Hypertension, Rheumatoid Arthritis, and Hypothyroidism in Women Born Preterm of the Women's Health Initiative

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HYPERTENSION, RHEUMATOID ARTHRITIS, AND HYPOTHYROIDISM IN WOMEN BORN PRETERM OF THE WOMEN’S HEALTH INITIATIVE

BY

PAMELA L. BREWER

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

NURSING

UNIVERSITY OF RHODE ISLAND

2022
Abstract

Advances in perinatal and neonatal management, along with improved healthcare technologies, have increased the long-term survival of individuals who were born preterm. Millions of preterm birth survivors now reach adulthood. Premature birth, defined as birth before 37 weeks gestation, predisposes individuals to adverse health risks later in life. The Developmental Origins of Health and Disease (DOHaD) theory was used as a framework for this dissertation. The main tenets of the DOHaD theory are that early birth infers immature organ development and when coupled with maternal, neonatal, and environmental stressors, long-term health consequences and/or chronic disease may result. International studies report that preterm-born adults are at higher risk for hypertension and cardiovascular disease (CVD) compared to adults born full term. High blood pressure, beginning earlier in life, increasing faster in women, and often undiagnosed, is the strongest risk factor for CVD. In the U.S., preterm-born adult research is limited, raising questions about the development of hypertension and risk for CVD-associated comorbidities, especially in women.

This dissertation examined preterm birth and adult hypertension, CVD risks, and comorbidity in three manuscripts. Manuscript I is a state-of-the-science report that informs nurse clinicians about emerging evidence on premature birth and adverse cardiovascular outcomes in adulthood. Manuscripts II and III are secondary data analyses of the Women’s Health Initiative Observational Study, a long-term national health study of 93,676 postmenopausal adult women, of which 2,303 were born preterm. Manuscript II examined the associations of hypertension and CVD in preterm-born women compared to their term-born peers. In Manuscript III, the cumulative prevalence of three CVD-
associated conditions (hypertension, rheumatoid arthritis (RA), and hypothyroidism) were investigated by birth status (preterm vs. full term) in postmenopausal adult women.

The results revealed that prematurity was associated with an elevated CVD risk. Women born preterm had higher prevalence, incidence, and earlier onset of hypertension that required more antihypertensive medications for blood pressure control than age-matched women born full term with hypertension. Preterm birth was also associated with higher occurrence of hypertension, RA, and hypothyroidism alone and in combination, potentially amplifying CVD risk. It is imperative for clinicians and preterm-born individuals to recognize that prematurity history may infer higher and earlier risk for CVD events. Early identification and treatment of hypertension and CVD comorbid conditions are important to mitigate the risk for CVD morbidity and mortality. In routine clinical encounters, birth history should be discussed and documented. Use of preemptive cardioprotective treatment strategies could prevent or reduce CVD for at-risk individuals who were born prematurely.
Acknowledgements

This dissertation was possible because of the many people who supported me.

My sincerest and deepest gratitude to my co-major professors, Dr. Mary Sullivan and Dr. Amy D’Agata, for your mentorship, patience, and support. It has been an honor to work with you. Your experience and expertise have been instrumental in my completing this work.

Mary, thank you for sharing your vast knowledge, experience, and passion. You provided opportunities to learn, shared your knowledge, research, dedicated scholarly assistance, encouragement, and persistence. I am thankful you agreed to see me through this process.

Amy, thank you for your willingness to impart your knowledge. I have learned much from you. Your wisdom, support, and invaluable input will stay with me forever.

I also express my sincerest gratitude to my committee members, Dr. Christie Ward-Ritacco, Dr. Ami Vyas, and Dr. Steve Cohen. Christie, your passion and devotion to teaching has encouraged me to enthusiastically pursue my professional goals. Thank you for being available to me, even at the last moment. Dr. Vyas, you inspired me to conceptualize health beyond nursing and forced me to broaden my perspective. You supported me and guided me in ways I could never have imagined. Steve, I felt an instant connection with you as a person I wanted to learn from. Your kind, supportive demeanor is an exemplar of a mentor, and your research inspires me to be a better scientist. Thank you to all of you for being so generous with your time and support during this process. I am very grateful.
Thanking those closest to me is hard because words will never suffice. I am truly blessed with a family that loves and supports me. There are no words to describe how thankful I am to my family - Rex, David, Gabrielle, and Ben - for all you have done to support me in my journey. I could not have done this without you. I love you and thank God for each one of you.

To my husband, Rex, for his enduring love and patience. Thank you for taking caring our family so I could focus on school and for your everlasting support, guidance, and encouragement. I am forever grateful to you and your sacrifices on my behalf.

To my children, my miracle babies, and my biggest fans - you bring tremendous joy to my life, and I hope my research will enable a better life for you. I pray I have inspired you to pursue your dreams, and I know I could not have done this without your love, support, and understanding.

Lastly, I would be remiss if I did not share a special thank you to Mary Roberts, my WHI data and statistical expert and Dr. Michelle Kelly, my Villanova confidant. I am blessed for all your support and guidance and for helping me stay on track. Your words of encouragement always arrived when most needed. Thank you.

I am professionally and personally indebted to this research. I pray these findings promote further research that will better the lives of individuals who have overcome the odds and survived preterm birth.
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Chapter 1: Introduction

Roughly 400,000 live-born infants, or one out of ten, are born preterm in the United States (U.S.) each year (Blencowe et al., 2013; Martin et al., 2021). Perinatal advancements have dramatically increased survival rates over the past three decades, introducing a new population of adults—adults born preterm. These individuals overcame an abrupt transition to extrauterine life at a time when organogenesis may have been incomplete. Postnatal exposure to hyperoxia, potentially unfavorable treatments, and inadequate nutrition may have enduring effects on underdeveloped body systems (Doyle et al., 2017; Martin et al., 2009; Raju, Buist, et al., 2017; Saugstad, 2001; Schreuder et al., 2011). Developmental programming through epigenetic modifications may cause permanent anatomical, physiological, and metabolic alterations that contribute to later-life disease (Barker, 2007; Wadhwa et al., 2009).

Preterm birth, defined by the World Health Organization (WHO), is a birth before 37 weeks gestation, that is further divided into subcategories based on weeks of completed gestation (World Health Organization, 2018). Epidemiological studies have associated preterm birth with increased metabolic and cardiovascular risks in adulthood (Andraweera et al., 2021; Darlow et al., 2019; Flahault et al., 2019; Kajantie & Hovi, 2014; Markopoulou et al., 2019; Morrison et al., 2016; Sipola-Leppanen, Vaarasmaki, et al., 2015). Previous studies have focused on those born with low or extremely low birth weight, irrespective of gestational age, despite 85% of preterm births being moderate–late preterm, defined as a birth between 32 to < 37 weeks gestation (Barker, 1998; Gluckman et al., 2008). Improved survival rates have enabled the study of those born with the lowest birth weights and earliest gestational ages (Crump, 2021; Risnes et al., 2021).
Surprisingly, emerging findings imply that adverse long-term health outcomes are not limited solely to those born extremely preterm (< 28 completed weeks of gestation). Adults born moderate-late preterm seem to be at as high risk, if not higher, than adults who were born extremely preterm (Kajantie et al., 2019).

Detection of increased adverse cardiovascular health risks for adults born preterm is prompting a shift in research from strict focus on perinatal and early neonatal management to an inclusion of survivors’ later-life health and functional outcomes. Findings in the literature support a strong association between preterm birth, elevated blood pressure, and risk for development of hypertension, which is inversely related to gestational age at birth and more pronounced in women (Crump et al., 2011b; Haikerwal et al., 2020; Jones et al., 2019; Mohamed et al., 2021; Skudder-Hill et al., 2019).

