protocol uses three 3T scanners (GE 750, Siemens Prisma, and Philips) to obtain MR images with harmonized acquisition parameters, processing, and quality checks. Participants were screened for contraindications such as braces, pacemakers, and metals and desensitized with a dummy machine. DTI processing uses multiband echo-planar imaging, 96

diffusion directions, seven b=0 frames, and four b-values[26]. Eddy current correction was used for diffusion patterns prediction[26]. DTI parameters, including FA, were obtained with tensor fitting using a standard linear estimation approach with log-transformed diffusion-weighted signals[26]. Morphometric measures like FV were obtained using fiber tract segmentation and labeled with AtlasTrack[26,27]. The ABCD diffusion MRI imaging protocol was designed to extend the benefits of high temporal and spatial resolution to multiple scanner systems and vendors, achieving this on all three manufacturers' 3 Tesla systems i.e., GE 750, Siemens Prisma, and Philips[26]. Real-time motion correction and motion monitoring are utilized to maximize usable subject data. The ABCD Data Analysis and Informatics Center (DAIC) performs centralized processing and analysis of MRI data using a software package called the Multi-Modal Processing Stream[26]. The ABCD imaging protocol includes five stages of processing and analysis: unpacking and conversion, processing, brain segmentation, analysis, and summarization[26]. The dMRI acquisition uses multiband EPI with slice acceleration factor 3 and includes 96 diffusion directions, seven b=0 frames, and four b-values for B_0 distortion correction (6 directions with b=500 s/mm2, 15 directions with b=1000 s/mm2, 15 directions with b=2000 s/mm2, and 60 directions with b=3000 s/mm2)[26,28]. The protocol was developed collaboratively with each scanner manufacturer to make imaging parameters as similar as possible[26]. The ABCD DAIC uses automated and manual methods to identify problems with data files, such as incorrect acquisition parameters, imaging artifacts, or corrupted files[26]. They check imaging series for completeness and adherence to imaging parameters using automated protocol compliance checks. Staff review out -of-compliance series and contact sites if corrective action is needed[26]. The DAIC tracks errors in the unpacking and processing of imaging data, which helps to identify the number of failures at each stage and prioritize efforts to prevent future errors[26].

The ABCD imaging protocol estimates head motion for dMRI series using a registering method to an image synthesized from a tensor fit. The overall head motion is quantified using the average estimated frame-to-frame head motion. Dark slices, an artifact indicating abrupt head motion, are identified as outliers[26]. Technicians perform manual quality control procedures, to flag and note unacceptable. Derived images include the average b=0 image, FA, MD, tensor fit residual error, and DEC FA map. All series are consensus rated by two or more reviewers, and rejected series are excluded from subsequent processing and analysis[26]. The dMRI preprocessing corrects for eddy currents, motion, and B_0 field inhomogeneity distortions. The eddy current correction predicts and corrects for displacement along the phase-encode direction and dark slices caused by abrupt head motion are excluded from tensor fits[26]. Rigid-body-registering corrects for head motion. B_0 field inhomogeneity is minimized using pairs of b=0 images with opposite phase encoding polarities, and the dMRI images are registered to T1w structural images[26]. The diffusion gradient matrix is adjusted for head rotation, and a registration matrix is provided for rigid-body transformation between dMRI and T1w images. The resulting dMRI images have 1.7 mm isotropic resolution[26]. The AtlasTrack method labels major white matter tracts using a probabilistic atlas-based approach[29]. It involves prior probabilities and orientation information for specific long-range projection fibers, including some additional fiber tracts not included in the original description[29]. The method registers sMRI images to the atlas using discrete cosine transforms, compares the DTI-derived diffusion orientations to the atlas fiber orientations, and refines the a priori tract ROIs, and excludes voxels containing mostly gray matter or cerebral spinal fluid (CSF)[26,30]. ABCD uses DTI to calculate FA and diffusivity measures (MD, LD, and TD) through a linear estimation approach with log-transformed DW signals[31]. Two tensor model fits are used, the DTI inner shell (DTIIS) and the DTI full shell (DTIFS), with the former excluding frames with b>1000 s/mm^2 [26].

Mean DTI measures are calculated for WM fiber tract ROIs and ROIs from FreeSurfer's subcortical segmentation[29,32]. Probability estimates are used to calculate weighted averages of DTI measures[26]. DTI measures are also sampled onto the cortical surface mesh to make maps of diffusion properties for cortical gray and white matter[33]. White and gray matter values are calculated using a weighted average based on the proportion of white or gray matter in each voxel[34]. For subcortical ROIs, weighting factors for each voxel in the ROI are calculated based on the difference of MD values relative to the median within each ROI to suppress partial voluming with CSF[26].

Post-processing quality control involves assigning numeric values of 0-3 to rate quality on five dimensions: residual B_0 distortion, registration to T1w image, image quality, segmentation integrity, and field of view cutoff[26]. An overall QC score of 1 or 0 is assigned, with 0 indicating that the series should be excluded if B_0 warp, registration, image quality, or segmentation are rated as severe (a value of 3). FOV cutoff is not considered in the overall QC score[26].

Quality checks were performed before including scan data in the analyses. Inclusion criteria for the DTI scans included dMRI registration to T1 and the maximum dorsal and ventral cutoff score (Table 3.2). Baseline and Year 2 follow-up measures of FA and FV were obtained for key WM tracts of interest for the left and right hemisphere separately. Tracts included fornix (FX), cingulum cingulate portion (CGC), cingulate Parahippocampal portion (CGP), corticospinal tract (CST), anterior thalamic radiation (ATR), uncinate (UNC), inferior longitudinal fasciculus (ILF), inferior-fronto-occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF), and superior corticostriate (SCS) Midline tracts included were the corpus callosum (CC), forceps major (F-MIN), and forceps minor (F-MAJ).

Covariates

Covariates were selected using a directed acyclic graph (DAG)and based on prior literature[35–43]. Maternal characteristics included were maternal age (years), income-to-needs ratio (INR) in 4 categories: “deep poverty”, “poverty/near poverty”, “middle income”, “high income”. The INR was calculated by dividing the participant’s household income by the federal poverty threshold for a given household size[44]. Also, included were prenatal alcohol exposure (PAE) and prenatal tobacco exposure (PTE) in the form yes/no. Child/participant characteristics included were age (in months), race, and ethnicity of participants categorized into four groups: “Asian/Multiple/Other”, “Black”, “Hispanic”, and “White” (Table 3.3).

Statistical Analysis

Hierarchical longitudinal mixed-effects models modeled the association between WM metrics and HDP, with random intercepts for subject ID nested within study sites. To account for potential confounding variables, a directed acyclic graph (DAG- Figure 3.2) to guide selection of covariates, which included child's age, race and ethnicity, maternal age, income-to-needs ratio (INR), prenatal alcohol exposure (PAE), and prenatal tobacco exposure (PTE) was used. To test the association between HDP and FA/FV in hemispheric -stratified models (Equation 3.1), random intercept b_{0j} was assumed to be normally distributed with mean 0 and variance τ^2 and estimated for each site nested within each measure of subject id. FA and FV were included as dependent variable in separate models. To model average FA/FV over time, fixed effects of age was added. Fixed and random parameters were estimated separately for FA and FV using maximum likelihood estimation, obtained by maximizing the likelihood function with the lmer package, which uses a combination of Newton-Raphson and EM algorithms[45]. The optimizer was set to the BOBYQA optimization algorithm, a derivative-free optimization for high-dimensionality, for models with

convergence issues[46]. Estimated parameters and their standard errors were checked for the accuracy of optimizer. Significance was calculated using the lmerTest package[47], which applies Satterthwaite's method to estimate degrees of freedom and generates p-values for mixed models. We also conducted residual diagnostics at each level using the HLMdiag package[48]. Correction for multiple comparisons was carried out using the false discovery rate (FDR) approach with a p-value threshold of <0.05[49]. FDR approach for multiple correction was chosen because it controls the expected proportion of falsely rejected null hypotheses among all rejections, making it more powerful than traditional multiple comparison correction methods[50], thereby, increasing the validity and reliability of the findings. Data was analyzed using the lme4 package in R version 4.1.3, estimating model parameters separately for FA and FV using maximum likelihood estimation[45,49]. Additionally, residual diagnostics were carried out at each level[48].

Equation 3.1.

$$y_{ijk} = \gamma_{00k} + \gamma_{10k}t_{ij} + b_{1j}X_{1j} + b_{2j}X_{2j} + b_{3j}X_{3j} + b_{4j}X_{4j} + b_{5j}X_{5j} + b_{6ij}X_{6ij} + b_{7ij}X_{7ij} + U_{[j]k} + \varepsilon_{ijk.}$$

where:

- y_{ijk} is the measured outcome FV/FA for timepoint i (0 = baseline, 1 = follow-up), participant j, from study site k.
- γ_{00k} is the overall intercept for study site k.
- $\gamma_{10k}t_{ij}$ represents the overall time effect for study site k.
- $b_{1j}X_{1j}$, $b_{2j}X_{2j,}$ $b_{3j}X_{3j,}$ $b_{4j}X_{4j}$ and $b_{5j}X_{5j}$ are the time-invariant covariates (HDP, PAE, PTE, maternal age, race/ethnicity) for participant j, with b_{1j}, $b_{2j,}$ $b_{3j,}$ b_{4j} and b_{5j} being their corresponding coefficients.
- $b_{6ij}X_{6ij}$ and $b_{7ij}X_{7ij}$ are the time-varying covariates (Age, Income to needs ratio) for participant j at time point i, with b_{6ij} and b_{7ij} being their corresponding coefficients.
- $U_{[j]k}$ is the random intercept term for participant j nested within study site k.
- ε_{ijk} is the error term for participant j at time point i, from study site k.

Results

Sample Characteristics

The final analytical sample included 5,903 females (Baseline: n=3,538 with mean [SD] age of 118 [7.4] months old; Year 2: n=2,365 with mean [SD] age of 142 [7] months; Table 3.4) and 6,668 males (Baseline: n=3,851, with mean [SD] age of 119 [7.5] months old; Year2: n=2,817, with mean [SD] age of 143 [7.2] months; Table 3.5). Among females, 5.3% were exposed to PR-HTN, and 5.8% were exposed to P/E. Among males, 4.7% were exposed to PR-HTN and 5.4% were exposed to P/E. In comparison to unexposed controls, females exposed to P/E had lower birthweights (mean [SD], 2948 [738] grams) and were more likely to be preterm (10.3%). Additionally, P/E-exposed females had a higher number of prenatal visits (mean [SD], 16.8 [5.9]) than other groups. The P/E group reported lower likelihood of PAE, while the PR-HTN group reported higher likelihood of PTE. A similar pattern of birth outcomes and co-exposures was observed among males (Table 3.5.).

Midline White Matter Tracts

Females

After FDR correction, among females, PR-HTN-exposure was associated with significantly lower FA and FV measures compared to No-HDP exposure (Figure 3.3), observed in the CC FA: b [95%CI]= -0.004 [-0.007, -0.001], *P*=.002; FV: b[95% CI] = -2656.04 [-4172.7, -1139.3] mm^3, *P*<.001), F-MAJ (FA: b [95%CI]= -0.006 [-0.01, -0.002], *P*=.003; FV: b [95% CI]= -636.7 [-944.6, -328.8]mm^3, *P*<.001), and F-MIN (b [95% CI]= -0.004 [-0.008, -0.0009], *P*=.01; FV: b [95%CI]= -599.8 [-1035.07, -164.5] mm^3, *P*=.006) [Table 3.6]. No findings associated with P/E were observed.

Males

Among males, PR-HTN-exposure was associated with lower FA, that did not survive FDR corrected, observed in the CC (b [95%CI] = -0.004 [-0.007, -0.0008], *P*= .01), F-MIN (b [95% CI] = -0.004 [-0.008, -0.0004], *P*=.03) and F-MAJ (b [95%CI] = -0.004 [-0.0086, 0.00007] , *P*=.05) [Table 3.7].

Right and Left Hemispheric White Matter Tracts

Females

Among females, PR-HTN-exposure was associated with significantly lower FV compared to No HDP exposure (Figure 3.4) in the FX (right hemisphere [RH]: b [95% CI]= -125.4 [-203.4, -47.5] mm^3, *P*=.001; left hemisphere [LH]: b [95% CI]= -125.5 [-205.73, -45.41] mm^3,*P*=.002), CGC (RH: b [95%CI]= -101.7 [-178.4, -24.9] mm^3, *P*=.009; LH: b [95% CI]= -84.8 [(-165.04, -4.6] mm^3, *P*=.04) , ATR (RH: b [95% CI]= -236.1 [-428.4, -43.9] mm^3, *P*=.01; LH: b [95% CI]= -319.2 [-520.9, -117.5] mm^3, *P*=.002), UNC (RH: b [95% CI]= -19.2 [-321.4, -61.07] mm^3, *P*=.003; LH: b [95% CI]= -187.4[-285.8, -88.9] mm^3,*P*<.001), ILF (RH: b [95% CI]= -371.4 [-590.6, -152.4] mm^3, *P*<.001; LH: b [95% CI]= -327.7[-554.3, -101.1] mm^3,*P*=.005) and IFOF (RH: b [95%CI] = -427.9 [-645.9, -209.9] mm^3, *P*<.001; LH: b [95% CI]= -453.9 [-654.1, -253.6] mm^3, *P*<.001) [Tables 3.8 & 3.9].

Additionally, PR-HTN-exposure was associated with lower FV that did not pass FDR correction in the CST (RH: b [95% CI] = -128.91 [-251.4, -6.4] mm^3, *P*=.03; LH: b [95% CI] = -160.9[-54.9, 25.05] mm^3,*P*=.01), SCS (RH: b [95% CI]= -253.4 [-465.6, -41.3] mm^3, *P*=.01; LH: b [95% CI]= -525.2[-888.5, -161.9] mm^3, *P*=.005), right CGP (b [95% CI]= -41.5 [-83.84, 0.71] mm^3, *P*=.05) and left SLF (b [95% CI]= -191.3 [-377.1, -5.5] mm^3, *P*=.04). Results that did not

pass FDR correction also showed that FA was significantly lower in the right CGC (b [95% CI] = -0.006 [-0.01, -0.0007], *P*=.02), right CGP (b [95% CI] = -0.005 [-0.009, -0.009], *P*=.01), right IFOF (b [95% CI] = -0.003 [-0.006,0.00005], *P*=.05) and bilateral ILF (RH: b [95% CI] = -0.004 [0.007, -0.0006], *P*=.02; LH: b [95% CI]= -0.004[-0.007, -0.0002], *P*=.04).

Males

Among males, PR-HTN-exposure was associated with lower FA that did not pass FDR correction observed in the right UNC (b [95% CI] = -0.004 [-0.008, -0.001], p=0.009), right FX (b [95% CI] = -0.003 [-0.006, -0.0003], *P*=.03), and left CGP (b [95%CI] = -0.0046 [-0.0090, -0.0002], *P*=.04).

P/E-exposure was associated with WM alterations that did not pass FDR correction observed as higher FA in the left ATR (b [95% CI]= 0.003 [0.0008, 0.007], *P*= .01) and lower FV of the left FX (b [95%CI]= -95.05 [-184.7588, -5.3482] mm^3, *P*=.03), left IFOF (b [95% CI]= -231.6 [-436.08, -27.1] mm^3, *P*=.02), and left SCS (b [95%CI]= -369.3 [-736.5, -2.2] mm^3, *P*=.04) [Tables 3.10 & 3.11].

Discussion

The present study reports novel findings on the association between *in utero* exposure to PR-HTN and white matter alterations in female adolescents aged 9-12 years. Specifically, we observed that among females, PR-HTN-exposure was associated with lower fiber volumes in midline and bilateral white matter tracts, as well as corresponding lower fractional anisotropy in midline tracts. Notably, WM alterations were significant only following PR-HTN exposure, and

not in P/E-exposure. These findings may have neurodevelopmental implications, as they point to the potential long-term effects of HDP exposure on the developing brain.

Symmetrical WM alterations were observed among females with PR-HTN findings, with increased sensitivity to commissural fibers, provides pertinent insight of into the timing and duration of PR-HTN-exposure insult, and the underlying neurodevelopmental mechanisms. Histological and in-vivo/ex-vivo MRI studies have characterized the spatiotemporal maturation pattern of microstructural connectivity[51]. The sequence of myelination of white matter tracts demonstrates a linear trajectory with gestational age, exhibiting a distinct tract-specific maturation trend influenced by complex processes in the *in utero* environment, including nutritional supply, gas exchange, and stress[52]. *In utero* brain development occurs in a bilaterally symmetric manner, with both left and right hemispheres developing simultaneously to form similar brain structures and neural connections[53,54]. This symmetrical sequence of microstructural connectivity suggests that HDP may influence the developing fetal brain, and not postnatal brain. Temporality is a critical factor in fetal neurodevelopment. Studies have demonstrated a temporal sequence of in-utero brain development, with commissural fibers preceding the development of the projection and association fibers. Midline structures develop earlier, making them more susceptible to early developmental insults or disruptions. Observed findings in the present study within commissural fibers (e.g., CC, F-MAJ, F-MIN), suggest that PR-HTN may impact WM development early in fetal life, manifesting within the developing fetus well before clinical manifestation of HDP in the pregnant person. Furthermore, at the end of the second trimester precursors for oligodendrocytes (OLGs) glial cells that make and maintain myelin for the development of the telencephalon (cortical structures, basal ganglia and limbic system) are sourced from the germinal center that is located at the lateral ventricles[55]. This area of the fetal brain remains the last to be vascularized, and therefore

is more susceptible to in -utero insults during this myelination precursor production period[56]. Moreover, due to the high dependence of growth factors impacted in HDP, OLG production, differentiation and survival may be disrupted[55,57–59]. The present study findings showed long-term differences in WM connectivity in tracts that mainly connect cortical functions and may point to an increased vulnerability or sensitization of WM connectivity following exposure to *in utero* disruptions such as PR-HTN[60,61].