Hypertension is the leading cause of cardiovascular disease (CVD), contributing to over 10 million deaths worldwide annually (Center for Disease Control and Prevention, 2021b). The physiological mechanisms that link preterm birth to elevated blood pressure are yet to be fully understood (Flahault et al., 2019). A suboptimal intrauterine environment and disrupted growth and development of the cardiovascular and renovascular systems are potential mechanistic and systemic links for higher blood pressure in adults born preterm. Blood pressure tends to rise with age, yet the trajectories and impact of elevated blood pressure on CVD risk in adults born preterm are unknown (Gurven et al., 2012). There is still much to learn and many unknowns that affect adult health outcomes for individuals born preterm (Lewandowski, 2022; Sullivan et al., 2008).

This dissertation is a cohesive document of secondary data designed to investigate the health trajectories and outcomes of adult women 50 years of age and older who were
Women who participated in the national Women’s Health Initiative Observational Study (WHI-OS), a longitudinal women’s health study, provided over eight years of health data for this dissertation. A more detailed description of the WHI will be discussed later in this chapter and again in Chapter 2.

Three separate, but related publication-quality manuscripts, assemble this manuscript-style dissertation. Each manuscript addresses a condition or adverse health effect associated with preterm birth. Manuscript I is a brief review that systematically summarizes the current research to show the adverse effects of prematurity on the cardiovascular system. Manuscripts II and III report the findings from two data-based research analyses in adult women born preterm.

This introductory chapter describes the importance of the problem, the supporting research evidence, and a brief introduction of the theoretical foundation that supports the three conditions presented. All discussions center on analyzing the significance of health outcomes in adult women born preterm. Chapter 2, “Literature Review,” presents findings from the most recent research pertinent to hypertension and its relationship with the two common non-communicable diseases. This research is examined through the lens of prematurity. Gaps in the literature and areas for further investigation are outlined. Chapter 3, “Methodology,” presents the research design, the sample population, definitions of outcomes, and statistical analyses. Chapter 4, “Manuscript I,” the publication “A new cardiovascular disease risk factor for young adults: Preterm birth” is a state-of-the-science review that identifies current knowledge about preterm birth, hypertension, and CVD risks in adults born prematurely. A comprehensive overview of research findings and clinical implications are included. Chapters 5, “Manuscript II” and
6, “Manuscript III” synthesize the findings of the two WHI-OS data-based research studies. Chapter 7, “Discussion and Implications” is the concluding chapter, summarizing each manuscript’s significant findings, discussions, and recommendations for research, clinical practice, theory, and policy. The dissertation chapters are integrated and progress logically, forming a unified and consistent report of the research undertaken.

Statement of the Problem

Millions of survivors of preterm birth are approaching adulthood or have already become adults. Emerging evidence associates preterm birth with a higher prevalence of a variety of adult chronic, non-communicable diseases such as ischemic heart disease, hypertension, hyperlipidemia, heart failure, diabetes, obstructive lung disease, and kidney disease in adulthood (Crump, 2020a; Crump, Howell, et al., 2019; Heikkila et al., 2021; Heo & Lee, 2021; Mohamed et al., 2021). Although mechanisms for increased cardiovascular risks are not yet fully understood, it is becoming apparent that adults born preterm may be prone to heart morphology and functional modifications (Schuermans & Lewandowski, 2022). The as-yet-unknown pathogenesis of these cardiac changes may put preterm-born individuals at increased risk for CVD (Lewandowski, 2022). Emerging and growing knowledge about these increased risks for adults born preterm makes it necessary to assess whether traditional strategies for reducing CVD risk are effective in this population. Likewise, the long-term impact of standardized neonatal screening and treatment as well as adult treatments and therapeutic approaches to disease prevention in adults born preterm must be called into question.

Large-scale birth registry and observational cohort studies have revealed an association between preterm birth and increased risk of hypertension in preterm-born
cohorts compared to age-matched, full-term born peers (Crump, 2020a; Crump et al., 2011b; Lewandowski et al., 2020; Sullivan et al., 2019). This association is independent of traditional biological risk factors, such as elevated cholesterol and blood glucose levels, implying different pathophysiological mechanisms (Flahault et al., 2020; Lewandowski et al., 2020; Schuermans & Lewandowski, 2022). This undetermined pathophysiology may be responsible for elevated CVD risk in preterm-born individuals (Flahault et al., 2020).

Most previous epidemiologic studies on developmental programming have focused on low birth weight, irrespective of gestational age, and its association with adult chronic disease (Barker, 1998; Gluckman et al., 2008). Studies relating gestational age to elevated blood pressure were primarily comprised of children and adolescents who were low birth weight infants (Cooper et al., 2009; Doyle et al., 2003; Hack et al., 2005; Johansson et al., 2005; Keijzer-Veen et al., 2010; Keijzer-Veen et al., 2005; Kistner et al., 2000; Lawlor et al., 2007; Siewert-Delle & Ljungman, 1998; Stevenson et al., 2001). Studies that have investigated the relationship between middle-aged preterm-born individuals and the risk of developing adult hypertension, the age when first diagnosed with hypertension, and the difficulty in controlling blood pressure are rare (Bertagnolli et al., 2016; Jones et al., 2019; Mohamed et al., 2021; Sipola-Leppanen, Karvonen, et al., 2015). Factors that could potentially mitigate the adult development of CVD associated with gestational age at birth and CVD development remain undetermined (Crump, Howell, et al., 2019; Kajser et al., 2008; Kajantie et al., 2015; Lawlor et al., 2005; Ueda et al., 2014; Zoller et al., 2015).
In 2018, 27.2% of U.S. adults (≥ 18 years of age) were living with multimorbidity, or the co-occurrence of two or more chronic, non-communicable diseases (Boersma et al., 2020; Heikkila et al., 2021). Multimorbidity was more common in U.S. women (28.4%) than men (25.9%) and increased with age (Boersma et al., 2020). Preterm birth may be a risk factor for other comorbidities besides the known CVD-related morbidities (Heikkila et al., 2021). Researchers estimate that preterm-born children and young adults have up to a four-fold increase in risk of metabolic, respiratory, neuropsychiatric, and cognitive comorbidities relative to the degree of prematurity compared to the general population of infants born full term (Crump et al., 2016; Heikkila et al., 2021). Similarly, women born preterm have a greater prevalence of comorbidities compared with their counterparts who were born full term (Crump, 2020a; Heikkila et al., 2021). Studies support the association of chronic disease multimorbidity in younger preterm-born populations and women, though the underlying mechanisms linking preterm birth and chronic disease are unclear (Crump, 2020a; Heikkila et al., 2021; Luu et al., 2016; Raju, Buist, et al., 2017).

Rheumatoid arthritis (RA), an autoimmune and chronic inflammatory disease, predominantly affects women more than men, beginning in the third decade of life (American College of Rheumatology, 2021; Favalli et al., 2019). The exact cause of RA is not fully understood, and there is no cure. The chronicity of the disease eventually elicits multisystem involvement, often causing visual impairment, inflammatory damage to the lungs and blood vessels, and CVD (Arthritis Foundation, 2021). The inflammatory process of RA triggers an excess of free radicals, creating a state of oxidative stress. Oxidative stress on organ and vascular systems contributes to dysfunctional and damaged
vasculature, resulting in increased blood pressure and atherosclerosis (Crowson et al., 2013). Results in the literature that associate preterm birth with immune and vascular immaturity substantiate the hypothesis that middle-aged preterm-born women might have a higher prevalence of chronic conditions like RA. Although plausible, this possible relationship is unknown because it has not been well-studied (Carlens et al., 2009; Simard et al., 2010).

*Hypothyroidism*, also known as underactive thyroid disease, is a chronic condition of thyroid dysfunction that results in deficient production of thyroid hormones (Muñoz-Ortiz et al., 2020). The reported prevalence of hypothyroidism in the U.S. varies between 0.3% and 3.7% (Muñoz-Ortiz et al., 2020). Hypothyroidism is more common than hyperthyroidism in the U.S. and is five to 10 times more common in women than men (Dunn & Turner, 2016; Muñoz-Ortiz et al., 2020). Hypothyroidism is also commonly detected in individuals with autoimmune disorders (Dunn & Turner, 2016; Muñoz-Ortiz et al., 2020). The occurrence of hypothyroidism increases with age, is a lifelong condition, predisposes the individual to CVD, and is often of unknown etiology (American Thyroid Association, 2020; Dunn & Turner, 2016; Garber et al., 2006).