WM alterations observed with PR-HTN-exposure, but not P/E-exposure, may be due to differences in treatment strategies employed to distinct types of HDP, influencing the time spent *in utero*. In P/E, delivering the placenta ends the pregnancy and may act as a protective factor by removing the fetus from the negative *in-utero* environment associated with PR-HTN such as cortisol metabolism, chronic hypoxia, and antihypertensive drug metabolites. Higher cortisol levels in PR-HTN may affect the hypothalamic–pituitary–adrenal (HPA) axis and WM microstructural development, potentially leading to the observed differences in the present findings[62,63,64,65,66]. Prolonged placental perfusion in PR-HTN may also cause hypoxic conditions *in-utero*, affecting fetal brain development and morphology[67,68]. Supporting this explanation, participants in the present study with PR-HTN-exposure exhibited a lower proportion of being delivered preterm than those with P/E-exposure, shorter gestations may, in part, protect fetal development. Antihypertensive drugs prescribed to treat PR-HTN may have uncertain teratogenic effects as they cross the placental barrier and appear in fetal circulation[69]. The literature on their effects is conflicting, with some studies reporting adverse child health outcomes and others reporting no effects resulting from prenatal exposure[70–72,73,74]. To further contextualize the findings within the PR-HTN exposed, some women with P/E receive magnesium sulfate (MgSO4) to prevent seizures. This treatment is also linked to a reduction in risk of cerebral palsy in the infants

(CP is linked to WM disruption, among other things), perhaps MgSo4 helps protect the P/E exposed adolescent relative to the PR-HTN[75,76]. Concerns arise because these drugs have a longer time to percolate in maternal and fetal circulation and previous studies have not been methodologically sound in assessing their safety throughout pregnancy[77,78]. Other co-occurring risk factors that can alter WM may be more likely with PR-HTN. In the present cohort, higher rates of co-prenatal tobacco exposure (PTE) were observed with PR-HTN, and not P/E, and has known teratogenic effects on neurodevelopment[79]. The effects of PTE were statistically adjusted, however, other co-occurring behavioral and ecological risk factors associated with PR-HTN may be at play. It is possible that a combination of these factors- high cortisol, hypoxia, antihypertensive drugs, and other co-occurring risk factors impact neurodevelopmental. Future research is needed to disentangle the effects of each.

The present study observed PR-HTN-exposure with changes in WM among biological females only, while biological males did not show the same results. The difference may be due to sexually dimorphic onset of WM maturation during adolescence and pubertal hormones, which typically occur earlier in females[80]. Dynamic WM maturation during the transition from childhood to adolescence may be necessary to observe PR-HTN alterations in WM among males[81]. As puberty onset is earlier in females[82], future iterations of WM data from males matched to pubertal maturation to females may reveal similar WM alterations with PR-HTN, further investigation is warranted.

The patterns of WM findings have implications for understanding the functional outcomes during adolescence. Adolescence is characterized by dynamic changes in behavior including behavioral inhibition, increases in risk-seeking behavior, and an increased susceptibility to mental health disorders[83]. However, it also provides us a window of opportunity for early interventions to

mitigate future disorders. Phenotypically, the adolescent brain undergoes structural differentiation that coincides with these changes[84]. While the breadth of neurodevelopmental functional outcomes was not within the scope of present analyses, descriptive findings demonstrate increased attention deficit hyperactive disorder (ADHD) symptomology in both biological sexes exposed to any type of HDP, consistent with previous research[85]. Previous literature has demonstrated that structural changes in these brain regions are associated with executive planning, higher-order cognitive processing, spatial and emotion processing[86,87]. Some, but not all, studies suggest that children exposed to HDP have been found to be at an increased risk of developing autism spectrum disorder, ADHD, epilepsy, depressive symptoms and generalized anxiety disorder compared with children born from normotensive pregnancies[10,11,88–96,97]. For increased understanding of functional outcomes of present WM alterations, further research is needed.

The longitudinal design allowed for examining HDP-exposure on age-related changes in WM tracts. The relatively large study sample better captured the geographical context and prevalence of HDP of the US population, which strengthens the generalizability of current findings and strengthened statistical power to disentangle the potential smaller effect sizes of PR-HTN and P/E. Limitations of the study are several. HDP-exposure was self-report from caregiver 9-10 years post-pregnancy, which may introduce recall bias and/or error. However, validation studies on maternal self-report have been shown to reliably capture both hypertension during pregnancy and preeclampsia [98,99–101]. Second, the separate effects of preeclampsia and eclampsia were not captured as they were asked together in the self-report retrospective questionnaire. This limitation is being corrected in current recollection of data in the ABCD study and will be in future data releases for use in subsequent analyses. Finally, while present findings report significant

differences in white matter morphometric measures, caution must be exercised while making inferences about overall connectivity and functional adaptions.

Conclusions

The present findings suggest that prenatal PR-HTN, but not P/E, exposure may impact subsequent WM development among females in early adolescence. With consideration that prevalence and incidence of prenatal HDP exposure is related to health inequities, increasing environmental concerns and the growing human population, the present findings emphasize that prenatal HDP-exposure is a major public health issue for future generations and require matched effort to intervene. These findings highlight the need for further research to better inform resources for affected offspring, as well as better utilization of existing resources to mitigate severity and prevalence of hypertension in pregnancy.

FIGURES

Figure 3.1. Analytical Sample Inclusion and Exclusion Flowchart

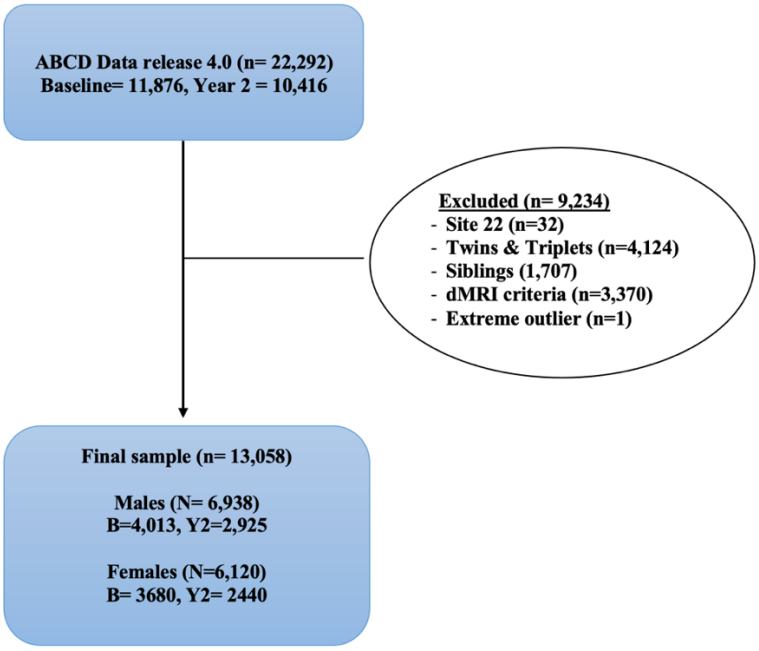


Figure 3.2: Directed Acyclic Graph (DAG)

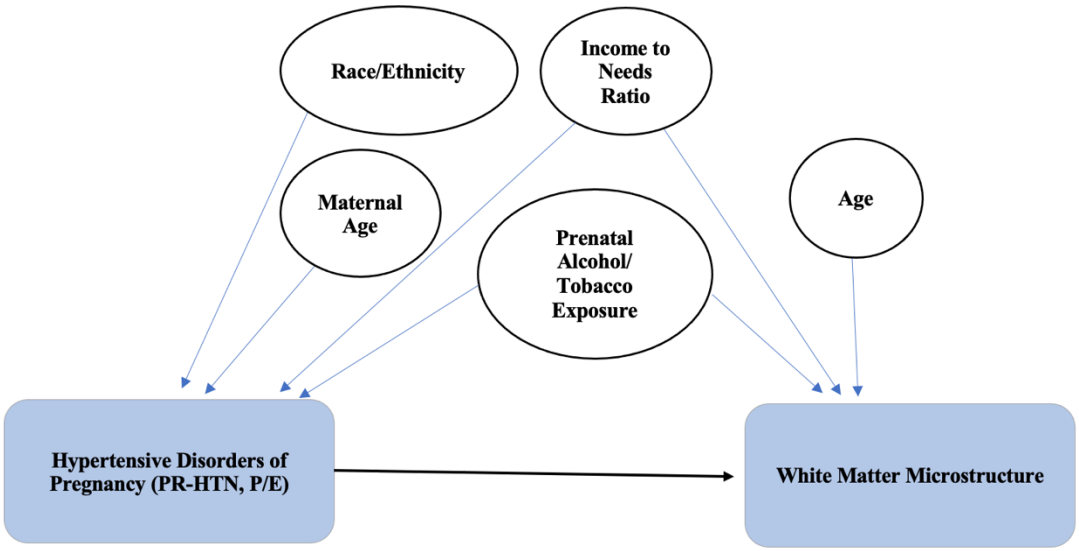


Figure 3.3. Longitudinal Age-Related Changes in Fiber Volume and Fractional Anisotropy in the Forceps Major, Forceps Minor and Corpus Callosum HDP-Exposed. Exposure to pregnancy-related hypertension is associated with decreases in fiber volume and fractional anisotropy across all midlines white matter tracts of interest. Sagittal illustrations of midline white matter tracts are provided for reference (A-C). Plots demonstrating the predicted slope for fiber volume (D-F) and fractional anisotropy (G-I) across age (months) for each HDP group are shown for midline white matter tracts. Regression coefficient plots reflect the 3 midline white matter models for fiber volume (J) and fractional anisotropy (K) demonstrating decreases in average fiber volume and fractional anisotropy over time for PR-HTN group. A indicates anterior, P-posterior, PR-HTN-pregnancy related hypertension, P/E-preeclampsia/eclampsia, PAE-prenatal alcohol exposure, PTE-prenatal tobacco exposure.

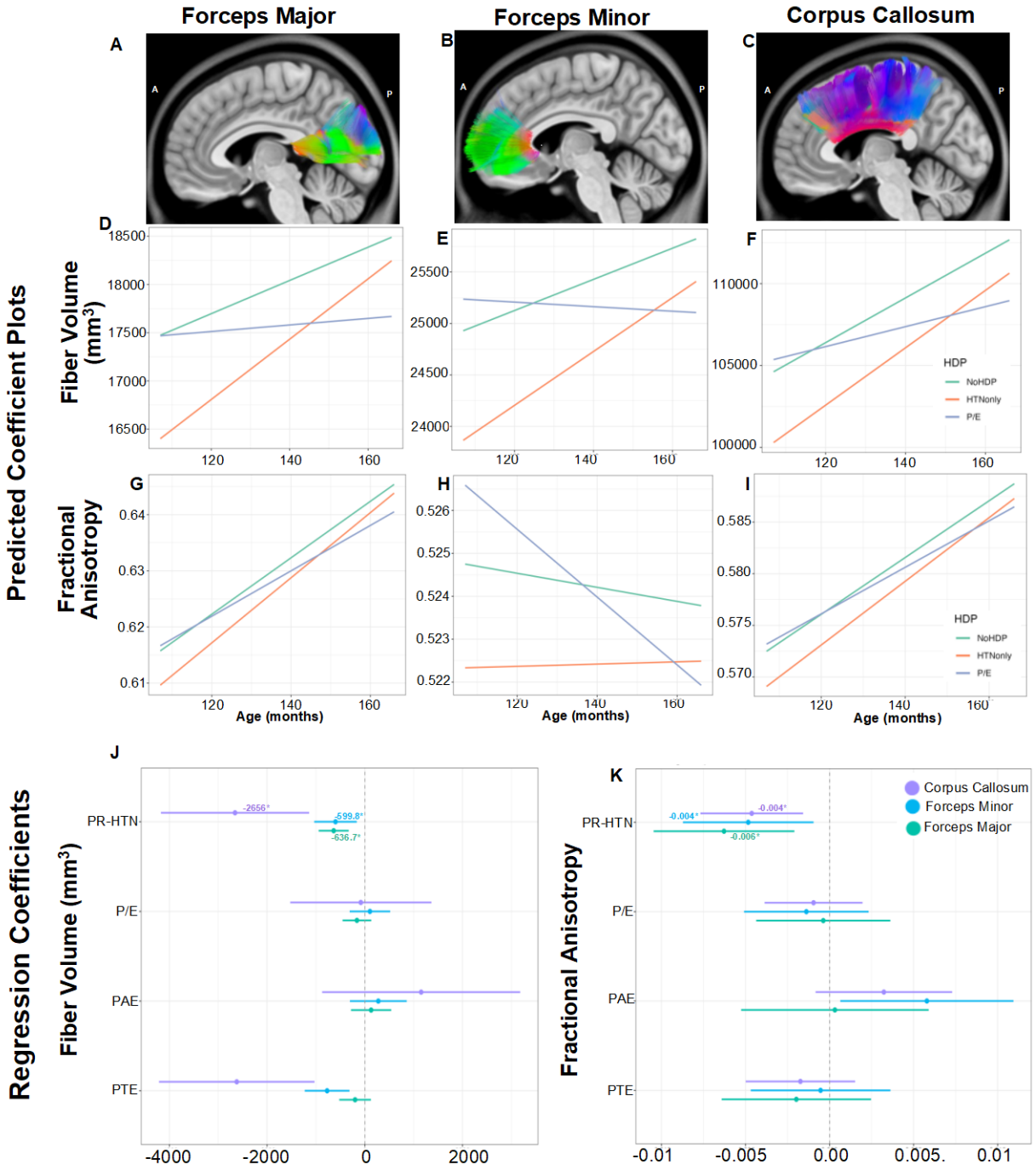
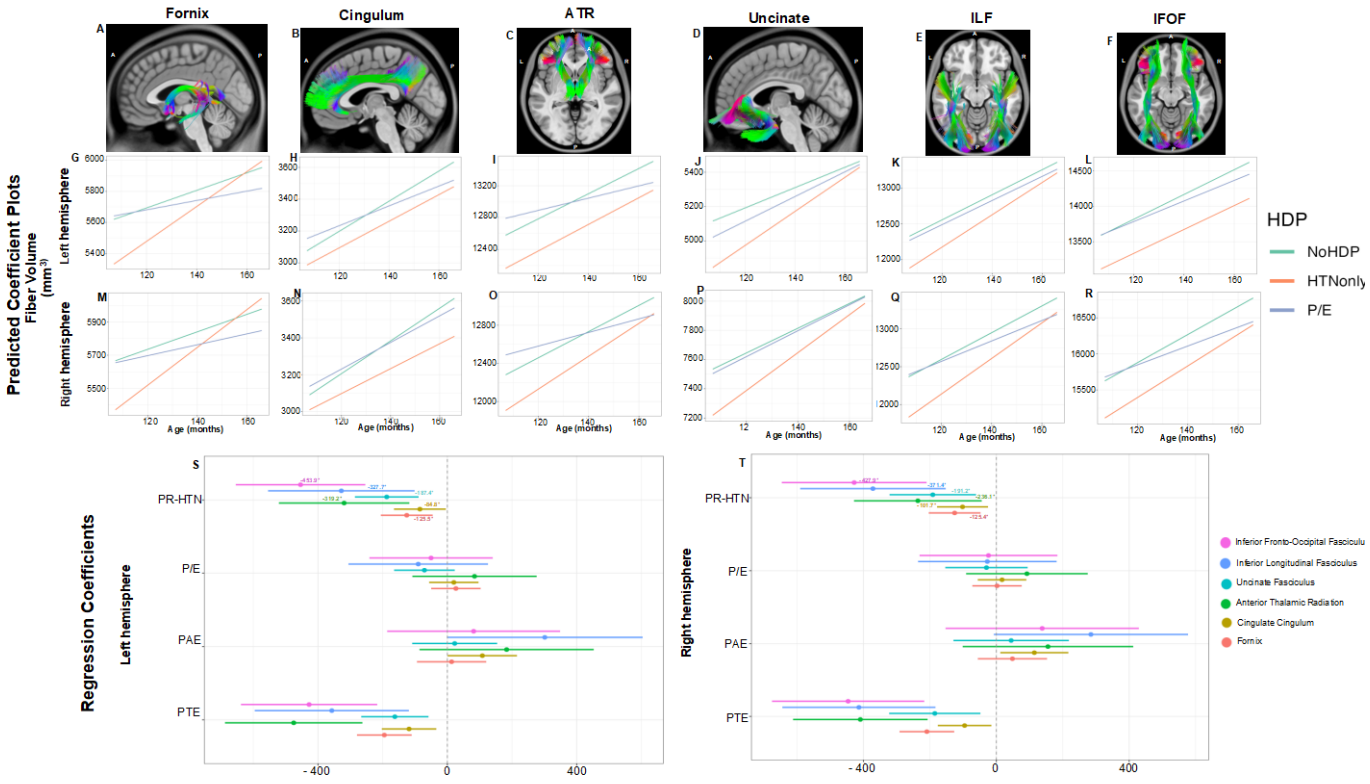

Forceps Major
Forceps Minor
Corpus Callosum
A
B
C
D
E
F
G
H
I
J
K
Predicted Coefficient Plots
Fiber Volume (mm³)
Fractional Anisotropy
Age (months)
HDP
NoHDP
HTNonly
P/E
Regression Coefficients
Fiber Volume (mm³)
Fractional Anisotropy
PR-HTN
P/E
PAE
PTE
Corpus Callosum
Forceps Minor
Forceps Major

Figure 3.4. Longitudinal Age-Related Changes in Fiber Volume in Fornix, Cingulate Portion of Cingulum, Anterior Thalamic Radiation Uncinate, Inferior Longitudinal Fasciculus and Inferior Fronto-Occipital Fasciculus of the Left and Right Hemisphere in HDP-Exposed. Exposure to pregnancy-related hypertension is associated with decreases in fiber volume and fractional anisotropy across 6 of the 9 white matter tracts of interest. Sagittal and coronal illustrations of hemispheric white matter tracts are provided for reference (A-F). Plots demonstrating the predicted slope for fiber volume for the left hemisphere (G-L) and right hemisphere (M-R) across age (months) are shown for HDP groups. Regression coefficient plots reflect 6 hemispheric-stratified white matter tract models for fiber volume in the left hemisphere (S) and right hemisphere (T) demonstrating decreases in average fiber volume over time for PR-HTN group. A indicates anterior, P-posterior, R-right hemisphere, L-left hemisphere, PR-HTN-pregnancy related hypertension, P/E-preeclampsia/eclampsia, PAE-prenatal alcohol exposure, PTE-prenatal tobacco exposure.



TABLES

Table 3.1. Exposure to HDP data: The category HDP was created based on the following questions:

ABCD variable Name	Variable Description	Variable Value
devhx_10c3_p	During the pregnancy with this child, did you/biological mother have any of the following conditions? Pre-eclampsia, eclampsia, or toxemia	1 = Yes; 0 = No; 999 = Don't know
devhx_10j3_p	During the pregnancy with this child, did you/biological mother have any of the following conditions? Pregnancy-related high blood pressure	1 = Yes; 0 = No; 999 = Don't know

Table 3.2: ABCD dMRI (DTI/RSI) Data Recommendations for Inclusion

1.	No serious MR findings
2.	dMRI series passed rawQC
3.	dMRI Total number of repetitions for all OK scans is 103 or more
4.	T1 series passed rawQC
5.	dMRI B_0 Unwarp available
6.	FreeSurfer QC not failed
7.	dMRI Manual Post-Processing QC not failed
8.	dMRI registration to T1w: less than 17
9.	dMRI Maximum dorsal cutoff score: less than 47
10.	dMRI Maximum ventral cutoff score: less than 54
11.	Derived results exist

Table 3.3. A description of each covariate used in the statistical analyses is as follows:

ABCD variable Name	Variable Description	Variable Value/Scale/Definition
Maternal Characteristics		
devhx_3_p	How old were you/biological mother when the child was born?	Continuous- in years
demo_comb_income_v2_l	Which of these categories best describes your TOTAL COMBINED FAMILY INCOME for the past 12 months? This should include income (before taxes and deductions) from all sources, wages, rent from properties, social security, disability and/or veteran's benefits,	1 = Less than $5,000. 2 = $5,000 - $11,999. 3 = $12,000 - $15,999. 4 = $16,000 - $24,999. 5 = $25,000 - $34,999. 6 = $35,000 - $49,999. 7 = $50,000 - $74,999. 8 = $75,000 - $99,999.

	unemployment benefits, workman's compensation, help from relative (include child payments and alimony), and so on. ?	9 = $100,000 - $199,999. 10 = $200,000 and greater. 999= Don't know. 777= Refuse to answer
demo_roster_v2_refuse_l	Include everyone who is living or staying at your address for more than 2 months. Include yourself if you have lived at your address for more than 2 months. Include anyone else staying at your address who does not have another place to stay, even if they are at your address for 2 months or less. Do not include anyone who is living somewhere else for more than 2 months, such as a college student living away or someone in the Armed Forces on deployment	Number of people.
devhx_9_alcohol	Once you /biomom knew you/she were pregnant, were you/biomom using any of the following? Alcohol	1 = Yes, 0 = No, 999 = Don't know.
devhx_9_tobacco	Once you /biomom knew you/she were pregnant, were you/biomom using any of the following? Tobacco	1 = Yes, 0 = No, 999 = Don't know.
Child Characteristics		
interview_age	Age in months at the time of the interview/test/sampling/imaging.	Age is rounded to chronological month. If the research participant is 15 days old at time of interview, the appropriate value would be 0 months. If the participant is 16-days-old, the value would be 1 month.
race_ethnicity	Child's race/ethnicity	1 = White; 2 = Black; 3 = Hispanic; 4 = Asian; 5 = Other. The 'Other'
demo_sex_v2	What sex was the child assigned at birth, on the original birth certificate?	1 = Male; 2 = Female; 3 = Intersex-Male; 4 = Intersex-Female; 999 = Don't know
Random Effects		
src_subject_id	Subject ID how it's defined in lab/project	
site_id_l	Anonymized site name for the participant and visit.	1-21

Table 3.4. Descriptive Statistics for Biological Females

		No HDP	HTN only	P/E	Total	p- value*
		n(baseline)= 3147 n (Year 2) = 2101	n(baseline)=186 n (Year 2) =125	n(baseline)=205 n (Year 2) =139	N(baseline)=3538 N (Year 2) =2365	
Age (months) mean (SD)	*Baseline*	118 (7.4)	118 (7.7)	118 (6.8)	118 (7.4)	0.5
	Year 2	142 (7.7)	142 (7.8)	142 (7.1)	142 (7.0)	0.6
Birthweight (g) mean (SD)	*Baseline*	3309 (532)	3168 (586)	2942 (738)	3280 (552)	<.001
	Year 2	3322 (529)	3237 (582)	3003 (755)	3299(548)	<.001
Gestational age at birth (weeks) Preterm Term	*Baseline*	266 (8.5%) 2878 (91.5%)	26 (14.2%) 157 (85.8%)	75 (37.1%) 127 (62.9%)	367(10.4%) 3162 (89.6%)	<.001
	Year 2	158 (7.5%) 1941 (92.5%)	12 (9.8%) 110 (90.2%)	49 (35.5%) 89 (64.5%)	297 (9.3%) 2140 (90.7%)	<.001
Pubertal Tanner Stages						0.02
Pre-puberty Early Puberty Mid-puberty Late Puberty Post Puberty	*Baseline*	71 (2.5%) 144 (5.2%) 2492 (89.4%) 3 (0.1%) 78 (2.8%)	3 (1.8%) 2 (1.2%) 148 (90.2%) 1 (0.6%) 10 (6.1%)	6 (3.3%) 5 (2.7%) 165 (89.7%) 1 (0.5%) 7 (3.8%)	80 (2.6%) 151 (4.8%) 2805 (89.4%) 5 (0.2%) 95 (3.0%)	
	Year 2	1 (0.1%) 1 (0.1%) 1237 (63.7%) 4 (0.2%) 699 (36%)	0 (0%) 0 (0%) 68 (60.2%) 0 (0%) 45 (39.8%)	1 (0.8%) 0 (0%) 73 (60.3%) 0 (0%) 47 (38.8%)	2 (0.1%) 1 (0.0%) 1378 (63.3%) 4 (0.2%) 791 (36.4%)	0.3
Race/Ethnicity						<.001
Asian/Other/Multiple Black Hispanic White	*Baseline*	396 (12.6%) 434 (13.8%) 741 (23.5%) 1567 (52.2%)	26 (14%) 52 (28%) 32 (17.2%) 76 (40.9%)	26 (12.7%) 46 (22.4%) 50 (24.4%) 83 (40.5%)	448 (12.7%) 532 (15.0%) 823 (23.3%) 1735(49.0%)	
	Year 2	270 (13.3%) 244 (12.1%) 428 (21.1%) 1082 (53.5%)	18 (15%) 19 (15.8%) 25 (20.8%) 58 (48.3%)	19 (14.8%) 21 (16.4%) 30 (23.4%) 58 (45.3%)	307 (13.5%) 284 (12.5%) 483 (21.3%) 1198 (52.7%)	0.4
CBCL ADHD score (t-score) Non-clinical range (≤ 59) At risk ((60 ≥ t-score ≥ 64) Clinical (≥ 65)	*Baseline*	2655 (88.5%) 195 (6.5%) 149 (5%)	138 (79.8%) 22 (12.7%) 13 (7.5%)	161 (83.4%) 15 (8.8%) 17 (8.8%)	2954 (87.8%) 232 (6.9%) 179 (5.3%)	0.001
Prenatal Alcohol Exposure						0.3
No PAE Yes PAE	*Baseline*	3039 (97.1%) 92 (2.9%)	175 (95.6%) 8 (4.4%)	196 (98%) 4 (2 %)	3410 (97%) 104 (3%)	
	Year 2	1962 (96.9) 62 (3.1%)	117 (97.5%) 3 (2.5%)	124 (96.9%) 4 (3.1%)	2203 (97%) 69 (3%)	0.9
Prenatal Tobacco Exposure						0.001
No PTE Yes PTE	*Baseline*	2997 (95.6%) 138 (4.4%)	166 (90.7%) 17 (9.3%)	186 (92.1%) 16 (7.9%)	3349 (95.1%) 171 (4.9%)	
	Year 2	1946 (96.1%) 78 (3.9%)	109 (90.8%) 11 (9.2%)	115 (89.8%) 13 (10.2%)	2170 (95.5%) 102 (4.5%)	<.001
Income to Needs Ratio						<.001
Deep Poverty Poverty & Near Poverty Mid Income High Income	*Baseline*	468 (15.3%) 653 (21.4%) 680 (22.3%) 1252 (41%)	32 (17.9%) 51 (28.5%) 49 (27.4%) 47 (26.3%)	46 (23.0%) 41 (20.5%) 43 (21.5%) 70 (35.0%)	546 (15.9%) 745 (21.7%) 772 (22.5%) 1369 (39.9%)	
	Year 2	232 (11.5%) 386 (19.1%) 476 (23.5%) 930 (45.9%)	16 (13.3%) 37 (30.8%) 24 (20%) 43 (35.8%)	20 (15.6%) 22 (17.2%) 35 (27.3%) 51 (39.8%)	268 (11.8%) 445 (19.6%) 535 (23.5%) 1024 (45.1%)	0.01
Maternal Age (years) Mean (SD)	*Baseline*	29 (6.4)	29 (6.2)	28 (6.1)	29 (6.3)	0.1
	Year 2	29 (6.2)	29 (6.1)	29 (6.1)	29 (6.2)	0.5

Prenatal Vitamin Intake						0.6
No Pre-Vitamin	*Baseline*	145 (4.7%)	11 (6.1%)	11 (5.5%)	167 (4.8%)	
Yes Pre-Vitamin		2954 (95.3%)	169 (93.9%)	188 (94.5%)	3311 (95.2%)	
	Year 2	81 (4%)	6 (5.1%)	6 (4.8%)	93 (4.1%)	0.7
		1923 (96%)	112 (94.9%)	119 (95.2%)	2154 (95.9%)	
Prenatal Visits Mean (SD)	*Baseline*	14.5 (5.4)	15.4 (5.8)	16.7 (10.3)	14.6 (5.8)	<.001
	Year 2	14.5 (4.8)	15.2 (4.8)	15.8 (5.5)	14.6 (4.9)	0.01

*p-values derived from ANOVA test (continuous variables) and Pearson's Chi Squared test (categorical variables).

Table 3.5. Descriptive Statistics for Biological Males

Sample Characteristics		**No HDP**	**HTN only**	**P/E**	**Total**	**p- value***
		n(baseline)= 3466 n (Year 2) = 2523	n(baseline)=181 n (Year 2) =134	n(baseline)=204 n (Year 2) =160	N(baseline)=3851 N (Year 2) =2817	
Age (months) mean (SD)	*Baseline*	119 (7.5)	119 (7.5)	118 (7.5)	119 (7.5)	0.05
	Year 2	143(7.7)	142(7.1)	142(8.0)	143(7.7)	0.06
Birthweight (g) mean (SD)	*Baseline*	3440 (545)	3386 (586)	3150 (767)	3423 (566)	<.001
	Year 2	3447(545)	3394 (592)	3128 (735)	3427 (565)	<.001
Gestational age at birth (weeks)	*Baseline*	312 (9.0%) 3146(91.0%)	29 (16.3%) 149 (83.7%)	53 (26.1%) 150 (73.9%)	397(10.3%) 3445 (89.7%)	<.001
Preterm Term	*Year 2*	232 (9.2%) 2288 (90.8%)	19 (14.5%) 112 (85.5%)	43 (26.9%) 117 (73.1%)	294 (10.5%) 2517 (89.5%)	<.001
Pubertal Tanner Stages						0.2
Pre-puberty	*Baseline*	159(4.6%)	9 (5.0%)	13 (6.4%)	181 (4.7%)	
Early Puberty		728 (21.1%)	32 (17.7 %)	45 (22.3%)	805 (21.0%)	
Mid-puberty		1538 (44.6%)	79 (43.6%)	85 (42.1%)	1702 (44.4%)	
Late Puberty		844 (24.5%)	52 (28.7%)	41 (20.3%)	937 (24.4%)	
Post Puberty		182 (5.3%)	9 (5.0%)	18 (8.9 %)	209 (5.5 %)	
	Year 2	6(0.2%)	0 (0.0%)	0 (0.0%)	6 (0.2%)	0.5
		179 (7.1%)	7 (5.3%)	4 (2.5%)	190 (6.8%)	
		944 (37.5%)	47 (35.3%)	60 (37.7%)	1051 (37.4%)	
		880 (35.0%)	51 (38.3%)	60 (37.7%)	991 (35.3%)	
		506 (20.1%)	28 (21.1%)	35 (22.0%)	569 (20.3)	
Race/Ethnicity						<.001
Asian/Other/Multiple	*Baseline*	406 (11.7%)	26 (14.4%)	25 (12.3%)	457 (11.9 %)	
Black		430 (12.4.%)	42 (23.2%)	48 (23.5%)	520 (13.5 %)	
Hispanic		793 (22.9%)	37 (20.4%)	46 (22.5%)	876 (22.7 %)	
White		1837 (53.0%)	76 (42.0%)	85 (41.7%)	1998(51.9%)	
	Year 2	278 (53.5%)	23 (17.2%)	20 (12.5%)	321 (11.4%)	<.001
		279 (21.1%)	26 (19.4)	38 (23.8%)	343 (12.2 %)	
		545 (12.1%)	24 (17.9%)	27 (15.9%)	596 (21.2 %)	
		1421 (13.3%)	61 (45.5%)	75 (46.9%)	1557 (55.3 %)	
CBCL ADHD score (t-score)	*Baseline*	2961 (85.5%)	137 (75.7%)	170 (83.3%)	3268 (84.9%)	.005
Non-clinical range (≤ 59)		259 (7.5%)	19 (10.5%)	16 (7.8%)	294 (7.6%)	
At risk ((60 ≥ t-score ≥ 64)		245 (7.1%)	45 (13.8%)	18 (8.8%)	288 (7.5%)	
Clinical (≥ 65)						
Prenatal Alcohol Exposure						0.9
No PAE	*Baseline*	3039 (97.1%)	175 (95.6%)	196 (98%)	3410 (97%)	
Yes PAE		92 (2.9%)	8 (4.4%)	4 (2 %)	104 (3%)	
	Year 2	2444 (97.5%)	129 (96.3%)	154 (95.0%)	2727 (97.5%)	0.6
		62 (2.5%)	5 (3.7%)	4 (2.5%)	71 (2.5%)	
Prenatal Tobacco Exposure						.001
No PTE	*Baseline*	3304(95.7%)	161 (89.9%)	192 (94.1%)	3657 (95.3%)	
Yes PTE		149 (4.3%)	18 (10.1%)	12 (5.9%)	179 (4.7%)	
	Year 2	2410 (95.9%)	118 (89.4%)	152 (95.0%)	2680 (95.6%)	.002
		102 (4.1%)	14 (10.6%)	8 (5.0%)	124 (4.4%)	
Income to Needs Ratio						.04
		542 (16.1%)	36 (20.5%)	37 (18.6%)	615 (16.4%)	
Deep Poverty	*Baseline*	657 (19.5%)	38(21.6%)	53 (26.6%)	748 (20.0%)	
Poverty & Near Poverty		782(23.2%)	43 (24.4%)	42 (21.1%)	867 (23.1%)	

Mid Income High Income		1391 (41.3%)	59 (33.5%)	67 (33.7%)	1517 (40.5%)	
	Year 2	345 (14.0%) 458 (18.6%) 529 (21.4%) 1137 (46.1%)	17 (13.1%) 33 (25.4%) 35 (26.9%) 45 (34.6%)	26 (16.6%) 36 (22.9 %) 25 (15.9%) 70 (44.6%)	388 (14.1%) 527 (19.1%) 589 (21.4%) 1252 (45.4%)	.04
Maternal Age (years) Mean (SD)	*Baseline*	29 (6.1)	29 (6.0)	29(6.8)	29 (6.2)	0.4
	Year 2	30 (6.2)	29 (5.9)	29 (6.7)	29 (6.2)	0.6
Prenatal Vitamin Intake						0.1
No Pre-Vitamin Yes Pre-Vitamin	*Baseline*	163 (4.8%) 3232 (95.2%)	13 (7.4%) 162 (92.6%)	7 (3.5%) 194 (96.5%)	183 (4.9%) 3588 (95.1%)	
	Year 2	116 (4.7 %) 2350 (95.3%)	10 (7.6%) 121 (92.4%)	3 (1.9 %) 155 (98.1%)	129 (4.7%) 2626 (95.3%)	.07
Prenatal Visits Mean (SD)	*Baseline*	14.3 (4.1)	15.1 (5.4)	17.4 (11.2)	14.6 (4.9)	<.001
	Year 2	14.4 (4.3)	15.1 (5.6)	17.8 (8.6)	14.7 (4.7)	<.001

*p-values derived from ANOVA test (continuous variables) and Pearson's Chi Squared test (categorical variables).