The research on hypothyroidism in adults born preterm, like RA, is rare. Few studies have explored thyroid levels in neonates and young children born preterm (Posod et al., 2017; Radetti et al., 2007; Vigone et al., 2014). One study of young adults (25.5–37.0 years) found the preterm cohort to be almost two times more likely to have hypothyroidism that required treatment compared to their counterparts of similar age who were born full term (Crump et al., 2011a).
Since the health trajectories and disease sequelae are understudied in U.S. preterm-born adult populations, the consequences of preterm birth and long-term health implications are largely unknown. As discussed, emerging research has found an association between prematurity and adverse cardiovascular health and related comorbidities. Women are at greater risk for many of these chronic conditions. Literature on women’s cardiovascular health is limited and literature on U.S. adult women born prematurely is rare; both public health issues warrant further study and understanding. Knowledge gaps exist regarding the prevalence, incidence, and health outcomes for the population of adults born preterm. Mechanistic pathways are hypothesized but are not substantiated. The knowledge gained from this research will facilitate greater understanding of health consequences for adults of preterm birth and could translate into evidence-based practice recommendations.

In review, it is reasonable that three potentially life-threatening medical conditions—hypertension, RA, and hypothyroidism—may be more common in preterm-born women who have altered physiology due to preterm birth compared to full-term born women. Adult cohorts of prematurely born individuals are few, so the WHI-OS was an ideal U.S.-based database to investigate and compare the occurrence of these conditions to women born full term. There was and continues to be no other U.S. sample of this size and population; the WHI-OS is comprised of 2,303 adult women born preterm.

The lack of research concentrated on health trajectories of U.S. adults born preterm led to this investigation. Knowledge gaps support the overarching research objectives for this dissertation. The implications of this research are essential for clinical
practice, theory, and subsequent research. For example, recognizing prematurity as a chronic health condition, as recommended by Raju et al. (2017), can positively change the practice behaviors and strategies of healthcare providers. Development of care guidelines unique to preterm-born populations across the lifespan is necessary in the same way that guidelines for other chronic conditions have been developed. Recognizing prematurity as a risk factor for CVD is imperative for healthcare providers. Educational implications for healthcare providers, family members/parents of the individual born preterm, and individuals themselves who were born preterm can result in early screening and identification, health promotion counseling, and strategies to lessen potential adverse health outcomes. Theoretical implications strengthen the underpinnings of the DOHaD framework and encourages more epigenetic research. Findings have the potential to advance knowledge about the long-term health implications of prematurity. Data from this study may reveal practical clinical implications for lifelong health outcomes in preterm-born individuals. This work may also inform future large prospective longitudinal research designed to understand the impact and timing of health consequences associated with prematurity. Hypertension, RA, and hypothyroidism are lifelong progressive diseases linked to increased morbidity and early mortality. The value of these findings is significant to all women regardless of birth status.

**Significance of Problem**

**Prematurity**

The long-term health outcomes of individuals born preterm are unknown. Thus, findings have not yet transitioned into practice. Few cohorts of adults born preterm exist, and those that do are small (Kajantie et al., 2021). Much of the knowledge regarding the
long-term health of adults born preterm originates from registry studies in Nordic areas or international case-control cohort studies (Kajantie et al., 2021; Raju, Buist, et al., 2017; Sullivan et al., 2008). Research has identified distinct anatomical and physiological modifications in the cardiopulmonary and renovascular systems of preterm-born individuals, labeling these features as “a unique phenotype of prematurity.” (Bates et al., 2020; Duke et al., 2022; Erickson et al., 2019; Heikkila et al., 2021; Leeson & Lewandowski, 2017; Lewandowski & Leeson, 2014). Current literature supports the heightened risk for comorbidities and chronic health conditions, recognizing a gradient of good-to-poor health outcomes based on gestational age. Yet how and which of these unique phenotypes of prematurity manifest during the aging process is unclear.

Since approximately 10% of all U.S. births are preterm, understanding the future risk of non-communicable diseases is of public health importance. Increasing numbers of individuals who were born prematurely are reaching adulthood and will become a normality in clinical practice, regardless of the practice area. Long-term health consequences for individuals who were born prematurely is a critical health issue that is understudied and is increasingly relevant to the healthcare community. The long-term health implications for adults born prematurely are uncertain, and what is known must be delineated so that health behaviors and treatment modalities may be altered or instituted if necessary. Some researchers advocate that preterm birth be considered “a chronic health condition with increased risk for long-term comorbidities” in later life (Raju, Buist, et al., 2017, p. 1409). Notably, findings have shown that the magnitude of increased risk for adults born preterm has differed across organ systems and has varied
among research studies (Raju et al., 2017). Today’s clinicians must recognize the higher risks in adults born preterm and incorporate outcome assessments into practice.

**Hypertension**

Hypertension is the strongest risk predictor for CVD across the lifespan, including atherosclerotic heart disease, left ventricular hypertrophy, valvular heart diseases, cardiac arrhythmias, cerebrovascular disease, and renal disease (Kjeldsen, 2018). The prevalence of hypertension has more than doubled in the past 20 years, with approximately 1 billion adults worldwide and over 100 million U.S. adults ≥ 20 years of age having hypertension (Go et al., 2014; Muntner et al., 2018; NCD Risk Factor Collaboration, 2021). This translates into 1 in every 2 U.S. adults with high blood pressure (Kochanek et al., 2019). More than 80% of adults diagnosed with hypertension (blood pressure ≥ 140/90 mmHg) do not have their blood pressure under control (< 140/90 mmHg), more than half of all hypertensive adults are not receiving treatment, and of those that are treated with antihypertensive medication(s), more than 50% of them are not controlled (Kochanek et al., 2019). Hypertension contributed to over half a million deaths in the U.S. in 2019 and carries a national burden of approximately $131 billion yearly (Center for Disease Control and Prevention, 2021c; Kirkland et al., 2018).

Hypertension management, especially in women, is a prime example of these findings’ importance. Diagnosing and treating elevated blood pressure in the general population is worrisome. As healthcare professionals, we are failing in hypertension management as the detection rates, initiation of treatment, and control rates have dropped significantly since 1999 (−3.4%, $p = 0.01$, −4.6%, $p = 0.004$, −6.0%, $p < 0.0001$, respectively; Egan et al., 2021). Adults born preterm seem to be more prone to
hypertension, but the question remains: by how much? Failure to recognize and treat hypertension is of more significant consequence to women; investigating the association between their preterm birth age, birth history, and subsequent development of hypertension would greatly benefit this population.

In essence, the compilation of recent evidence suggesting higher overall health risks for those born prematurely, coupled with the identification of hypertension and hypertension-related conditions in adults born preterm, have important implications for early detection and clinical management, and improved health outcomes.

**Purpose of the Study**

The purpose of this dissertation research was to compare cardiovascular health and cardiovascular-related comorbidities in a cohort of U.S. adult women compared by preterm versus full-term birth status. The WHI-OS, a large-scale, racially and ethnically diverse, well-characterized, longitudinal database of U.S postmenopausal women (≥ 50 years of age) was used to evaluate the association between cardiovascular health and birth status (Anderson et al., 2003; Langer et al., 2003). The prevalence and incidence of each condition by birth status provided a comprehensive comparison of disease occurrence.

The scope of this research was broad since multiple associations (e.g., health-related risk factors, sociodemographic, lifestyle covariates) were investigated, and the study aims were designed to identify phenotypes that associated prematurity with chronic health conditions. Little is known about the reasons why some individuals born preterm lead healthy, functional lives and others are plagued with chronic disease. The goal of
this research was to provide insight into the long-term health outcomes for those born prematurely with the intent to increase awareness of the unique health problems.

The WHI-OS provided the foundation for this researchers’ data-based publications, Manuscript II and Manuscript III. A total of 93,676 women were enrolled in the WHI-OS. Among the total, 88,343 women (94%) provided self-reported birth history (born full term or four or more weeks premature), and 2,303 women (2.4%) self-reported being born preterm. The large sample size and the quantity of data collected over many years enhanced the reliability of findings.

In this research, chronic conditions and comorbidities in age-matched women born preterm compared to women born full term were analyzed to provide insight into the development, trajectory, management, and outcomes of the specified/captured non-communicable disorders. Clinical outcomes such as blood pressure and disease control, age at disease diagnosis and sequencing of related conditions, and the rates of CVD events were measured.

The overall research questions were posed with specific aims for each manuscript. How does preterm birth impact women’s adult health, specifically cardiovascular health and cardiovascular-associated conditions? What can we learn from examining the life course of later-aged women born preterm that can be translated to younger preterm populations?

The findings of this research contribute to the less known health complexities of adult women born preterm and how the presumed phenotype of prematurity impacts cardiovascular health manifested over a lifetime. Before the WHI-OS database, research on adults born preterm was almost non-existent in the U.S. due to a lack of cohorts to
study (Sullivan et al., 2022; Sullivan et al., 2008; Sullivan et al., 2019). Based on over 2,000 adult women who were born prematurely, the rarity and magnitude of the WHI-OS sample population is unprecedented. Such a large group of preterm-born adults has never been studied in this country before now.

Aims and Hypotheses

This manuscript-style dissertation consists of three manuscripts for publication on the health and outcomes of adult women born preterm. Individual aims with related hypotheses for each manuscript are described below. Overall, this dissertation aimed to identify associations and early markers for increased hypertension and CVD risk in adult women born preterm compared to adult women born full term.

Manuscript I

The aims of Manuscript I, “A new cardiovascular disease risk factor for young adults: Preterm birth,” were three-fold (Brewer et al., 2022). They derive from growing evidence about increased cardiovascular risk for adults born prematurely, which is important knowledge for advanced practice nurses (APNs) who provide care for this population.

Aim 1. To review the emerging research, from infancy through adulthood, associating premature birth with lifelong health issues.

Underpinning(s). Unique anatomical and physiological alterations to the cardiovascular system, referred to in the literature as a “unique cardiac phenotype of prematurity,” have been linked to higher prevalence of hypertension, congestive heart failure, and premature heart disease in adults born preterm. CVD remains the leading cause of death worldwide. The number of people born preterm each year continues to
rise, as does the percentage of individuals who survive. Understanding the increased risk for adverse cardiovascular health for those born preterm is a priority for all clinicians regardless of health setting.

Aim 2. To increase awareness that preterm birth is a risk factor for increased CVD morbidity and mortality.

Underpinning(s). Nurse clinicians are ideally positioned to stratify CVD risk because of our unique role in caring for patients across their entire lifespan. Identifying and developing preventative strategies and interventions for the at-risk preterm birth population is crucial. Clinicians, specifically APNs, are essential in translating new evidence and implementing changes into clinical practice, which may prove especially beneficial to preterm-born individuals who have been identified to have significant risk for CVD. As millions of survivors of preterm birth are reaching adulthood, APNs can facilitate the identification of those preterm-born adults who have increased CVD risk by ascertaining birth history at each clinical encounter.

Aim 3. To present knowledge gaps about preterm births, including morphological and physiological cardiac modifications and the factors that influence the cardiac phenotype of prematurity.

Underpinning(s). Large-scale cohort studies of individuals born preterm, with lifelong follow-up, are needed to corroborate previous findings and determine to what extent cardiac pathophysiology impacts long-term cardiovascular mortality. Further research that provides mechanistic insight into the pathogenesis of cardiac modifications is necessary so that targeted biomarkers, preventive strategies, and intervention
approaches to reduce CVD risk in the at-risk preterm birth population can be implemented.

**Manuscript II**

The aims for Manuscript II, “Association of preterm birth with prevalent and incident hypertension, early hypertension, and cardiovascular disease in the Women’s Health Initiative,” were three-fold. They are based on growing evidence that indicates risk for higher blood pressure, greater prevalence of hypertension development, and risk of CVD in adults born preterm compared to age-matched peers born full term.

**Aim 1.** To examine whether the prevalence of hypertension, the age at hypertension diagnosis, and incidence of hypertension is higher and occurs at earlier onset in women born preterm compared to women full-term born.

**Hypothesis 1.** Recent literature on altered cardiac morphology and organogenesis supports the hypothesis that women born preterm will have a higher prevalence, a greater incidence, and an earlier age of onset and diagnosis for hypertension, than women born full term.

**Aim 2.** To determine whether hypertensive women born preterm require more antihypertensive agents for control than hypertensive women born full term.

**Hypothesis 2.** Based on recent hypertension research, it is hypothesized that women born preterm who have an existing diagnosis of hypertension are more likely to have resistant or difficult-to-control hypertension, thus requiring more antihypertensive agents compared to women with hypertension who were born full term.

**Aim 3.** To examine the combined effect of birth status and the prevalence of hypertension on the incidence of coronary heart disease (CHD) and CVD events.
**Hypothesis 3.** Hypertension portends a greater incidence of stroke and other cardiovascular events; women born preterm experience the greatest risk. It is hypothesized that women born preterm who have an existing diagnosis of hypertension will experience more cardiovascular events than women with hypertension who were born full term.

**Manuscript III**

The aims for Manuscript III, “The association between preterm birth and the co-occurrence of the cumulative prevalence of hypertension, rheumatoid arthritis, and hypothyroidism in the Women’s Health Initiative” were four-fold. They are derived from growing evidence that impaired immunity, sustained inflammation, and disrupted organogenesis predispose preterm-born individuals to the development of chronic disease in adulthood. This study investigated the associations between preterm birth and the development of three female predominant chronic, cardiovascular risk-related conditions.

**Aim 1.** To determine the cumulative prevalence of RA, alone or as a comorbid condition, and its association with preterm versus full-term birth status in a cohort of age-matched postmenopausal adult women.

**Hypothesis 1.** Research has supported strong associations linking hypertension and preterm birth as well as hypertension and RA, that suggests women born preterm will exhibit a higher cumulative prevalence of RA than women born full term.

**Aim 2.** To determine the cumulative prevalence of hypertension and its association with the prevalence of RA in preterm versus full-term birth status in a cohort of age-matched postmenopausal adult women.
Hypothesis 2. Research findings on endothelial dysfunction and impaired organogenesis supports the hypothesis that, in women who have RA, those born preterm will experience a higher incidence of hypertension than women born full term.

Aim 3. To determine the cumulative prevalence of hypothyroidism and its association with preterm versus full-term birth status in a cohort of age-matched postmenopausal adult women.

Hypothesis 3. Impaired thyroid function and lower thyroid hormone levels from birth are the basis for the hypothesis that the cumulative prevalence of hypothyroidism will be higher in women born preterm compared to women born full term.

Aim 4. To determine the association between prevalent hypertension and prevalent hypothyroidism in preterm versus full-term birth status in a cohort of age-matched postmenopausal adult women.

Hypothesis 4. Based on current literature, it is hypothesized that hypertension as a comorbidity will be greater in women born preterm who have hypothyroidism compared to women born full term who have hypothyroidism.