Table 3.6. Hierarchical analyses of the association between HDP & midline white matter tracts in females (FDR corrected results are highlighted in red)

Females	**Pregnancy related HTN** **b** **(95%CI)**	**Preeclampsia/Eclampsia** **b** **(95%CI)**
Fractional Anisotropy		
Corpus Callosum	-0.004** (-0.007, -0.001)	-0.0009 (-0.003, 0.001)
Forceps Major	-0.006** (-0.01, -0.002)	- 0.0003 (-0.004, 0.003)
Forceps Minor	-0.004* (-0.008, -0.0009)	- 0.001 (-0.005, 0.002)
Fiber volume		

Corpus Callosum	-2656.04*** (-4172.7, -1139.3)	-81.2 (-1525.6 ,1363.04)
Forceps Major	-636.7*** (-944.6, -328.8)	-161.2 (-454.4, 131.9)
Forceps Minor	-599.8** (-1035.07, -164.5)	105.1 (-309.3, 519.6)

Table 3.7. Hierarchical analyses of the association between HDP & midline white matter tracts in males

Males	**Pregnancy related HTN** **b** **(95%CI)**	**Preeclampsia/Eclampsia** **b** **(95%CI)**
Fractional Anisotropy		
Corpus Callosum	-0.004* (-0.007, -0.0008)	0.001 (-0.002, 0.003)
Forceps Major	-0.004* -0.008, 0.00006)	0.001 (-0.002, 0.005)
Forceps Minor	-0.004* (-0.008, -0.0004)	0.001 (-0.002, 0.005)
Fiber volume		

Corpus Callosum	-1394.5 (-3010.6, 221.5)	-1350.3 (-2854.8, 154.2)
Forceps Major	-174.7 (-504.5, 154.9)	-217.5 (-524.5, 89.4)
Forceps Minor	-271.4 (-738.4, 195.6)	-361.1 (-795.8, 73.6)

Table 3.8 Hierarchical analyses of the association between HDP & right hemisphere white matter tracts in females. FDR corrected results are highlighted in red.

Females	**Pregnancy related HTN** **β** **(95%CI)**	**Preeclampsia/Eclampsia** **β** **(95%CI)**
Fractional Anisotropy		
Fornix	-0.001 (-0.005, 0.001)	-0.001 (-0.004, 0.001)
Cing. Cingulum	-0.006* (-0.01, -0.0007)	0.001 (-0.003, 0.006)
Parahipp. Cing.	-0.005* (-0.009, -0.0009)	- 0.003 (-0.007, 0.005)
Corticospinal tracts	-0.002 (-0.005, 0.001)	0.001 (-0.001, 0.004)
ATR	-0.002 (-0.005, 0.0003)	-0.0005 (-0.003, 0.002)
Uncinate	-0.002 (-0.005,0.007)	-0.001 (-0.004, 0.001)
ILF	-0.004* (-0.007, -0.0006)	-0.001 (-0.003, 0.003)

IFOF	-0.003*	0.001
	(-0.006, 0.00005)	(-0.001, 0.004)
SLF	-0.009	-0.004
	(-0.004, 0.002)	(-0.003, 0.002)
SCS	0.0005	0.003
	(-0.002, 0.004)	(-0.0002,0.006)
Fiber volume		
Fornix	-125.4**	2.1
	(-203.4, -47.5)	(-72.2, 76.4)
Cing. Cingulum	-101.7**	17.2
	(-178.4, -24.9)	(-55.8, 90.3)
Parahipp. Cing.	-41.5*	2.3
	(-83.8, 0.7)	(-38.01, 42.5)
Corticospinal tracts	-128.9*	68.09
	(-251.4, -6.4)	(-48.4,184.6)
ATR	-236.1*	92.1
	(-428.4, -43.9)	(-90.9,275.2)
Uncinate	-191.2**	-29.6
	(-321.4, -61.07)	(-153.6,94.2)
ILF	-371.4***	-27.05
	(-590.6, -152.4)	(-235.6,181.5)
IFOF	-427.9***	-23.6
	(-645.9, -209.9)	(-231.1,183.8)
SLF	-142.1	-26.02
	(-342.9,56.6)	(-216.3,164.2)
SCS	-253.4*	68.4
	(-465.6, -41.3)	(-133.5,270.5)

Table 3.9 Hierarchical analyses of the association between HDP & left hemispheric white matter tracts in females (FDR corrected results are highlighted in red)

Females	**Pregnancy related HTN b (95%CI)**	**Preeclampsia/Eclampsia b (95%CI)**
Fractional Anisotropy		
Fornix	-0.001	-0.002
	(-0.004, 0.002)	(-0.005, 0.001)
Cing. Cingulum	-0.005	0.003
	(-0.01, 0.0002)	(-0.01, 0.0002)
Parahipp. Cing.	-0.003	-0.003
	(-0.007, 0.001)	(-0.007, 0.001)
Corticospinal tracts	-0.001	0.001
	(-0.005, 0.001)	(-0.002, 0.004)
ATR	-0.0007	0.0006
	(-0.004, 0.003)	(-0.002, 0.004)
Uncinate	-0.003	-0.003
	(-0.006, 0.001)	(-0.006, 0.001)
ILF	-0.004*	-0.003
	(-0.007, -0.0002)	(-0.006, 0.0007)

IFOF	-0.002 (-0.005, 0.0008)	0.0002 (-0.002,0.003)
SLF	-0.002 (-0.005, 0.001)	-0.0008 (-0.003,0.002)
SCS	0.0004 (-0.002, 0.003)	0.004* (0.0008, 0.006)
Fiber volume		
Fornix	-125.5** (-205.7, -45.4)	26.4 (-49.9, 102.7)
Cing. Cingulum	-84.8** (-165.04, -4.6)	19.9 (-56.3, 96.3)
Parahipp. Cing.	-14.9 (-54.9, 25.05)	13.2 (-24.8, 51.3)
Corticospinal tracts	-160.9* (-284.4, -37.3)	86.2 (-31.3, 203.7)
ATR	-319.2* (-520.9, -117.5)	84.03 (-108.05 ,276.1)
Uncinate	-187.4** (-285.8, -88.9)	-70.8 (-164.5, 22.8)
ILF	-327.7*** (-554.3, -101.1)	-90.05 (-305.7, 125.6)
IFOF	-453.9*** (-654.1, -253.6)	-50.3 (-241.05, 140.2)
SLF	-191.3* (-377.1, -5.5)	13.1 (-163.7, 190.08)
SCS	-525.2* (-888.5, -161.9)	152.7 (-193.2, 498.6)

Table 3.10. Hierarchical analyses of the association between HDP & right hemisphere white matter tracts in males.

Males	**Pregnancy related HTN** **b** **(95%CI)**	**Preeclampsia/Eclampsia** **b** **(95%CI)**
Fractional Anisotropy		
Fornix	-0.003* (-0.006, -0.0003)	-0.001 (-0.004, 0.002)
Cing. cingulum	-0.002 (-0.008, 0.003)	0.0007 (-0.004, 0.006)
Parahipp. cingulum	-0.002 (-0.007, 0.001)	-0.001 (-0.005, 0.002)
Corticospinal tract	-0.001 (-0.004, 0.002)	-0.0002 (-0.003, 0.002)

ATR	-0.0002 (-0.003, 0.002)	0.002 (-0.0003, 0.005)
Uncinate	-0.004* (-0.008, -0.001)	0.001 (-0.001, 0.004)
SLF	-0.002 (-0.005, 0.001)	0.002 (-0.001, 0.005)
ILF	-0.003 (-0.006, 0.0002)	0.001 (-0.001, 0.004)
IFOF	-0.002 (-0.006, 0.0004)	0.0007 (-0.002, 0.003)
SCS	0.0004 (-0.003, 0.004)	-0.0007 (-0.004, 0.002)
Fiber volume		
Fornix	-106.3* (-193.2, -19.3)	-55.6 (-136.5, 25.2)
Cing. cingulum	-62.8 (-145.5, 19.9)	-48.5 (-125.4, 28.4)
Parahip. cingulum	-8.2 (-53.9, 37.5)	8.5 (-33.9, 51.1)
Corticospinal tract	6.4 (-124.3, 137.3)	-54.1 (-175.8, 67.5)
ATR	-100.5 (-303.1, 102.1)	-147.7 (-336.3, 40.7)
Uncinate	-104.5 (-248.7, 39.6)	-43.8 (-177.9, 90.2)
SLF	-8.7 (-222.9, 205.5)	45.8 (-153.5, 245.3)
ILF	-123.3 (-358.1, 111.4)	33.3 (-185.006, 251.7)
IFOF	-60.3 (-291.8, 171.2)	-166.04 (-381.4, 49.3)
SCS	-116.6 (-341.4, 108.05)	-128.8 (-338.05, 80.2)

Table 3.11. Hierarchical analyses of the association between HDP & left hemisphere white matter tracts in males.

	Pregnancy related HTN	**Preeclampsia/Eclampsia**

Males	**b (95%CI)**	**b (95%CI)**
Fractional Anisotropy		
Fornix	-0.001 (-0.004, 0.002)	-0.001 (-0.004, 0.001)
Cing. cingulum	-0.001 (-0.007, 0.004)	-0.001 (-0.006, 0.003)
Parahipp. cingulum	-0.004* (-0.009, -0.0002)	0.000001 (-0.004, 0.004)
Corticospinal tract	-0.002 (-0.005, 0.001)	-0.0004 (-0.003, 0.002)
ATR	-0.001 (-0.004, 0.002)	0.003* (0.0008, 0.007)
Uncinate	-0.002 (-0.006, 0.001)	0.0006 (-0.003, 0.004)
SLF	-0.001 (-0.005, 0.001)	0.0008 (-0.002, 0.004)
ILF	-0.001 (-0.005, 0.001)	0.002 (-0.0005, 0.006)
IFOF	-0.002 (-0.005, 0.001)	-0.0002 (-0.003, 0.003)
SCS	-0.001 (-0.004, 0.001)	-0.0007 (-0.003, 0.002)
Fiber volume		
Fornix	-95.05* (-184.7, -5.3)	-47.3 (-130.8, 36.1)
Cing. cingulum	-57.1 (-143.9, 29.7)	-31.3 (-112.07, 49.4)
Parahipp. cingulum	-28.7 (-72.7, 15.3)	-4.14 (-45.1, 36.8)
Corticospinal tract	-67.2 (-201.6, 67.2)	-47.9 (-172.9, 77.1)
ATR	-97.6 (-312.6, 117.3)	-134.3 (-334.3, 65.7)
Uncinate	12.3 (-96.6, 121.4)	-40.6 (-142.06, 60.8)
SLF	-72.05 (-279.3, 135.2)	-53.2 (-246.1, 139.7)

ILF	-103.02 (-347.09, 141.03)	76.9 (-150.1, 303.9)
IFOF	-146.2 (-366.02, 73.5)	-231.6* (-436.08, -27.1)
SCS	-348.8 (-743.3, 45.7)	-369.3* (-736.5, -2.2)

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CHAPTER 4

Associations between Prenatal Exposure to Hypertensive Disorders in Pregnancy and Postnatal Androgen Hormone Maturation in Adolescence

ABSTRACT

Background: Hypertensive disorders of pregnancy (HDP), including pregnancy-related hypertension, preeclampsia, and eclampsia, are associated with increased androgenic hormones in the pregnant individual and may lead to metabolic dysregulation in postpartum health. Prenatal exposure to high levels of androgenic hormones, such as testosterone and dehydroepiandrosterone (DHEA), may affect fetal endocrine development and result in hormonal differences during pubertal. However, the effects of HDP on exposed fetuses have not been thoroughly investigated. While prior research has linked prenatal exposure to preeclampsia, one type of HDP, to altered androgenic hormone profiles in children, limited studies have examined longitudinal hormonal trajectories in adolescents following multiple types of HDP exposures. Here, associations between prenatal exposure to HDP types and longitudinal salivary levels of testosterone, DHEA, and the testosterone-to-DHEA (T: DHEA) ratios in participants were examined during the transition from childhood to adolescence.

Methods: Longitudinal measures of salivary testosterone and DHEA were utilized from the baseline, year 1 and year 2 assessments of the Adolescent Brain Cognitive Development (ABCD) Study ©, a multisite US cohort of 11,888 adolescents. We assessed hormonal levels at three timepoints: ages 9-10 years (baseline), 10-11 years (follow-up 1), and 11-12 years (follow-up 2). HDP were identified at baseline visit and categorized as pregnancy-related hypertension (PR-HTN), preeclampsia/eclampsia (P/E), or no HDP. Hierarchical mixed-effects models analyzed the relationship between prenatal exposure to HDP and postnatal levels of testosterone, DHEA, and T:D ratios across time. Analyses were stratified by biological sex.

Results: Females exposed to P/E showed higher levels of testosterone and DHEA compared to the no HDP group. In males, distinct associations were observed for both PR-HTN and P/E exposure compared to the no HDP exposure group. Males exposed to P/E demonstrated sustained elevations in DHEA, while PR-HTN exposure was significantly associated with higher levels of testosterone and DHEA. Moreover, males exposed to either PR-HTN or P/E had lower T:DHEA ratios.

Conclusion: Prenatal exposure to PR-HTN and P/E is associated with significant differences in postnatal androgenic hormones during pubertal development in a large cohort of adolescents. Our findings highlight that these androgenic hormone alterations depend upon the specific HDP exposure and biological sex. These novel findings underscore the importance of considering common *in utero* exposures relating to obstetric conditions, including HDP, for understanding endocrine development.

Introduction

Prenatal exposure to elevated androgen levels has been demonstrated to influence fetal development, subsequently impacting childhood, and adolescent growth, as well as metabolic processes[1,2]. Hypertensive disorders of pregnancy (HDP) represent a prevalent complication, affecting approximately 18 million pregnancies globally with the rate of incidence increasing to 10.2% from 1990-2019[3]. These disorders encompass pregnancy-related hypertension (PR-HTN), preeclampsia, and eclampsia (P/E): all of which have been linked to unfavorable hormonal alterations within the maternal system[4–6]. The pathophysiological mechanisms underlying HDP result in dysregulation of the placental capacity, which subsequently interferes with the synthesizes of crucial hormones such as dehydroepiandrosterone (DHEA), estradiol (E), and testosterone (T). The production of these hormones within the placenta- which acts as an incomplete steroidogenic organ- is contingent upon the availability of cholesterol and androgenic precursors derived from the maternal and fetal systems[7]. Pregnancies complicated by HDP have been correlated with excessive production of androgen hormones[8]. The altered hormonal pattern observed in HDP-affected pregnancies warrant further investigation into the potential consequences for fetuses exposed to such conditions *in utero.* These hormonal deviations may extend into puberty, thereby altering maturation of endocrine systems of the developing child. Furthermore, evidence suggests that children with prenatal exposure to HDP are at an increased risk of developing adverse metabolic and cardiovascular disorders later in life, underscoring the need to understand long-term implications of prenatal androgen exposure resulting from HDP.

Puberty represents a dynamic and transformative period characterized by several phenotypic changes. This phase is of particular significance for understanding how *in utero* exposure to excess androgens may impact transitional states from childhood to adolescence, such

as maturation of endocrine systems during puberty. Typically commencing between 4-6 years of age, puberty is initiated by adrenarche, a process characterized by the maturation of the adrenal cortex and the subsequent production of adrenal hormones including DHEA and androstenedione. DHEA production gradually increases throughout childhood, peaking during late puberty or early adulthood[9]. As a precursor to other sex hormones, including testosterone and estrogen, DHEA is metabolized to DHEA sulfate (DHEAS)[10]. DHEAS is then converted to DHEA and testosterone, thus the androgen profile increases culminate with phenotypic changes such as pubic and axillary hair growth (pubarche) and breast enlargement (thelarche). DHEA and DHEAS have been implicated in various of physiological processes, including immune function, brain function, bone metabolism, and cardiovascular health[11]. Testosterone production predominantly occurs in the testes for males and, to a lesser extent, in the ovaries for females[12]. The production of testosterone is predominantly regulated by the hypothalamic-pituitary-gonadal (HPG) axis[12]. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH)[13]. LH subsequently promotes testosterone production by acting on Leydig cells in the testes (for males) and theca cells in the ovaries (for females)[12]. During adolescence, testosterone levels notably increase, particularly in males, facilitating the development of secondary sexual characteristics. DHEA and testosterone play pivotal roles in adolescent development by contributing to the maturation of secondary sexual characteristics and regulating various physiological processes. Balancing DHEA and testosterone during adolescence is crucial for growth, maturation, and overall health. Aberrant hormone levels may result in developmental concerns, such as delayed or precocious puberty, and are associated with various adult health conditions, including polycystic ovary syndrome (PCOS), insulin resistance, asthma, and cardiovascular disease[14–17] .

Interestingly, a study reported elevated levels of DHEAS and testosterone in children with prenatal exposure to mild-to-moderate preeclampsia. However, in the same investigation, females exposed to severe preeclampsia exhibited lower levels of DHEAS, suggesting that pubertal timing may be differentially affected by the clinical severity of HDP. The differential impacts may indicate that the specific type of HDP may carry substantial importance. Nevertheless, the aforementioned studies did not differentiate between types of HDP and solely examined the clinical severity of preeclampsia, categorized as mild, moderate, and severe. Furthermore, the study analyzed DHEAS and testosterone levels at a single timepoint. Given the rapid and dynamic nature of pubertal changes across childhood and adolescence, cross-sectional data on hormonal levels may not provide an accurate representation of pubertal hormonal fluctuations. Additionally, the focus on DHEAS in the study warrants further discussion, while DHEAS serves as a circulating reservoir for DHEA and can be converted when needed. DHEA may be a more suitable measure for investigating pubertal changes in adolescences due to the widespread conversions to various sex hormones (T & E) during this time. As a direct precursor to these sex hormones, DHEA may offer valuable insight into trajectorial hormonal process in adolescence.

Considering the potential long-term consequences of maternal androgen profiles on the child's health, investigating the effects of prenatal exposure to HDP on postnatal pubertal hormones may offer valuable insights into the underlying mechanisms responsible for observed health outcomes. Evaluation of postnatal hormonal outcomes can advance understanding of the underlying *in utero* mechanisms in which prenatal exposure to HDP impacts the development of endocrine systems. With this increased understanding, researchers can develop strategies to prevent or mitigate adverse hormonal or metabolic consequences that may be associated with prenatal exposure to HDP. In pursuit of this objective, we assessed longitudinal salivary levels of

DHEA, and testosterone at three timepoints in adolescents: aged 9.0-10.99 years at baseline, 10.0-11.99 years at follow-up 1, and 11.0-12.99 years at follow-up 2 in the Adolescent Brain Cognitive Development (ABCD) Study©. The primary aim of our investigation was to elucidate patterns of androgenic hormones, specifically DHEA and testosterone, in children with prenatal exposure to PR-HTN and P/E. We hypothesized that adolescents exposed to HDP would exhibit higher levels of these androgens compared to those not exposed to any HDP. Due to distinct pubertal maturation rates between biological males and females, we analyzed these groups separately.

Methods

Participants

The present secondary analyses leveraged data from release 4.0 from the ABCD Study©: an ongoing nationwide longitudinal cohort comprising approximately 11,888 adolescents aged 9.0-10.99 years at their baseline visit. Data collection for baseline assessment occurred between 2016 and 2018. The participants were recruited from 21 sites across the United States[18]. Exclusion criteria for ABCD encompassed non-English fluency, major neurological disorder, gestational age below 28 weeks or birthweight under 1,200 grams, a history of traumatic brain injury, and current diagnoses of schizophrenia, autism spectrum disorder (moderate to severe), intellectual disability, or alcohol/substance use disorder[19–21].

The institutional review board at the University of California, San Diego, centrally granted approval for the ABCD Study, while local approval was obtained from the authors from both the NIH's NDA site and UCI's IRB as Human Subjects Exempt Status. The present analyses utilized salivary hormone data collected at three timepoints (e.g., Baseline= B, Year 1= Y1, and Year 2= Y2) and excludes participants who were twins and triplets (n= 4,146), had a gestational age of less

than 28 weeks (n = 44), or had missing or substandard salivary measurements. Detailed exclusion of observations based on salivary sample criteria is described in the *Outcome measures* subsection of this manuscript. The analytical sample comprised 9,020 female and 10,031 male participants (Figure 4.1). For females, the baseline sample size was 3,969, with 3,482 participants at year 1 follow-up was and 1,569 at year 2 follow-up. For males, baseline sample size was 4,366, with 3,905 at year 1 follow-up and 1,569 at year 2 follow-up. This investigation adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines[22].

Exposure Measures: Hypertensive disorders of Pregnancy

Hypertensive disorders were categorized into 3 groups based on the caregiver's retrospective report (9-10 years later) of experiencing HDP during pregnancy. These categories were derived from the ABCD questionnaire (Table 4.1). Individuals who responded "Yes" to having experienced pregnancy-related hypertension or high blood pressure during pregnancy were assigned to the pregnancy-related hypertension group (PR-HTN). Those who responded "Yes" to experiencing preeclampsia and/or eclampsia during pregnancy were assigned to the "Preeclampsia/Eclampsia" group (P/E). Notably, individuals who responded "Yes" to both PR-HTN and P/E questions were included exclusively in the P/E group. Individuals who responded "No" to both categories were placed in the No HDP group. Lastly, individuals who responded "Don't know" were assigned a NA.

Outcome Measures: Salivary DHEA and Testosterone

At each timepoint, participants and their parent/guardian reported to their local study site at a predetermined scheduled time that was based on researcher's and participant's availability. Arrival times therefore fluctuated across participants and were not held constant within or across

sites, or across subsequent annual visits within participants (see Mariko & Uban, *Under Revision*). Whole saliva samples were collected from participants across the 21 sites in ABCD using the passive drool method. Trained research assistants (RA) oversaw the collection process to ensure adherence to the saliva self-collection protocol. Participants were not asked to refrain from vigorous physical activity 12 hours prior to sampling, or abstain from caffeine intake 12 hours prior to sampling, making these important methodological covariates in the present study. Participants were instructed not to consume any food, beverages (except water), gum, candy, or mints within 30 minutes prior to sample collection, and if sampling after a lunch break, waited 60 minutes before saliva collection[23]. To remove particulates, participants rinsed their mouths with water 10 minutes prior to providing the sample. The RA recorded the collection start date/time and end date/time, the stored the samples in an on-site freezer at temperatures between -80 and -20 degrees Celsius, also recording the date/time sample was put in freezer[24]. Within 2-6 months, the samples were shipped on dry ice to Salimetrics (Carlsbad, CA- an independent laboratory) for assaying and analysis[24]. Saliva samples were assayed for three pubertal hormones: DHEA, testosterone, and estradiol (biological females only at these study timepoints) using Salimetrics' immunoassay protocol. The DHEA assay had a calibrator range of 10.2-1,000 pg/ml, a lower limit of sensitivity of 5 pg/ml, an incubation time of 3.5 hours and a 0.86 correlation with serum levels. The testosterone assay had a calibrator range was 6.1- 600 pg/ml, a lower limit of sensitivity of 1pg/ml, an incubation time of 1.5 hours, and a 0.96 correlation with serum levels[24]. Multiple hormones were assayed in duplicate within a single day to prevent multiple freeze-thaw cycles.

In the present analysis, assayed hormone levels for each timepoint (e.g., B, Y1 and Y2) were determined using a decision tree of quality checks. Saliva samples were excluded if any of the following criteria were met: (1) data did not confirm the participant's sex at birth prior to

sample collection, (2) missing or out-of-range collection time (before 7am or after 9pm) (*Males: n@- B=6, Y1=10, Y2=1; Females: B=4, Y1=8, Y2=6*) (3) missing or excessive collection duration (over 15 minutes) (*Males: B=416, Y1=313, Y2=126; Females: B=442, Y1=287, Y2=111*), (4) missing or implausible wake-to-saliva-collection time (less than 0 seconds or greater than 15 hours) (*Males: B=24, Y1=15, Y2=8; Females: B=23, Y1=14, Y2=7*), (5) missing or negative duration to freezer (*Males: B=73, Y1=38, Y2=19; Females: B=56, Y1=49, Y2=20*), (6) endorsing vigorous physical activity but lasted less than 20 minutes (*Males: Y1=1; Females: B=1, Y2=1*), and (7) missing replicate values across all analytes (*Males: B=302, Y1=695, Y2=1557; Females: B=289, Y1=673, Y2=1377)*. For samples with low intra-assay coefficient of variance (IACV) ≤ 10% and an upper limit of quantification (ULOQ) above the assay's calibrator range, the upper value of the calibrator range was used as a substitute. Substituting LLOQ values with one half of the LLOQ or substituting is an acceptable approach if 10% or less of the observations are substituted[25,26]. Among samples with IACV below 10%, approximately 0.1% to 0.7% of observations across all timepoints were substituted with one half the LLOQ or the value of the ULOQ of DHEA or testosterone. To address samples with high IACV > 10%, participants with insufficient saliva quantity in either replicate value were removed (*Males: B=0.14%*). For participants with high IACV and LLOQ or ULOQ values outside the calibrator range, and if the samples were flagged by a research assistant facilitating saliva collection (for discoloration, chunks, blood, other), those participants were excluded (*Males: B=1.2%, Y1=0.81%, Y2=0.73%; Females: B=0.29%, Y1=2.5%, Y2=0.32%)*. In cases where samples had no IACV because samples were run in singlet, the same exclusion strategy was employed for those participants with LLOQ or ULOQ values outside the calibrator range and flagged by the research assistant (*Males: B=1.4%, Y1=3.7%, Y2=0.69%; Females: B=3.4%, Y2=4.3%).* Where samples had no IACV and

hormone values were LLOQ or ULOQ, yet were not flagged for quality concerns, observations were substituted with one half the LLOQ or the value of the ULOQ (*Males: B=19.1%, Y1=20.1%, Y2=22.4%; Females: B=8.6%, Y1=35.1%, Y2=30.4%).* To maintain the external and internal validity of the study, participants were included in the analyses only if their samples met the quality control metrics outlined.

Covariates

Covariates were identified based on previous literature and a directed acyclic graph (DAG) guided the selection of variables (Figure 4.3). The chosen covariates included child participant's age (months), body mass index (BMI in kg/m), wake-to-collection time (hours), prenatal alcohol exposure (PAE), prenatal tobacco exposure (PTE), rigorous physical activity in past 12 hours (yes/no), and caffeine intake in past 12 hours (categorized as Yes/No). Research has shown that BMI significantly correlates with puberty and impacts hormone levels. In a study involving adolescent males, those with the highest BMI had a greater likelihood of delayed puberty compared to those with lower BMI, while in females, higher BMI was associated with earlier puberty[27,28]. Furthermore, elevated BMI has been linked to lower testosterone levels in obese pubertal males and higher testosterone levels in obese pubertal females[29,30]. Previous research has shown an association between PAE and PTE with HDP and adolescent pubertal development[31–35]. These findings suggest that PAE and PTE may act as potentially act as confounders. To account for diurnal fluctuations in DHEA and testosterone levels, we estimated wake-to-collection time by calculating the difference between when the participant woke up and when the sample was taken[36]. Further, considering the independent associations between caffeine intake, physical activity, DHEA and testosterone levels, both caffeine intake and physical activity were included in our

analyses to ensure methodological precision[37–39]. A description of the variables, as per the NIH NDA data dictionary, is presented in table 4.2.

Statistical Analysis

To investigate the associations between prenatal exposure to HDP and adolescent DHEA and testosterone, we employed separate hierarchical mixed-effects models for each hormone. The full model incorporated HDP-by-age interaction, BMI, PAE, PTE, wake-to-collection time, caffeine intake, and physical activity as fixed effects. To account for the multilevel data structure, a random intercept for the site and random slopes for age and subject ID were included, which allowed for individual variability by age (equation 4.1). All analyses were conducted using R version 4.1.3 (R Foundation for Statistical Computing) with the lme4 package[40,41]. Both fixed and random parameters were estimated using the maximum likelihood method. To address convergence issues, we employed the BOBYQA optimizer and checked model parameters for optimizer accuracy. P-values were obtained using Satterthwaite's method with the lmerTest package[42]. Residual diagnostics were performed at all levels using the HLMdiag package[43]. The models were run separately for biological males and females.

Equation 4.1

$$y_{ijk} = \gamma_{00k} + b_{0j}*age_{ij} + b_{1j}*HDP_j + b_{2j}HDP_j*age_{ij} + b_{3ij}*BMI_{ij} + b_{4j}*alcj + b_{5j}*tob_j + b_{6ij}*waketocol_{ij} + b_{7ij}caf_{ij} + b_{8ij}act_{ij} + U_{[k]} + V_{[j]}k*age_{ij} + \varepsilon_{ijk}.$$

where:

- y_{ijk} is the measured outcome for observation i, participant j, and study site k.
- γ_{00k} is the overall intercept for study site k.
- $b_{0j}*age_{ij}$ represents the overall age/time effect for participant j
- $b_{1j}*HDP_j$, $b_{4j}*alcj$ and $b_{5j}*tob_j$ are the time-invariant covariates (HDP, PAE, and PTE) for participant j, with b_{1j}, $b_{4j,}$ and b_{5j} being their corresponding coefficients.
- $b_{3ij}*BMI_{ij}$, $b_{6ij}*waketocol_{ij}$, $b_{7ij}caf_{ij}$ and $b_{8ij}act_{ij}$ are the time-varying covariates (BMI, wake-to-collection time, caffeine intake and physical activity) for participant j at observation i, with b_{3ij}, b_{6ij}, b_{7ij} and b_{8ij} being their corresponding coefficients.
- $b_{2j}HDP_j*age_{ij}$ represents the interaction effect between HDP and age for participant j
- $U_{[k]}$ is the random intercept term for study site k.
- $V_{[j]}k*age_{ij}$ is the random slope term for age of participant j.
- ε_{ijk} is the error term for participant j at observation i, from study site k.

Results

Table 4.3 and Table 4.4 display descriptive statistics for biological females and males, respectively, across three categories of HDP (No HDP, PR-HTN, and P/E) at three timepoints. The total sample size for females was 8,650, with 3,808 at B, 3,336 at Y1 and 1,506 at Y2. The baseline sample sizes for no HDP, PR-HTN, and P/E were 3,400, 193 and 215, respectively. The mean age was comparable across all HDP groups at each timepoint (mean [SD]: baseline = 118 [7.5] months, year 1= 130 [7.6] months and year 2 = 142[7.6] months). Birthweight was lower for P/E exposed females. This trend persisted across all three timepoints for P/E exposed. Additionally, the proportion of preterm births and mean prenatal visits were higher among P/E exposed females compared to the other groups across all timepoints. No statistical significance was found in prevalence of PAE and PTE as a function of HDP exposure for females. With regard to the pubertal developmental stage, the proportion of participants in mid puberty was highest across all groups and timepoints. As expected, there was an increasing proportion of participants in the late/post pubertal group by year 2.

The total sample size for males was 9,625, with 4,195 at B, 3,744 at Y1 and 1,686 at Y2. The baseline sample sizes for no HDP, PR-HTN and P/E were 3,767, 196 and 232 respectively. The males in this study had a mean age that was similar across all HDP groups at each timepoint (mean [SD]: baseline = 118 [7.6] months, year 1= 130 [7.7] months, year 2= 143 [7.7] months. Birthweight showed significant differences between groups, with the highest mean birthweight seen in the No HDP group and lowest in the P/E group across all sub-samples of participants used at each timepoint. A higher proportion of preterm births were observed in the P/E group, which also had a higher mean number of prenatal visits. The prevalence of PAE was low in all groups, while PTE prevalence was higher in the PR-HTN group, compared to the other groups.

Females

In female participants, significant associations between P/E exposure and higher levels of testosterone (b = 3.8, 95% CI= 2, 6) and DHEA (b=9.5, 95% CI= 3, 16) were observed, compared to the no HDP group (Table 4.5 & Figure 4.4). Notably, the effects of P/E exposure on elevated testosterone and DHEA levels were consistent across time points. No significant differences were observed in the PR-HTN group with either hormone. No significant associations were observed for either PR-HTN nor P/E exposure for T:DHEA ratios.

Males

In male participants (Table 4.6), significant associations between P/E exposure and elevated DHEA levels (b=7, 95% CI= 3,11) and lower T:DHEA ratios (b= -0.1 95% CI= -0.2, -0.006) were observed compared to the No HDP group (Figure 4.5). While DHEA levels increase with age in all HDP groups, the increase with age on DHEA levels was larger in the P/E group in comparison to the increase with age in the no HDP group (b= 7, 95% CI= 3, 11). Among males, elevated testosterone (b= 3.3, 95% CI= 0.8, 5.7) and DHEA (b= 10.7, 95% CI= 5,16) and lower T:DHEA ratios (b= -0.09, 95% CI= -0.2, -0.002) were significantly associated with PR-HTN

exposure, relative to the no HDP group. Additionally, increase with age on the T:DHEA ratio was smaller in the PR-HTN group in comparison to the increase with the in the no HDP group (b= -0.09*, 95% CI= -0.2, -0.002).