Definitions

Birth Categories

The World Health Organization categorizes births into three gestational-age groups according to completed gestational age (WHO, 1977):

- **preterm birth:** < 37 completed weeks (less than 259 completed days) of gestation;
- **term birth:** 37 to 41 completed weeks (259 to 293 days) of gestation; and
- **post-term birth:** 42 or more completed weeks of gestation.
**Prematurity**

*Prematurity* is defined as a birth before the completion of 37 weeks gestation (World Health Organization, 2018). Before ultrasound technology, gestational age was based on the mother’s recall of her last menstrual cycle. Since this method was unreliable, birth weight was often used to estimate gestational age. Birth weight is objective and easy to attain. Unfortunately, birth weight is not synonymous with preterm birth. Infants may reach full gestational age and still have a low birth weight due to intrauterine growth restriction (IUGR) or placental insufficiency. A preterm birth reflects the underdevelopment of vital organs and is not solely dependent on birth size.

Preterm birth is divided into the following subcategories by gestational age (Blencowe et al., 2013; Engle et al., 2007; World Health Organization, 2018):

- *extremely preterm*: less than 28 weeks;
- *very preterm*: 28 to less than 32 weeks; and
- *moderate–late preterm*: 32 to less than 37 weeks completed weeks of gestation.

Most preterm births (85%) are moderate–late preterm, 10% are very preterm, and 5% are extremely preterm (Blencowe et al., 2013; Martin et al., 2021). In this dissertation, birth status was categorized as “full term” or preterm “4 or more weeks premature,” although exact gestational ages of the WHI-OS participants were not available.

Subgroups of infants born preterm can also be defined based on birth weight (Cutland et al., 2017; World Health Organization, 2004):

- *extremely low birth weight* (ELBW): < 1000 grams;
• *very low birth weight* (VLBW): < 1500 grams; and

• *low birth weight* (LBW): < 2500 grams.

A weight-based definition of preterm birth does not consider gestational age at the time of birth or other aspects like IUGR that might affect weight, so birth weight is an unreliable measurement of prematurity in this sample population (Cutland et al., 2017). However, women who participated in the WHI-OS study self-reported birth weight into four subcategories with the lowest category being < 6 pounds (Anderson et al., 2003; Langer et al., 2003).

*Preterm birth risk* includes maternal risk factors, pregnancy-related risk factors, and maternal medical conditions. This information was not reported by WHI-OS participants (Blencowe et al., 2013; Romero et al., 2014).

**Hypertension**

Previously, the 1988 4th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-IV) defined *hypertension* as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, and this was the definition used to determine hypertension status at the start of WHI-OS data collection (Chobanian et al., 1988). In 2017, the American College of Cardiology and the American Heart Association redefined hypertension, which was the first change in 14 years (American Heart Association & American Stroke Association, 2017; Whelton et al., 2018; Whelton & Pollock, 2017). *Hypertension* is now defined as SBP ≥ 130 mmHg and/or DBP ≥ 80 mmHg (Whelton et al., 2018). This change was implemented to reduce the growing number of cardiovascular events (Whelton et al., 2018). See Table 1. *Classification of Blood Pressure (1988-2014).*
Table 1

Classification of Blood Pressure (1988-2014)

<table>
<thead>
<tr>
<th>Classification</th>
<th>BP range (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diastolic</strong></td>
<td></td>
</tr>
<tr>
<td>Normal BP</td>
<td>&lt; 85</td>
</tr>
<tr>
<td>High normal BP</td>
<td>85–89</td>
</tr>
<tr>
<td>Mild hypertension</td>
<td>90–104</td>
</tr>
<tr>
<td>Moderate hypertension</td>
<td>105–114</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>≥ 115</td>
</tr>
<tr>
<td><strong>Systolic, when diastolic &lt;90</strong></td>
<td></td>
</tr>
<tr>
<td>Normal BP</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>Borderline isolated systolic hypertension</td>
<td>140–159</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥ 160</td>
</tr>
</tbody>
</table>

Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of death worldwide (World Health Organization, 2021). Cardiovascular diseases are disorders of the heart and the blood vessels. There are four main types of CVD (World Health Organization, 2021):

- coronary or ischemic heart disease;
- cerebrovascular disease;
- peripheral artery disease; and
- aortic disease.

Characteristics, conditions, and behaviors that increase susceptibility (or risk, commonly referred to as risk factors) for cardiovascular disease can be divided into two categories:

1. **Modifiable risk factors.** Modifiable risk factors for CVD are risks that can be controlled and prevented. The following are modifiable risk factors for CVD (Bundhun et al., 2015; Pencina et al., 2019):

- diabetes: fasting blood glucose (FBG) level of > 7.0 mmol/L or an oral glucose tolerance test (OGTT) > 11.1 mmol/L observed at least on 2 different occasions;
- overweight or obese: body mass index (BMI) of > 25 and > 30 kg/m², respectively;
- hypertension: a blood pressure > 130/80 mmHg [or >140/90 mmHg during WHI-OS enrollment] on at least 2 separate occasions;
- dyslipidemia: an LDL level of > 130 mg/dL or an HDL level of < 40 mg/dL;
- metabolic syndrome: a condition in which at least 3 of the followings risk factors are present – obesity*, hypertension*, high fasting glucose*, high
triglyceride levels $\geq 150$ mg/dL, and low-high-density lipoproteins (HDL)*;

*other values as previously noted:

- smoking/tobacco use;
- poor/unhealthy diet; and
- sedentary lifestyle/physical inactivity.

2. **Non-modifiable risk factors.** Non-modifiable risk factors for CVD are risks that cannot be changed or adjusted. The following are non-modifiable risk factors for CVD (Brown et al., 2022):

- advancing age - the prevalence of CVD increases after the age of 35 years for both men and women;
- gender;
- ethnicity - Blacks carry the greatest risk of CVD morbidity and mortality of all ethnic groups; and
- family history/genetics - individuals with a family history of premature cardiac disease ($< 50$ years of age) have an increased CVD mortality risk.

3. In addition to the traditional modifiable and non-modifiable risk factors, novel or emerging risk factors may include (Brown et al., 2022):

- chronic kidney disease (reported as an independent risk factor for CVD);
- systemic lupus erythematosus (SLE);
- rheumatoid arthritis (RA);
- inflammatory bowel disease (IBD);
- human immunodeficiency virus (HIV);
- thyroid disease, specifically hypothyroidism;
• testosterone (low testosterone levels with aging);
• low socioeconomic status; and
• preterm birth.

Of the twelve traditional modifiable and non-modifiable risk factors, hypertension is the strongest risk factor for CVD morbidity and mortality worldwide (Brown et al., 2022). A 20 mmHg reduction in systolic blood pressure and a 10 mmHg reduction in diastolic blood pressure can reduce the risk of CVD mortality by 50% for individuals aged 40-49 years and approximately 33% for those aged 80-89 years (Brown et al., 2022).

This dissertation focuses on the association between preterm birth and hypertensive blood pressure status and the impact on CVD, CHD, and other blood pressure-related health conditions as outcome variables in the WHI-OS analyses.

**Rheumatoid Arthritis**

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation (Center for Disease Control and Prevention, 2020). The autoimmune disease can significantly shorten life expectancy by 10-15 years (Houge et al., 2020; RheumatoidArthritis.org, 2018). Women participants in the WHI-OS self-reported a history of RA at the enrollment visit and on annual medical history questionnaires during follow-up years.

There are four distinct stages to RA, yet not everyone progresses through all four stages. The stages are based on joint involvement (Kourilovitch et al., 2014):

1. *Early*: the synovial membrane, or joint lining, is inflamed. Pain, stiffness, and swelling are common.
2. **Moderate**: damage has spread from the synovium to the adjacent cartilage. Pain, stiffness, and swelling continue, range of motion decreases, and activity limitations are noted.

3. **Severe**: joint damage has spread to the bone, causing joint deformities that further limit activity.

4. **End-Stage**: the inflammatory process lessens yet the joint and bone pain and stiffness remain. Other organ systems are damaged by RA.