Discussion

The current novel findings demonstrate associations between types of prenatal HDP-exposures and subsequent alterations in androgenic hormones during pubertal development in a large pediatric cohort, during the developmental transitional from childhood to adolescence. Specifically, females exposed to P/E showed elevations in testosterone and DHEA. In males, distinct associations were observed for both PR-HTN and P/E exposure. Males exposed to P/E demonstrated elevations in DHEA, while PR-HTN exposure was significantly associated with elevations in testosterone and DHEA. Moreover, males exposed to either PR-HTN or P/E had lower T:DHEA ratios. Our findings highlight that observation of postnatal androgenic hormone differences in females and males depend upon the specific HDP exposure, biological sex, and their interaction with age.

The observed elevations in levels of testosterone and DHEA levels among females exposed to P/E mirrors the androgenic pattern previously reported in preeclampsia-exposed females[44]. A key point to note from the referenced study is the elevated testosterone levels in females with clinically severe preeclampsia, while those exposed to mild-to-moderate preeclampsia were shown to have lower testosterone levels. This observation suggests that the severity of HDP may differentially influence hormonal profiles during puberty. Severe preeclampsia might impose a greater degree of stress on the maternal-fetal systems, potentially resulting in disruptions in cortisol production, which could, in turn, impact testosterone and DHEA levels[45]. However, it is important to note that the current study population lacks information regarding the severity of P/E, or the

disentangling of preeclampsia from eclampsia. Additionally, the referenced study's cross-sectional design precludes definitive conclusions about the relationship between P/E severity and the observed hormonal alterations. Furthermore, the absence of significant associations between testosterone and DHEA levels in females exposed to PR-HTN in our study presents additional interpretative challenges. The observed associations in P/E exposed females may suggest P/E experiences in this study's cohort were severe, contributing to the observed similarities and differences in hormonal profiles. Testosterone and DHEA levels typically surge in adolescent females, coinciding with the developmental stage of adrenarche, which manifests phenotypically as pubarche and increased adrenal activity[9]. Nonetheless, these processes generally follow thelarche in typical female pubertal development[46]. Previous research has indicated that pubarche is initiated before thelarche in females prenatally exposed to preeclampsia[47], suggesting an androgenic influence that may be evident in this population of adolescents. The mechanisms through which females enter puberty may have implications for their future health[48]. Studies have proposed that the advancement of adrenarche, accompanied by elevated levels of testosterone and DHEA, may result in precocious puberty, which could negatively impact a female's hormonal trajectory later in life[46]. Consequently, excessive testosterone and DHEA levels corresponding with the early onset of adrenarche in females during adolescence have been associated with ovarian dysfunction, impaired fertility, polycystic ovary syndrome, and metabolic conditions such as hyperinsulinism and dyslipidemia, type 2 diabetes, and clinical depression[49–53].

Similarly, distinct hormonal patterns in males exposed to different types of HDP were observed. Males exposed to PR-HTN exhibited elevated levels of both testosterone and DHEA. Intriguingly, however, males exposed to P/E displayed elevated levels of DHEA only. The observed disparities between the P/E and PR-HTN groups could be attributed to the presence of

co-occurring factors associated with PR-HTN, including a higher proportion of PTE observed in the PR-HTN group. Prior research has shown that PTE may lead to increased testosterone levels during pubertal development in exposed adolescents[54]. Consequently, it is plausible that PTE may contribute to the observed testosterone elevation in the PR-HTN group. The differential impact of HDP underscores the complex interplay between various prenatal and postnatal factors and their potential influence on hormone profiles during adolescence, necessitating further investigation. Regarding the T:DHEA ratio, our study found that males exposed to both PR-HTN, and P/E exhibited a decreased T:DHEA ratio compared to unexposed males. This decreased T:DHEA ratio in HDP-exposed males might be attributable to the elevated levels of unbound DHEA observed in both PR-HTN and P/E exposed males. This pattern may either represent a typical hormonal trajectory or signal accelerated puberty, an outcome previously reported in children exposed to HDP[55–57]. It is worth noting that the acceleration of puberty often plateaus, and subsequently, affected children may lag behind their peers in terms of further pubertal milestones [58]. However, to ascertain the validity of this hypothesis within HDP-exposed populations in pubertal hormones, future analyses should include all stages of puberty, as well as the post-puberty phase, as the majority of males in the present study were actively undergoing pubertal maturation and not yet post-puberty. Nonetheless, the initiation of androgen activity prior to typical timing in males has been associated with elevated risk-seeking behavior, depression, anxiety, and testicular cancer later in life[59–61].

Hormone measurements during pubertal development are characterized by substantial dynamism and individual variability. The strength of our study lies in leveraging a large epidemiologically representative sample size that includes both biological sexes and the repeated annual hormone measurements during critical periods of hormonal changes. This enabled us to

estimate the individual variability observed in hormone levels during pubertal development. Additionally, while most studies focused primarily on preeclampsia-exposed participants, our study examined PR-HTN as well as P/E, thereby disentangling group differences with regard to the type of HDP. However, the study has certain limitations. One such limitation is the retrospective nature of the HDP questionnaire, which could lead to recall bias or error. Despite this concern, self-reported HDP has been demonstrated to be a reliable depiction of HDP manifestation[62]. Another limitation is the potential for misclassification error, as we cannot ascertain whether the pregnant individuals had a history of chronic hypertension prior to the PR-HTN or P/E. Disentangling chronic history of hypertension from PR-HTN or P/E remains a significant challenge in the field. Moreover, although blood serum levels of hormone are considered the gold standard for measuring circulating hormone levels, the use of salivary measures in our study may lead to overestimation or underestimation of these levels, as they measure unbound testosterone and DHEA levels. Nonetheless, estimates of testosterone and DHEA via saliva have been strongly correlated with blood serum levels showing a correlation of 0.96 for testosterone and 0.86 for DHEA[63,64].

While the findings offer valuable insight into individual variation in androgen hormonal patterns during pubertal development in relation to prenatal HDP exposure and highlights the importance of considering obstetric disorders that result in excessive exposure to androgen hormone *in utero*, further research is necessary to address the limitations and enhance our understanding of the complex interplay between co-occurring prenatal and postnatal factors that may contribute to endocrine alterations. Future studies should consider incorporating a higher frequency of repeated measures to capture tempo of pubertal development as well as measure post pubertal development, utilize more precise hormone measurements to capture bound hormones

and examine potential mediators and modifiers that may affect hormone profiles. Moreover, while this study serves as a foundation for identifying deviations from typical development, future research should delve into the potential long-term health consequences of these hormonal variations, including the risk of developing reproductive, metabolic, or psychiatric disorders.

Conclusions

These novel findings demonstrate associations between types of prenatal HDP-exposures and subsequent alterations in androgenic hormones during pubertal development in a large pediatric cohort. The presence of endocrine alterations during pubertal maturation, from a prenatal HDP exposure underscores the importance of considering common *in utero* exposures relating to obstetric conditions. Overall, these findings emphasize that common exposures such as prenatal HDP are not only a health challenge for the pregnant person, but also impact the developing fetus well beyond the *in utero* exposure, and into postnatal development, making HDP a public health priority.

FIGURES

Figure 4.1. Analytical Sample Inclusion and Exclusion Flowchart

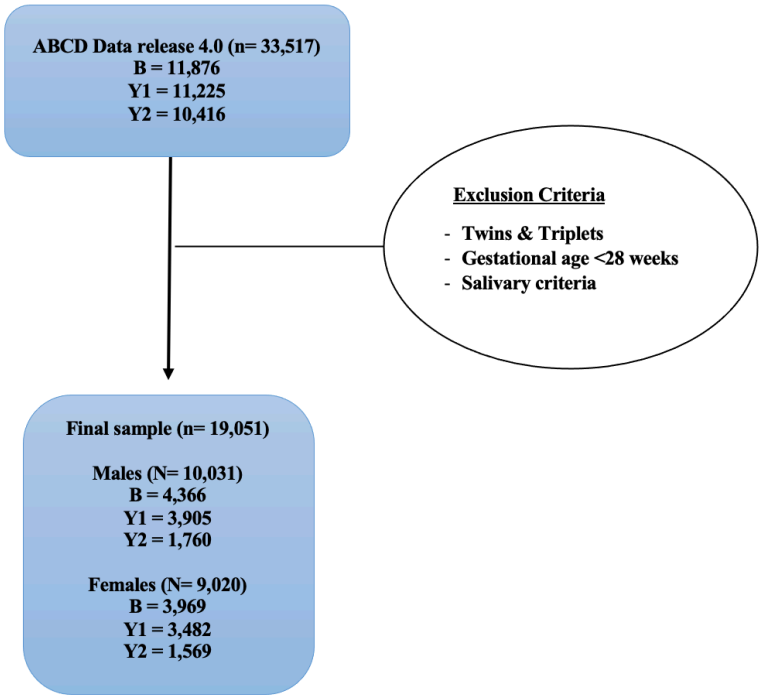


Figure 4.2: Directed Acyclic Graph (DAG)

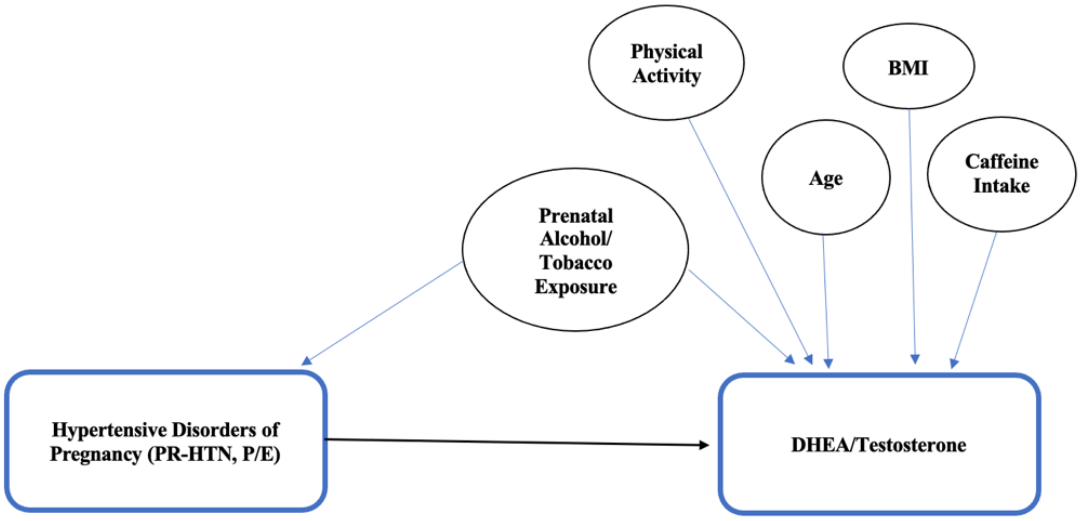


Figure 4.3: Age -related Hormone Profiles in Females Categorized by HDP. For each HDP group (no HDP, PR-HTN and P/E), predicted hormone levels and their corresponding ratio are depicted across age (in months) as follows: (a) Testosterone levels, (b) DHEA levels, (c) Testosterone-to-DHEA ratio. Notably, significant associations were identified between both testosterone (a) and DHEA (b) levels in P/E exposed group.

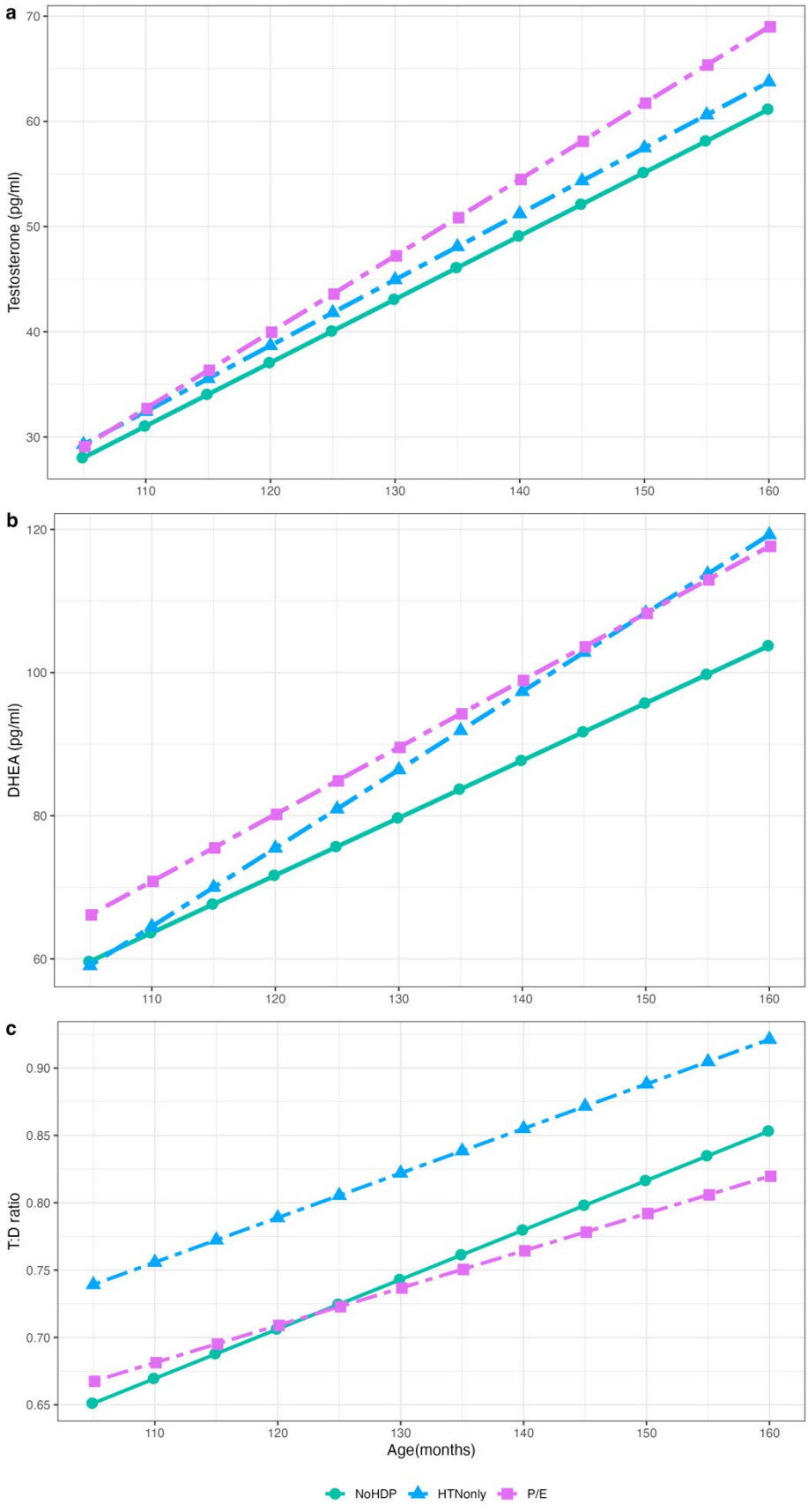
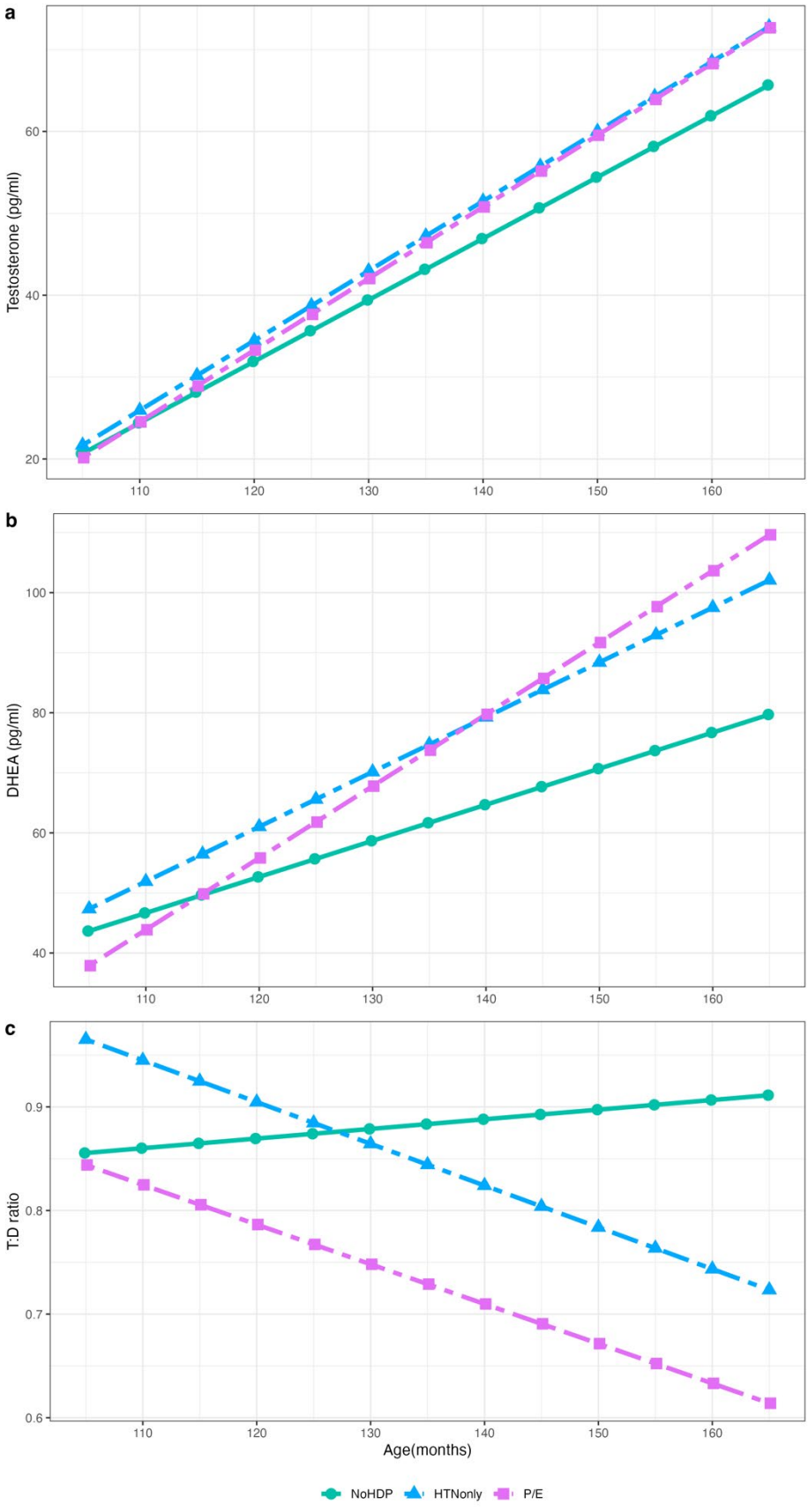

a
Testosterone (pg/ml)
70
60
50
40
30
110
120
130
140
150
160
b
DHEA (pg/ml)
120
100
80
60
110
120
130
140
150
160
c
T:D ratio
0.90
0.85
0.80
0.75
0.70
0.65
110
120
130
140
150
160
Age(months)
NoHDP
HTNonly
P/E