Individuals with RA have a two-fold increased risk of CVD (Anyfanti et al., 2021; Baghdadi et al., 2015; Castañeda et al., 2016; Chodara et al., 2017; Dhawan & Quyyumi, 2008; England et al., 2018; Jagpal & Navarro-Millán, 2018; Nurmohamed et al., 2015; Semb et al., 2020). Hypertension is the most common risk factor for CVD in individuals who have RA (Anyfanti et al., 2021; Bartels et al., 2014; Crowson et al., 2013; Manavathongchhai et al., 2013; Midtbo et al., 2016; Panoulas et al., 2007; Singh et al., 2003). The exact cause of RA is not fully understood. However, numerous studies have shown a complex interaction between the release of synovial fibroblasts, which are the primary cells of the joint synovium, and pro-inflammatory cytokines that lead to tissue and cartilage degradation (Dayer, 2002; Imrich & Rovenský, 2010; Kuller et al., 2014). Cytokines associated with the inflammatory process of RA include tumor necrosis factor-B (TNF-B), interleukin-1C (IL-1C), and IL-6 (Dhawan & Quyyumi, 2008). Consequently, these pro-inflammatory cytokines cause arterial stiffening, endothelial dysfunction, and decreased production of endothelial progenitor cells, which are the “repair” cells that line the lumen of damaged vessels. These pathogenic mechanisms,
together or alone, result in elevated blood pressure and atherosclerosis (Dhawan & Quyyumi, 2008).

**Hypothyroidism**

The thyroid gland produces two forms of thyroid hormone: thyroxine (T4) and triiodothyronine (T3; Dunn & Turner, 2016). In the endocrine system, production of thyroid hormones is regulated by the pituitary gland yet these hormones exhibit significant physiological effects on the cardiovascular system (Yamakawa et al., 2021). Thyroid hormones circulating in blood are comprised of T4 (95%) and T3 (5%). When the pituitary gland detects low levels of T4 and T3, it increases production of thyroid-stimulating hormone (TSH). In turn, TSH triggers the thyroid gland to increase T4 and T3 production. This feedback loop is designed to maintain a state of equilibrium between the endocrine system and thyroid hormone production (Dunn & Turner, 2016; Yamakawa et al., 2021).

Hypothyroidism, characterized by elevated levels of TSH and low levels of T4, is associated with higher risks of CVD morbidity and mortality (Cappola et al., 2019). Low T4 and T3 levels can result in cardiovascular manifestations such as reduced ventricular contractility, impaired ventricular relaxation, bradycardia, increased vascular resistance, and reduced cardiac output and stroke volume (Toft & Boon, 2000). Pathophysiological consequences can include hypertension, heart failure, ventricular arrhythmias, and hyperlipidemia (Danzi & Klein, 2014; Klein & Danzi, 2016).

Hypothyroidism can be classified as (1) overt hypothyroidism or (2) subclinical hypothyroidism based on TSH, T4, and T3 levels (Khandelwal & Tandon, 2012; Selmer et al., 2014). Total T4 is a measure of protein bound T4 and free T4. Free T4 is
unaffected by binding proteins. When total T4 level is normal, total T3 is used to confirm hypothyroidism. Free T3 is rarely tested. Normal thyroid levels in adults are:

- TSH: 0.2-5.0 mIU/L;
- Total T4: 60-140 mmol/L;
- Free T4: 9-22 pmol/L; and
- Total T3: 80-220 ng/dL.

Individuals with overt hypothyroidism have a (1) TSH level > 5.0 mIU/L often >10 mIU/L, (2) a total T4 < 60 mmol/L, and (3) free T4 < 9 pmol/L and should receive pharmacologic treatment. Subclinical hypothyroidism is a grade of hypothyroidism in which TSH is > 5 mIU/L, but T4 and T3 levels are within normal limits. Subclinical hypothyroidism advances to overt hypothyroidism in 2–5% of the cases (Khandelwal & Tandon, 2012).

The etiological basis of hypothyroidism is divided into four groups (Chaker et al., 2017):

- primary hypothyroidism- caused by a thyroid hormone deficiency.
- secondary hypothyroidism- caused by a TSH deficiency.
- tertiary hypothyroidism- caused by a thyrotropin-releasing hormone deficiency.
- peripheral hypothyroidism- congenital hypothyroidism which causes permanent inactivation of thyroid hormone metabolism.

Noncommunicable Diseases, Chronic Conditions, and Comorbidities

A noncommunicable disease (NCD) is synonymous with chronic disease or chronic condition. An NCD is likely of long duration and results from genetic,
physiological, environmental, or behavioral factors (World Health Organization, 2022b). People of all ages can be afflicted with an NCD; however, modifiable and behavioral risk factors such as unhealthy lifestyles (i.e., poor diet and substance use), and metabolic risk factors like obesity, high blood pressure, and blood glucose levels increase their risk. The leading metabolic risk factor for CVD mortality worldwide is high blood pressure (GBD 2015 Risk Factors Collaborators, 2016; World Health Organization, 2021).

Cardiovascular disease, chronic pulmonary disease, and diabetes are the three most prevalent NCDs globally (World Health Organization, 2022b).

Similar in terminology, *comorbidity* means more than one disease or condition exists in the same individual simultaneously (Center for Disease Control and Prevention, 2018). Like NCD, comorbidities are often of long duration, but not always. A prime example is an infectious process like influenza. Influenza can co-occur with other chronic health conditions, making it a comorbidity; however, it is not a NCD due to its transmissible nature. *Coexisting condition* and *co-occurring condition* are terms used synonymously with comorbidity.

Throughout this research, assessment of NCDs and comorbidities that are associated with hypertension include: diabetes, hyperlipidemia, angina, atrial fibrillation, transient ischemic attack, heart failure, RA, hypothyroidism, CHD, CVD, and cerebrovascular disease.

**Phenotype**

A *phenotype* is an observable or measurable characteristic or trait that is produced by or the result of interaction between environmental influences on an individual’s genetic make-up (National Human Genome Research Institute, 2022).
Theoretical Framework – Developmental Origins of Health and Disease

The DOHaD theory underpins this research. The foundational pillars of the DOHaD theory are that adverse prenatal and perinatal environmental exposures and events can permanently influence an individual’s health and susceptibility to chronic diseases from childhood to adulthood (Barker, 1998). The phenotype(s) of prematurity, which evolved from Barker’s hypothesis and discussed in Chapter 2, is supported by two underlying mechanisms (Barker et al., 1989). For infants born preterm, the first and most relevant mechanism for the phenotype of prematurity is impaired organogenesis or disrupted organ development, which may lead to anatomical and physiological alterations of the affected organ (Kanda et al., 2020). Compelling epidemiological and experimental studies have shown that insults during sensitive and vulnerable periods of fetal development can result in developmental adaptations contributing to later-life disease (Kwon & Kim, 2017; Wadhwa et al., 2009).

The second mechanism for the phenotype of prematurity is epigenetic modifications (Gluckman et al., 2016; Vehaskari, 2007). Broadly speaking, *epigenetic modifications* arise from an adverse influence during early neonatal life which can force one’s biological system to adapt to its environment by altering DNA methylation patterns, but not the underlying DNA sequence (Bertagnolli et al., 2016; Ingelfinger & Nuyt, 2012; Kwon & Kim, 2017; Murphy & Cairns, 2016). Alterations in DNA methylation and early life stress play a vital role in the development of later-life disease (Murphy & Cairns, 2016). Although epigenetics impact developmental programming, the primary focus of this study is on disrupted organogenesis. The theoretical structure of the
DOHaD was appropriate for examining the lifelong health trajectories and outcomes of women born preterm who participated in the WHI-OS.