Figure 4.4: Age-related Hormone Profiles in Males by HDP. For each HDP group (no HDP, PR-HTN and P/E), predicted hormone levels and their ratio are depicted across age (in months) as follows: (a) Testosterone levels, (b) DHEA levels, (c) Testosterone-to-DHEA ratio. Notably, significant associations were observed between P/E exposed and the T:DHEA ratio (c) as well as DHEA levels (b), DHEA levels demonstrated an age-dependent pattern. Additionally, PR-HTN exposure was associated with testosterone (a) and DHEA(b) levels, with age-dependent variations observed in the T:DHEA ratio (c).


a
Testosterone (pg/ml)
20
40
60
110
120
130
140
150
160
b
DHEA (pg/ml)
40
60
80
100
110
120
130
140
150
160
c
T:D ratio
0.6
0.7
0.8
0.9
110
120
130
140
150
160
Age(months)
NoHDP
HTNonly
P/E

TABLES

Table 4.1: Prenatal exposure to HDP data. The category HDP was created based on the following questions:

ABCD variable Name	Variable Description	Variable Value
devhx_10c3_p	During the pregnancy with this child, did you/biological mother have any of the following conditions? Pre-eclampsia, eclampsia, or toxemia	1 = Yes; 0 = No; 999 = Don't know
devhx_10j3_p	During the pregnancy with this child, did you/biological mother have any of the following conditions? Pregnancy-related high blood pressure	1 = Yes; 0 = No; 999 = Don't know

Table 4.2. ABCD Description of Covariates used in the study.

ABCD variable Name	Variable Description	Variable Value/Scale/Definition
anthroweight1lb	Make sure shoes and unnecessary layers of clothes (jackets or hats) have been removed before taking weight measurement.) 1. Okay, make sure you empty your pockets for this next measurement. Please stand completely still in the center of the scale with your feet close together, your hands at your side, and your head looking straight ahead. Please stay as still as possible while I measure your weight. (OBTAIN & RECORD WEIGHT #1 (in lbs.))	WEIGHT #1 (measured to the nearest 0.1 pounds)
anthroweight2lb	2. Ok, you can relax and step away from the scale. 3. Now step back on the scale again for another measurement and remember to stand completely still in the center of the scale with your feet close together, your hands at your side, and your head looking straight ahead. Please stay as still as possible while I measure your weight. (OBTAIN & RECORD WEIGHT #2 (in lbs.))	WEIGHT #2 (measured to the nearest 0.1 pounds)
anthroweight3lb	If measurements differ by > 0.1 pounds, the program will prompt you to take a third measurement. 4. Ok,	WEIGHT #3 (measured to the nearest 0.1 pounds

	you can relax and step away from the scale. 5. Please step back on the scale again for another measurement and remember to stand completely still in the center of the scale with your feet close together, your hands at your side, and your head looking straight ahead. Please stay as still as possible while I measure your weight. (OBTAIN & RECORD WEIGHT #3 (in lbs.))	
anthro_weight1_hybrid_lb	Make sure shoes and unnecessary layers of clothes (jackets or hats) have been removed before taking weight measurement.)	[sched_hybrid] = '1'
anthro_1_height_in	STANDING HEIGHT #1 (in inches)	1 ft = 12 inches, 2 ft = 24 inches, 3 ft = 36 inches, 4 ft = 48 inches, 5 ft = 60 inches, 6 ft = 72 inches, 7 ft = 84 inches
anthro2heightin	STANDING HEIGHT #2 (in inches)	1 ft = 12 inches, 2 ft = 24 inches, 3 ft = 36 inches, 4 ft = 48 inches, 5 ft = 60 inches, 6 ft = 72 inches, 7 ft = 84 inches
anthro3heightin	STANDING HEIGHT #3 (in inches)	1 ft = 12 inches, 2 ft = 24 inches, 3 ft = 36 inches, 4 ft = 48 inches, 5 ft = 60 inches, 6 ft = 72 inches, 7 ft = 84 inches
anthroheightcalc	Standing Height Average (inches): If three measurements were obtained, the two closest measurements will be averaged. Should the third measurement fall equally between the first two measurements, all three will be averaged.	if([anthro_3_height_in] <> '', mean([anthro_1_height_in], [anthro_2_height_in], [anthro_3_height_in]), mean([anthro_1_height_in], [anthro_2_height_in]))
hormone_sal_wake_y	What time did you wake up today?	24-hour clock time
hormone_sal_start_y	Hormone saliva sample time collection started?	24-hour clock time

devhx_9_alcohol	Once you /biomom knew you/she were pregnant, were you/biomom using any of the following? Alcohol	1 = Yes, 0 = No, 999 = Don't know.
devhx_9_tobacco	Once you /biomom knew you/she were pregnant, were you/biomom using any of the following? Tobacco	1 = Yes, 0 = No, 999 = Don't know.
hormone_sal_caff_y	Have you had any caffeine in the last 12 hours?	1 = Yes, 0 = No
hormone_sal_active	In the last 12 hours, did you exercise vigorously (sweating, breathing hard) for at least 20 minutes?	1 = Yes, 0 = No
interview_age	Age in months at the time of the interview/test/sampling/imaging.	Age is rounded to chronological month. If the research participant is 15 days old at time of interview, the appropriate value would be 0 months. If the participant is 16-days-old, the value would be 1 month.
src_subject_id	Subject ID how it's defined in ABCD	
site_id_l	Anonymized site name for the participant and visit.	1-21

Table 4.3. Descriptive Statistics for Biological Females

		No HDP	PR-HTN	P/E	Total	p- value*
		n(Baseline)= 3400 n (Year 1) = 2982 n (Year 2) = 1345	n(baseline)=193 n (Year 1) = 166 n (Year 2) = 70	n(Baseline)= 215 n (Year 1) = 188 n (Year 2) =91	N(Baseline)=3808 N (Year 1) = 3336 N (Year 2) = 1506	
Age (months) mean (SD)	*Baseline*	118 (7.5)	117 (7.7)	118 (7.3)	118 (7.5)	.5
	Year 1	130 (7.6)	130 (7.6)	130 (7.3)	130 (7.6)	.8
	Year 2	142 (7.6)	141 (8)	142 (7.4)	142 (7.6)	.3
Birthweight (g) mean (SD)	*Baseline*	3312 (538)	3190 (570)	2984 (747)	3287 (559)	<.001
	Year 1	3327 (533)	3240 (552)	3014 (700)	3305 (549)	<.001
	Year 2	3336 (519)	3336 (491)	2994 (779)	3315(543)	<.001
Gestational term Preterm Term	*Baseline*	268 (7.9%) 3127 (92.1%)	25 (13.2%) 165 (86.8%)	70 (32.9%) 143 (67.1%)	363 (9.6%) 3435 (90.4%)	<.001
	Year 1	216 (7.3%) 2762 (92.7%)	17 (10.4%) 146 (89.6%)	58 (31.4%) 127 (68.6%)	291 (8.7%) 3035 (91.3%)	<.001
	Year 2	87 (6.5%) 1257 (93.5%)	4 (5.7%) 66 (94.3%)	35 (38.5%) 56 (61.5%)	126 (8.4%) 1379 (91.6%)	<.001
Race/Ethnicity Asian/Other/Multiple Black Hispanic White	*Baseline*	448 (13.2%) 471 (13.9%) 800 (23.5%) 1681 (49.4%)	26 (13.5%) 55 (28.5%) 40 (20.7%) 72 (37.3%)	29 (13.5%) 50 (23.3%) 42 (19.5%) 94 (43.7%)	503 (13.2%) 576 (15.1%) 882 (23.2%) 1847 (48.5%)	<.001
	Year 1	393 (13.2%) 349 (11.7%) 692 (23.2%) 1548 (51.9%)	25 (15.1%) 40 (24.1%) 33 (19.9%) 68 (41.0%)	24 (12.8%) 41 (21.8%) 40 (21.3%) 83 (44.1%)	442 (13.2%) 430 (12.9%) 765 (22.9%) 1699 (50.9%)	<.001

	Year 2	161 (12.4%) 120 (8.9%) 311 (23.1%) 747 (55.5%)	10 (14.3%) 14 (20 %) 11 (15.7%) 35 (50%)	11 (12.1%) 15 (16.5%) 20 (22%) 45 (49.5%)	188 (12.5%) 149 (9.9%) 342 (22.7%) 827 (54.9%)	.01
Pubertal Development Stage Pre-puberty Early puberty Mid-puberty Late/Post puberty	*Baseline*	975 (29.1%) 872 (26.1%) 1399 (41.8%) 100 (3%)	41 (21.5%) 51 (26.7%) 86 (45%) 13 (6.8%)	48 (22.9%) 46 (21.9%) 106 (50.5%) 10 (4.8%)	1064 (28.4%) 969 (25.9%) 1591 (42.5%) 123 (3.3%)	.002
	Year 1	321 (15%) 439 (20.6%) 1102 (51.6%) 272 (12.7%)	11 (9.5%) 23 (19.8%) 61 (52.6%) 21 (18.1%)	13 (10.0%) 20 (15.4%) 73 (56.2%) 24 (18.5%)	345 (14.5%) 482 (20.3%) 1236 (51.9%) 317 (13.3%)	.07
	Year 2	17 (5.1%) 40 (12%) 154 (46.1%) 123 (36.8%)	1 (5.6%) 0 (0%) 12 (66.7%) 5 (27.8%)	0 (0%) 3 (12%) 10 (40%) 12 (48%)	18 (4.8%) 43 (11.4%) 176 (46.7%) 140 (37.1%)	.3
Prenatal Alcohol Exposure No PAE Yes PAE	*Baseline*	3296 (97.5%) 86 (2.5%)	182 (95.8%) 8 (4.2%)	207 (98.6%) 3 (1.4 %)	3685 (97.4%) 97 (2.6%)	.2
	Year 1	2890 (97.3%) 79 (2.7%)	156 (95.1%) 8 (4.9%)	179 (98.4%) 3 (1.6%)	3225 (97.3%) 90 (2.7%)	.1
	Year 2	1299 (96.8%) 43 (3%)	67 (95.7%) 3 (4.3%)	87 (100%) 0 (0%)	1453 (96.9%) 46 (3.1%)	.2
Prenatal Tobacco Exposure No PTE Yes PTE	*Baseline*	3238 (95.6%) 148 (4.4%)	169 (88.9%) 21 (11.1%)	197 (92.9%) 15 (7.1%)	3604 (95.1%) 184 (4.9%)	<.001
	Year 1	2845 (95.7%) 128 (4.3%)	147 (89.6%) 17 (10.4%)	172 (93.5%) 12 (6.5%)	3164 (95.3%) 157 (4.7%)	<.001
	Year 2	1299 (96.8%) 43 (3.2%)	62 (88.6%) 8 (11.4%)	81 (91%) 8 (9%)	1442 (96.1%) 59 (3.9%)	<.001
Household Income < 50k ≥ 50k - <100k ≥ 100k	*Baseline*	981 (31.7%) 857 (27.7%) 1255 (40.6%)	82 (45.8%) 55 (30.7%) 42 (23.5%)	77 (38.9%) 56 (28.3%) 65 (32.8%)	1140 (32.9%) 968 (27.9%) 1362 (39.3%)	<.001
	Year 1	770 (28.0%) 745 (27.1%) 1238 (45.0%)	59 (37.3%) 55 (34.8%) 44 (27.8%)	64 (37.0%) 52 (30.1%) 57 (32.9%)	893 (29%) 852 (27.6%) 1339 (43.4%)	<.001
	Year 2	307 (24.7%) 360 (28.9%) 578 (46.4%)	21 (32.3%) 23 (35.4%) 21 (32.3%)	22 (26.8%) 30 (36.6%) 30 (36.6%)	350 (25.1%) 413 (29.7%) 629 (45.2%)	.09
Maternal Age (years) Mean (SD)	*Baseline*	28 (6.3)	29 (6.2)	27 (6.1)	28 (6.3)	.01
	Year 1	29 (6.2)	29 (6.4)	28 (6)	29 (6.2)	.06
	Year 2	29 (6.2)	29 (6.4)	28 (6.3)	29 (6.2)	.7
Prenatal Visits Mean (SD)	*Baseline*	14.4 (4.9)	15.2(5)	16.6 (9.9)	14.6 (5.3)	<.001
	Year 1	14.3 (4.4)	14.9 (4.2)	16.1 (6.4)	14.5 (4.6)	<.001
	Year 2	14.4 (3.6)	14.5 (3)	15 (4.3)	14.5 (3.6)	.09

*p-values derived from ANOVA test (continuous variables) and Pearson's Chi Squared test (categorical variables).

Table 4.4. Descriptive Statistics for Biological Males

		No HDP	**HTN only**	**P/E**	**Total**	**p- value***
		n(Baseline)= 3767 n (Year 1) = 3358 n (Year 2) = 1532	n(baseline)=196 n (Year 1) = 180 n (Year 2) = 74	n(Baseline)= 232 n (Year 1) = 206 n (Year 2) =80	N(Baseline)=4195 n (Year 1) = 3744 N (Year 2) = 1686	
Age (months) mean (SD)	*Baseline*	118 (7.6)	118 (7.4)	117 (7.9)	118 (7.6)	.09
	Year 1	130 (7.7)	130 (7.7)	129 (8.2)	130 (7.7)	.1
	Year 2	143 (7.6)	142 (7.9)	141 (8.7)	143 (7.7)	.3
Birthweight (g) mean (SD)	*Baseline*	3434 (552)	3367 (594)	3125 (754)	3414 (572)	<.001
	Year 1	3445 (550)	3404 (628)	3144 (716)	3427 (568)	<.001
	Year 2	3458 (550)	3267 (664)	3115 (701)	3433 (569)	<.001
Gestational term Preterm	*Baseline*	337 (9%) 3420 (91%)	28 (14.5%) 165 (85.5%)	65 (28%) 167 (72%)	430 (10.3%) 3752 (89.7%)	<.001

Term	*Year 1*	299 (8.9%) 3051 (91.1%)	27 (15.3%) 150 (84.7%)	57 (27.8%) 148 (72.2%)	383 (10.3%) 3349 (89.7%)	<.001
	Year 2	138 (9%) 1391 (91%)	12 (16.7%) 60 (83.3%)	26 (32.5%) 54 (67.5%)	176 (10.5%) 1505 (89.5%)	<.001
Race/Ethnicity Asian/Other/Multiple Black Hispanic White	*Baseline*	468 (12.4%) 513 (13.6%) 850 (22.6%) 1936 (51.4%)	24 (12.2%) 48 (24.5%) 37 (18.9%) 87 (44.4%)	34 (14.7%) 53 (22.8%) 51 (22.0%) 94 (40.5%)	526 (12.5%) 614 (14.6%) 938 (22.4%) 2117 (50.5%)	<.001
	Year 1	409 (12.2%) 390 (11.6%) 766 (22.8%) 1793 (53.4%)	24 (13.3%) 32 (17.8%) 38 (21.1%) 86 (47.8%)	24 (11.7%) 47 (22.8%) 45 (21.8%) 90 (43.7%)	457 (12.2%) 469 (12.5%) 849 (22.7%) 1969 (50.9%)	<.001
	Year 2	156 (10.2%) 125 (8.2%) 334 (21.8%) 917 (59.9%)	9 (12.2%) 13 (17.6%) 18 (24.3%) 34 (45.9%)	10 (12.5%) 16 (20%) 16 (20%) 38 (47.5%)	175 (10.4%) 154 (9.1%) 368 (21.8%) 989 (58.7%)	<.001
Pubertal Development Stage Pre-puberty Early puberty Mid-puberty Late/Post puberty	*Baseline*	1273 (34.1%) 1685 (45.2%) 706 (18.9%) 67 (1.8%)	61 (31.1%) 85 (43.4%) 43 (21.9%) 7 (3.6%)	80 (34.8%) 102 (44.3%) 41 (17.8%) 7 (3%)	1414 (34%) 1872 (45%) 790 (19%) 81 (1.9%)	.3
	Year 1	879 (38.1%) 989 (42.9%) 403 (17.5%) 36 (17.5%)	47 (39.2%) 44 (36.7%) 28 (23.3%) 1 (0.8%)	42 (30.9%) 58 (42.6%) 34 (25.0%) 2 (1.5%)	968 (37.8%) 1091 (42.6%) 465 (18.1%) 39 (1.5%)	.1
	Year 2	134 (36.2%) 143 (38.6%) 73 (19.7%) 20 (38.6%)	11 (52.4%) 4 (19%) 6 (28.6%) 0 (0%)	3 (30%) 5 (50%) 1 (10%) 1 (10%)	148 (36.9%) 152 (37.9%) 80 (20%) 21 (5.2%)	.3
Prenatal Alcohol Exposure No PAE Yes PAE	*Baseline*	3652 (97.6%) 89 (2.4%)	189 (97.4%) 5 (4.2%)	225 (97.4%) 6 (2.6 %)	4066 (97.6%) 100 (2.4%)	.9
	Year 1	3242 (97.3%) 91 (2.7%)	172 (95.6%) 8 (4.4%)	199 (97.5%) 5 (2.5%)	3613 (97.2%) 104 (2.8%)	.3
	Year 2	1480 (97.2%) 43 (2.8%)	69 (93.2%) 5 (6.8%)	75 (96.2%) 3 (3.8%)	1624 (97.0%) 51 (3.0%)	.1
Prenatal Tobacco Exposure No PTE Yes PTE	*Baseline*	3574 (95.2%) 179 (4.8%)	176 (90.7%) 18 (9.3%)	218 (94.4%) 13 (5.6%)	3604 (95.1%) 184 (4.9%)	.01
	Year 1	3189 (95.4%) 155 (4.6%)	163 (91.6%) 15 (8.4%)	195 (95.1%) 10 (4.9%)	3547 (95.2%) 180 (4.8%)	.07
	Year 2	1469 (96.3%) 57 (3.7%)	67 (93.1%) 5 (6.9%)	72 (91.1%) 7 (8.9%)	1608 (95.9%) 69 (4.1%)	.03
Household Income < 50k ≥ 50k - <100k ≥ 100k	*Baseline*	1041 (30.5%) 954 (27.9%) 1419 (41.6%)	83 (45.1%) 53 (28.8%) 48 (26.1%)	89 (41.8%) 53 (24.9%) 71 (33.3%)	1213 (31.8%) 1060 (27.8%) 1538 (40.4%)	<.001
	Year 1	889 (28.8%) 844 (27.3%) 1359 (44.0%)	59 (35.1%) 48 (28.6%) 61 (36.3%)	68 (36.0%) 50 (26.5%) 71 (37.6%)	1016 (29.5%) 942 (27.3%) 1491 (43.2%)	.06
	Year 2	332 (23.3%) 397 (27.8%) 697 (48.9%)	19 (27.9%) 25 (36.8%) 24 (35.3%)	22 (30.1%) 22 (30.1%) 29 (39.7%)	373 (23.8%) 444 (28.3%) 750 (47.9%)	.1
Maternal Age (years) Mean (SD)	*Baseline*	29 (6.1)	28 (6.0)	28 (6.8)	29 (6.1)	.3
	Year 1	29 (6.1)	29 (6.2)	28 (6.8)	29 (6.1)	.3
	Year 2	29 (6.1)	29 (5.7)	29 (7.3)	29 (6.1)	.9
Prenatal Visits Mean (SD)	*Baseline*	14.4 (4.1)	15.4(5)	18 (12)	14.6 (5)	<.001
	Year 1	14.3 (4.1)	15 (5.1)	18.6 (12.5)	14.6 (5)	<.001
	Year 2	14.3 (4.1)	15.2 (5.3)	17 (8.8)	14.5 (4.5)	<.001

*p-values derived from ANOVA test (continuous variables) and Pearson's Chi Squared test (categorical variables).

Table 4.5. Regression coefficients for associations between HDP groups and subsequent testosterone, DHEA and T:DHEA ratios among female participants (No HDP as reference group).

Females	**Testosterone (pg/ml)**	**DHEA (pg/ml)**	**T:DHEA ratio**
	b (95%CI)	**b (95%CI)**	**b (95% CI)**

PR-HTN	1.8 (-0.5, 4.1)	5.9 (-1.0, 12.8)	0.07 (-0.0004, 0.16)
P/E	3.8*** (1.5, 6.1)	9.5** (2.8, 16.1)	-0.004 (-0.08, 0.07)
Age (mos.)	7.1*** (6.6, 7.5)	9.4*** (8.2, 10.7)	0.04*** (0.02, 0.06)
PR-HTN*Age	0.3 (-1.4, 2.0)	3.4 (-1.8, 8.7)	-0.004 (-0.07, 0.06)
P/E*Age	1.5 (-0.2, 3.1)	1.5 (-3.4, 6.5)	-0.01 (-0.07, 0.05)
BMI (kg/m)	0.7*** (0.5, 0.7)	2.3*** (1.9, 2.5)	-0.02*** (-0.02, -0.01)
PAE	-2.3 (-5.4, 0.8)	-6.6 (-15.4, 2.1)	0.02 (-0.1, 0.08)
PTE	0.4 (-2.0, 2.8)	-1.6 (-8.5, -5.2)	0.04 (-0.04, 0.1)
Wake to collect time (hr.)	-0.3 (-0.3, -0.1)	-0.5** (-0.8, -0.1)	-0.002 (-0.007, 0.002)
Caffeine intake	1.6* (0.3, 2.9)	1.6 (-2.1, 5.3)	-0.02 (-0.07, 0.03)
Physical activity	-0.6 (-1.6, 0.4)	-1.3 (-4.3, 1.8)	-0.02 (-0.05, 0.02)
Observations	8546	8517	8494
Log likelihood	-36644	-45534	-8755
Akaike Inf. Crit.	73322	91102	17545
Bayesian Inf.Crit	73442	91222	17665

Table 4.6. Regression coefficients for associations between testosterone, DHEA and T:DHEA ratios with HDP categories among male participants (No HDP as reference group).

Males	**Testosterone (pg/ml)**	**DHEA (pg/ml)**	**T:DHEA ratio**
	b (95%CI)	**b (95%CI)**	**b (95% CI)**
PR-HTN	3.3**	10.7***	-0.04

	(0.8, 5.7)	(5, 16)	(-0.2, 0.06)
P/E	2.3 (-0.008, 4.6)	7.7** (2, 13)	-0.1* (-0.2, -0.006)
Age (mos.)	8.8*** (8.3, 9.4)	7.1*** (6, 8)	0.1*** (0.10, 0.14)
PR-HTN*Age	1.1 (-1.3, 3.6)	3.6 (-0.8, 8.2)	-0.09* (-0.2, -0.002)
P/E*Age	1.4 (-0.8, 3.8)	7** (3, 11)	-0.05 (-0.1, 0.03)
BMI (kg/m)	0.003 (-0.006, 0.01)	0.01 (-0.009, 0.03)	-0.0002 (-0.0006, 0.0001)
PAE	-0.6 (-3.7, 2.4)	-0.9 (-8, 6)	-0.02 (-0.2, 0.1)
PTE	3.5** (1.2, 5.9)	7.3** (2, 13)	-0.04 (-0.1, 0.06)
Wake to collect time (hr.)	-0.5*** (-0.6, -0.3)	-0.6*** (-0.9, -0.3)	0.002 (-0.004, 0.007)
Caffeine intake	1.01 (-0.4, 2.4)	3.4* (0.2, 7)	-0.04 (-0.1, 0.02)
Physical activity	-1.5** (-2.6, -0.4)	0.4 (-2, 3)	-0.03 (-0.07, 0.02)
Observations	9485	9363	9335
Log likelihood	-42061	-48719	-11756
Akaike Inf. Crit.	84156	97472	23547
Bayesian Inf.Crit	84278	97593	23668

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CONCLUSIONS

The global rise in hypertension and related disorders during pregnancy is alarming. Numerous studies have explored the detrimental health consequences of HDP on pregnant individuals, providing evidence that pregnancy can serves as a window into their future health. However, the potential implications of HDP on the long-term health of the exposed fetus have received limited attention. My dissertation study aimed to address this knowledge gap by investigating whether HDP could also offer insights into the child's future health trajectory.

In human life, there are two critical developmental stages that lay the groundwork for an individual's future health trajectory: the fetal stage and the adolescent stage. Both periods are characterized by rapid differentiation and a need for hemodynamic balance of growth factors. During these stages, the central nervous system and the endocrine system provide a foundation for other essential neurophysiological systems including the cardiovascular and metabolic systems. Despite their importance, few studies have examined the long-term impact from disruptions in one stage to the next using physiological biomarkers, which often serve as indicators of health or potential health issues. In my dissertation, relatively non-invasive biophysiological measures (structural magnetic resonance imaging (sMRI), diffusion tensor imaging (DTI), salivary hormone levels) were leveraged to identify differences in developmental brain and endocrine patterns with prenatal HDP-exposure, with the overarching aim to inform future tools to identify and predict risks for pathological health challenges.

As the fetal stage establishes the architectural foundation for neurodevelopment and subsequent postnatal development, I hypothesized that early adolescence, marked by heightened sensitivity in neurodevelopment and pubertal maturation, may exhibit more discernable

differences resulting from short-term fetal adaptations. I examined whether changes in the cortical and subcortical brain areas, white matter tracts, and peripheral androgen hormone profiles contribute to deviations in developmental patterns among adolescents with prenatal exposure to HDP.

The Developmental Origins of Health and Disease (DOHaD) framework served as the theoretical foundation for this dissertation, examining fetal adaptations in response to challenging *in utero* conditions and their potential long-term physiological consequences throughout an individual's life. Given a robust literature demonstrating that *in utero* disruptions can lead to adverse future health, I argued that it is crucial to investigate the effects of these disorders in adolescence. A comprehensive understanding of these long-term adaptations may offer insights into diseases that contribute significantly to the US health burden, including neurobehavioral and neurocognitive disorders, metabolic syndrome, and vascular dementia. These conditions are all potential candidates for enduring health impacts resulting from prenatal HDP exposure and the postnatal alterations identified in my dissertation.

Summary of Findings

In chapter 2, I examined the association between HDP and longitudinal measures of structural cortical and subcortical brain volume in adolescents. I considered three distinct categories of HDP: pregnancy-related hypertension, preeclampsia/eclampsia and no HDP, which represent different pathophysiological manifestations of the disorder. Additionally, I investigated the extent to which intracranial volume (ICV), reflecting individual differences in brain development, mediated this association. I found that:

Within the pregnancy-related hypertension group,

1. Females showed a lower volume that was partially mediated by ICV in 3 bilateral hemispheric regions and 1 left hemispheric region- bilateral insular cortex, bilateral putamen, bilateral nucleus accumbens, and the left caudate nucleus.
2. Males showed a lower volume, that was not mediated by ICV, in the 2 bilateral hemispheric region and 5 right hemisphere regions: bilateral superior frontal gyri, bilateral caudate nuclei, the right insular cortex, the right caudal middle frontal, the right isthmus cingulate, right lateral orbitofrontal, right medial orbitofrontal.

Within the Preeclampsia/Eclampsia group,

1. Females showed a lower volume, not mediated by ICV, in 1 bilateral region: bilateral putamen
2. Males showed a lower volume, that was partially mediated by ICV, in 2 bilateral region, 1 left hemispheric region and 1 right hemispheric region: bilateral pars orbitalis, bilateral caudate nuclei, left insula cortex and right rostral middle frontal.

Direct effects of P/E were observed in subcortical regions, such as the putamen and caudate nucleus, which are common sites for hemorrhagic stroke in neonates exposed to HDP. These findings raise the possibility that cerebrovascularization may well be affected to a lesser extent, not resulting in mechanical stress and thus a stroke, but instead leading to reduced perfusion and lower subcortical volume as a long-term adaptation. Additional support for the observed findings being attributable to *in utero* perturbations, rather than postnatal factors associated with HDP, is the increased sensitivity of right-brain structures to HDP. This finding aligns with the theory that right-brain structures develop earlier in gestation, making them more susceptible to *in utero* insults.

The distinct direct effects of HDP on males and females, where females experience direct impacts from P/E and males from PR-HTN, raise questions about sex differences in fetal coping mechanisms during *in utero* development. These findings may partially support the hypothesis that male fetuses tend to withstand hypertension (often leading to preeclampsia in late gestation), while female fetuses, when distressed due to HDP, are more likely to induce early labor.

In chapter 3, I focused on the longitudinal impact of HDP on white matter connectivity in adolescents. I hypothesized that HDP would be a significant predictor of white matter characteristics, given that fetal development is when the blueprint of white matter tracts is laid out and adolescence is a period of synaptic pruning and myelination of these tracts. Using fiber volume and fractional anisotropy as characteristics of white matter development, I found support for the *a priori* hypothesis that prenatal exposure to HDP may be a predictor of white matter development but only in females exposed to PR-HTN. I found:

1. Females exposed to PR-HTN showed lower fractional anisotropy and lower fiber volume in 3 midline regions- the corpus callosum, forceps minor, and forceps major.

2. Females exposed to PR-HTN showed lower fiber volume in 6 bilateral white matter tracts- fornix, cingulum, anterior thalamic radiation, uncinate fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus.

Arguably, these findings offer some support for the brain-sparing mechanism of the DOHaD framework. However, it is more plausible that the brain may not be entirely spared. It could be that specific fetal brain structures, such as centers for respiration and movement, are spared, while other areas that develop during adolescence or are more important in later life

are compromised. From an evolutionary perspective, this adaptation may be beneficial for the *in utero* environment, but it may be less advantageous during adolescence and later life.

In chapter 4, I assessed the extent to which HDP contributed to androgenic hormonal variations in longitudinal testosterone and DHEA measures among the adolescents. I tested whether PR-HTN or P/E was associated with levels of salivary testosterone, DHEA, and T:DHEA ratios. Similar to existing literature, my results confirm an androgenic pattern in those exposed to HDP. I also observed distinct patterns dependent upon type of HDP when compared to the unexposed group:

1. Females exposed to P/E had elevations in testosterone and DHEA levels
2. Males exposed to P/E had age-related increases in DHEA levels and a lower T:DHEA ratio
3. Males exposed to PR-HTN had elevated testosterone and DHEA levels and age-related decreases in T:DHEA ratios.

These findings emphasize the significance of considering prenatal HDP exposure for expanding and accelerating understanding of pubertal development and may implicate several physical and mental health challenges linked with endocrine alterations.

Study Implications

The findings of this dissertation have significant contributions to the literature. The results reveal that different types of HDP exposures can have varying impacts on child and adolescent development. This complements existing studies that emphasize the need to examine how HDP may be associated with physiological alterations during adolescence that may be on the path to pathological challenges. Although few studies focus on PR-HTN, this dissertation offers

preliminary empirical evidence that it should be considered more in research. Moreover, the treatment strategies and behavioral modifications employed for P/E during pregnancy may have some protective effects on the child. Thus, when hypertension is detected and treated early and effectively, it may benefit both the pregnant individual and the child.

This research also has important implications for the broader literature on adolescent health and development. Numerous co-occurring factors, such as the pandemic (pre and post resources), socioeconomic status, and adverse childhood experiences (ACEs), could contribute to the observed deviations. All these factors might further contribute to the mismatch between prenatal and postnatal environments. While postnatal experiences such as ACEs have received more attention, many studies still treat influences on adolescent development as homogenous factors, which essentially masks the differential cumulative impact that prenatal factors during sensitive period of development may have. This is a significant limitation given the rise in HDP and the increasing maternal morbidity crisis in the US. Furthermore, this study highlights that the *in-utero* environment may uniquely shape how we physiologically respond to adverse experiences during adolescence. It is crucial to distinguish between factors that disrupt development and those that are based on developmental plasticity and may have adaptive value. Since development is dynamic, especially for the brain and endocrine systems during sensitive years, growth catch-up may occur later in life, implying that these findings do not necessarily indicate causal pathways. However, the impact of these factors may depend on the timing of exposure during critical windows of susceptibility. Additionally, the most relevant exposure may not be a single event but may instead reflect multiple hits over time. Given that development is influenced by various factors, studying only one prenatal factor may not provide a complete picture of the actual impact, which could be due to a constellation of pre- and post-natal factors and is therefore, contextual. For instance, in

this study population, prenatal tobacco exposure (PTE) was found to be more prevalent among those with PR-HTN, suggesting that co-occurring exposures associated with PTE may partly contribute to some of the lasting developmental alterations related to HDP. However, since PTE was observed in only a minority of participants, HDP still has long-term effects above and beyond co-occurring exposures.

In conclusion, HDP occurring during time-specific phases of fetal development may interact with genotypic variations and postnatal factors, resulting in a cumulative, time-dependent heightened vulnerability to long-term maladaptation. This may partially account for the patterns of chronic disease manifestation observed in our communities. It is essential to recognize that the origins of diseases begin during developmental stages of life. Future research should explore the interplay between prenatal and postnatal factors associated with HDP in adolescent health, as well as the specific functional outcomes of the observed brain and endocrine alterations.