Summary

In summary, this chapter introduced definitions associated with preterm birth, the growing evidence of higher CVD risk in adulthood for individuals born preterm, the WHI-OS database, the DOHaD theoretical framework, and the overall purpose of this dissertation and its three-manuscript format. Advances in health care and technology have improved the survival rates of those born preterm, and millions of preterm birth survivors are now reaching middle age. Adults born preterm have an increased risk of developing chronic health conditions. Three chronic, non-communicable conditions have been briefly described and suggested to have a greater prevalence in adult women born preterm. Understanding prematurity and the potential health outcomes are essential for those caring for these individuals.
Chapter 2: Literature Review

Evidence is building that adults born preterm have increased risks for poorer cardiovascular health. This chapter explores both a theoretical explanation for the increased risk and the literature describing the health risks. The chapter is organized into three parts. First is the theoretical framework underpinning the dissertation, the Developmental Origins of Health and Disease (DOHaD). Next, three specific non-communicable conditions associated with cardiovascular health—hypertension, rheumatoid arthritis (RA), and hypothyroidism—the focus of three manuscripts, are described. Specifically, the prevalence and incidence of these three conditions and the health implications for women and those born preterm are discussed. Using the DOHaD theory as a foundational support for this study provides a structural lens to analyze each condition associated with later-life health of women who were born preterm. Lastly, the aims of each of the three manuscripts supported by the literature are reviewed.

Theoretical Framework

The DOHaD theory supported this research. The DOHaD theoretical framework conceptualizes how in utero environmental factors in individuals born preterm can influence health trajectories later in life (Newnham, 2007; Rueda-Clausen et al., 2011). Further, the theory mandates a life course approach, which aligns well with this secondary analysis of longitudinal WHI-OS data (Baird et al., 2017). Examining the life course of adult women who were born preterm may afford a greater understanding of the onset and trajectories of health sequelae. Findings may also lead to the development of more timely preventive interventions for individuals born preterm.
Origins of the DOHaD Theory

The field of DOHaD research is relatively new (Wadhwa et al., 2009). The first publication to introduce the hypothesis that environmental circumstances during the first years of life may influence health in adulthood was presented by Kermack et al. in 1934 (Kermack et al., 1934, 2001; Smith & Kuh, 2001). Work by British and Scandinavian researchers provided the foundation for David Barker’s seminal work in the 1980s (Smith & Kuh, 2001). Succinctly, Barker hypothesized that intrauterine exposures and stressful events negatively impacted fetal development, which increased the risk for certain diseases decades later (Almond & Currie, 2011).

Barker’s epidemiological research led to his premise that poor nutrition and high infection rates during infancy correlated with higher rates of CVD and diabetes in adults later in life (Barker, 1998; Barker & Osmond, 1986; Kwon & Kim, 2017). Barker reasoned that these adverse conditions occurred during critical periods of fetal development, likely influencing the individual’s health in later life (Barker & Osmond, 1988; Barker et al., 1989). In 1989, after reviewing large-scale birth registry data, Barker published his first report that associated low birth weight with elevated blood pressure and early CVD mortality (Barker & Osmond, 1988; Barker et al., 1989; Wadhwa et al., 2009). In 1990, the “fetal origins hypothesis” was first proposed. In 1992, it was renamed the Fetal Origins of Adult Disease, based on his epidemiological research.

Barker expanded his hypothesis to address birth phenotypes, which differentiated preterm birth from intrauterine growth restriction as the cause of low birth weight. He also proposed that epigenetic adaptations in utero were the pathological mechanisms responsible for increased risks for various chronic diseases in adulthood (Calkins &
Devaskar, 2011). In 2005, the Fetal Origins of Adult Disease theory was renamed to the Developmental Origins of Health and Disease (DOHaD) theory at the 3rd International Congress on Developmental Origins of Health and Disease meeting in Toronto, Canada (Gillman et al., 2007).

**The DOHaD Theory**

The DOHaD theory is based on the premise that adverse prenatal and perinatal environmental exposures and events can increase susceptibility to chronic disease and permanently alter health outcomes from childhood to adulthood (Barker et al., 1989). The theory is supported by two underlying mechanisms (Vehaskari & Woods, 2005; Wadhwa et al., 2009). The first is immature organ development, found in infants born preterm, may lead to anatomical and physiological alterations of the affected organ (Kanda et al., 2020). Compelling epidemiological and experimental studies have shown that adverse or stressful exposures or events during sensitive and vulnerable periods of fetal development can result in developmental adaptations that contribute to later-life disease (Kwon & Kim, 2017; Wadhwa et al., 2009).

Besides preterm birth, the second mechanism that can lead to pathophysiological alterations in fetal development is epigenetic modifications (Gluckman et al., 2016; Lacagnina, 2019; Vehaskari, 2007). Broadly speaking, an adverse influence during early neonatal life elicits adaption of the biological system to its environment by altering DNA methylation patterns without altering the underlying DNA sequence (Bertagnolli et al., 2016; Ingelfinger & Nuyt, 2012; Kwon & Kim, 2017; Lacagnina, 2019; Murphy & Cairns, 2016). In other words, epigenetic changes are reversible modifications to DNA segments that do not change the sequence of DNA building blocks or cause hereditary
genetic changes (Kubota et al., 2015; Lacagnina, 2019; Lynch et al., 2022). Epigenetic alterations lead to disease but can be reversed. Figure 1. *The Theory of the Developmental Origins of Health and Disease* depicts how alterations in DNA methylation and early life stress play a vital role in the development of later-life disease (Lacagnina, 2019; Murphy & Cairns, 2016). The DOHaD’s theoretical structure was the ideal foundation for this longitudinal study on lifelong health trajectories and outcomes in women born preterm and enrolled in the WHI-OS.

**Figure 1**

*The Theory of the Developmental Origins of Health and Disease*

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*Note.* This figure summarizes the most current understanding of causal mechanisms that underlie the developmental origins of health and disease. A variety of health-related stressors during fetal and early life can negatively impact tissues as they undergo critical periods of development. Altered tissue structure and/or altered patterns of epigenetic markers may result, which may adversely impact long-term gene expression patterns and

**Mechanism 1, Organ Development.** Environmental factors that impact growth and development must be considered when seeking to reduce the burden of non-communicable diseases (Mandy & Nyirenda, 2018). The DOHaD theory posits that adaptive anatomical and physiological changes occur in response to environmental insults (Lacagnina, 2020; Starr & Hingorani, 2018). The abruptness of premature birth can trigger physiological responses necessary for survival, such as rapid downregulation of organ function and, consequently, immature development of organs (Kubota et al., 2015). Compensatory physiological responses may facilitate survival in the short term but ultimately may have detrimental consequences for overall health (Kubota et al., 2015; Starr & Hingorani, 2018).

The recent detection of structural and functional myocardial alterations in individuals born preterm may be the consequences of compensatory mechanisms triggered by preterm birth (Aye et al., 2017; Lewadowski, Augustine, et al., 2013; Lewadowski, Bradlow, et al., 2013). Specifically, fetal development of the myocardium may be disrupted by premature birth, which forces immature cardiomyocytes to adapt to and function abnormally in extrauterine life. The hemodynamic transition from fetal to neonatal circulation that occurs at birth on ill-prepared, immature cardiomyocytes is also a time of complex cellular and interstitial myocardial changes or remodeling of the postnatal heart (Bensley et al., 2010; Burchert & Lewadowski, 2019; Crispi et al., 2020;
Cardiac remodeling, or adaptations in heart size, shape, and function, can lead to distinct cardiac anomalies and inferior cardiac performance (Aye et al., 2017; Harris et al., 2020; Lewandowski, Augustine, et al., 2013; Lewandowski, Bradlow, et al., 2013). Echocardiography and cardiac magnetic imaging have been used to find clinically significant cardiac remodeling patterns (Burchert & Lewandowski, 2019).

Structural changes in cardiac ventricular walls have been detected in infants born preterm and as young as three months corrected age, or the chronological age minus the number of weeks or months early the infant was born (Kozák-Bárány et al., 2001; Ley et al., 2019; Mikkola et al., 2007; Tan & Lewandowski, 2020). Researchers have used cardiac imaging to measure biventricular hypertrophy, increased ventricular mass, and smaller ventricular cavities and volumes resulting in systolic and diastolic dysfunction, reduced myocardial reserve, and impaired contractility (Lewandowski, Augustine, et al., 2013; Lewandowski, Bradlow, et al., 2013; Lewandowski et al., 2021). Unique phenotypes associated with immature cardiovascular systems may account for a higher prevalence of arrhythmias, such as atrial fibrillation due to electrical remodeling; congestive heart failure due to ventricular hypertrophy and interstitial fibrosis; and, hypertension due to systolic and diastolic dysfunction in young adults born preterm (Carr et al., 2017; Cocco et al., 2018; Crump et al., 2021; Crump et al., 2011b; Murphy et al., 2017; Sandboge et al., 2016).

Longitudinal retrospective and prospective cohort data, combined with animal studies, have aided the discovery of cardiac phenotypes in individuals born preterm, leading to a greater understanding of adaptive mechanisms and maladaptive
consequences at structural, cellular, and physiological levels (Bensley et al., 2016; Bensley et al., 2018; Burchert & Lewandowski, 2019; Le et al., 2018; Tan & Lewandowski, 2020). See Figure 2. *Unique Cardiac Phenotypes.*

**Figure 2**

*Unique Cardiac Phenotypes*

Note. Representation of mechanisms that contribute to the unique cardiac phenotype of prematurity.

Anatomical and physiological alterations due to prematurity have also been discovered in renal and vascular systems, and potentially pulmonary and autonomic nervous systems, although they are still under evaluation (Duke et al., 2022; Haraldsdottir et al., 2018; Mandy & Nyirenda, 2018). Briefly, nephrogenesis begins in the 20th week of gestation, with more than half of the total nephrons developing in the last four weeks of pregnancy (Heo & Lee, 2021). The kidneys are unique in that nephrogenesis continues for approximately six weeks into the postnatal period (Heo & Lee, 2021). Premature birth often occurs during a critical stage of nephron development. Disrupted nephron development results in lower nephron endowment, which is the number of functioning nephrons at birth (Crump, Sundquist, et al., 2019). Low nephron count causes compensatory hypertrophy of the existing nephrons, which ultimately leads to reduced
renal function. With stressful postnatal environments and medical interventions, hampered nephrogenic processes can predispose the individual born preterm to kidney complications later in life (Crump, Sundquist, et al., 2019).

Endothelial cells undergo altered growth patterns similar to nephrons and cardiomyocytes (Arima & Fukuoka, 2020; Arima et al., 2018; Murphy et al., 2017). Mature blood vessels consist of three layers, with endothelial cells lining the two inner layers of the vessels (Arima et al., 2018). When vasculogenesis is interrupted, immature endothelial cells must support the blood vessels. Subtle manifestations develop, leading to endothelial dysfunction and impaired vasodilatory responses. This is a simplistic description of the vasculature system; the degree of vascular dysfunction is unique to each organ’s development (Arima et al., 2018; Cocco et al., 2018; Mandy & Nyirenda, 2018).

Findings from animal and human research support the assertion that alterations in organ system development and growth are due to premature birth (Bensley et al., 2018; Bensley et al., 2010; Bertagnolli et al., 2014; Goss et al., 2017; Lewandowski, Augustine, et al., 2013; Lewandowski, Bradlow, et al., 2013). Adverse structural and functional adaptations suggest an underlying pathway associated with later adult cardiovascular and renovascular disease (Chehade et al., 2018). The DOHaD theory supports both the use of a life course approach to clinical research, as well as the finding that disruptions at premature births result in predisposition to later disease. Borrowing the DOHaD’s foundational perspective of viewing health across the life span, perinatal and neonatal medicine have a more expanded understanding about the association between early life influences and later health outcomes. Further study of the postnatal developmental
window may provide a more detailed understanding of the impact of early interventions on structural and functional physiological changes (Sutton et al., 2016). Directions for future research on the outcomes of disrupted growth and development due to preterm birth are undefined (Sutton et al., 2016).

**Mechanism 2, Alterations in Gene Expression.** Epigenetics is the study of how the developmental environment alters gene expression without changing the genetic code (Gluckman et al., 2016; Gluckman et al., 2010). DOHaD research shows that in addition to specific organ vulnerability, environmentally-induced epigenetic modifications can be switched on or off based on an individual’s behaviors and environment (Gluckman et al., 2016). Epigenetic processes, including DNA methylation, histone modification, and various RNA-mediated processes, can reverse gene expression by adding or removing methyl groups from regions of the DNA, leading to epigenetic modifications that may appear later in life (Gluckman et al., 2016; Lacagnina, 2019; Sutton et al., 2016). To illustrate, Lewandowski et al. (2016) found that infants born preterm and exclusively breastfed exhibited better myocardial function and fewer myocardium structural modifications compared to infants born preterm who were formula-fed.

A rising research area of epigenetics centers on maternal behaviors and the fetal environment during pregnancy (Gluckman et al., 2016). After the Dutch Hunger Winter Famine (1944–1945), it was determined that offspring born to women who were pregnant during the famine were more likely to develop heart disease, schizophrenia, and type 2 diabetes later in life (Arima & Fukuoka, 2020; Mandy & Nyirenda, 2018). Years after the famine, researchers detected different epigenetic modifications in those born during the famine compared to siblings born after the famine, which potentially explains the
increased prevalence of disease in infants born to malnourished mothers (Arima & Fukuoka, 2020). Pernicious maternal influences other than malnutrition, such as exposures to toxins and psychological stress like anxiety and depression have been inextricably linked to suboptimal developmental outcomes in fetuses (Gluckman et al., 2016). Maternal behavioral and environmental factors are not the only health disparities to consider (Msall et al., 2018; Sullivan et al., 2008). As individuals who were born preterm age, their lifestyle choices and high-risk socioeconomic living conditions can amplify any adverse epigenetic modifications they developed in utero (Forsdahl, 1977; Hanson & Gluckman, 2015; Sullivan et al., 2008).

In summation, fetal exposure to adverse stimuli, events, or environments may impose epigenetic modifications that are necessary for survival. These resulting developmental programming changes may have lifelong health consequences, including an increased risk of disease in adulthood (Arima & Fukuoka, 2020; Goyal et al., 2019; Ismaili M'hamdi et al., 2018).

**Mechanisms Underlying the Development of Hypertension**

According to the DOHaD theory, early life insults cause developmental programming for later-life diseases like hypertension or elevated blood pressure (Nuyt & Alexander, 2009). Developmental programming, or the lifelong consequences caused by permanent physiological and epigenetic changes of an individual, often begins in utero but can be influenced by postnatal life (Nuyt & Alexander, 2009; Singhal et al., 2001; Sutton et al., 2016). Prenatal exposures include maternal determinants like the mother’s nutritional status, her overall state of health, and substance use (Hsu & Tain, 2021). Environmental factors include exposure to toxins and medications with unfavorable
profiles (Hsu & Tain, 2021). Pathogenic mechanisms for the developmental programming of hypertension are still unclear. Potential mechanisms implicit in the programming of hypertension include maternal glucocorticoids and cortisol secretion, impaired kidney function and low nephron counts, immature cardiomyocytes, altered vascular structure and function, oxidative stress and inflammation, and an underdeveloped hypothalamic-pituitary-adrenal (HPA) axis with resulting changes in sympathetic activity (Kwon & Kim, 2017; Mohn et al., 2007; Nuyt & Alexander, 2009; Skogen & Overland, 2012; Sullivan et al., 2017). Each mechanism, likely associated with disrupted development of an organ or organ system, alone or together, can contribute to the pathogenesis of hypertension.

**Ethical Considerations**

Studies in the field of DOHaD may pose ethical dilemmas. Communicating and interpreting DOHaD research often disproportionately or unfairly targets the mother by focusing on potentially problematic implications, assigning misplaced blame on the mother (Ismaili M’hamdi et al., 2018; Sharp et al., 2018). Without question, a mother’s health is critical in the lives of her offspring. However, the complexity of fetal development and epigenetic programming cannot be reduced to a unilateral causal pathway that pits a mother’s nutritional choices versus her infant’s long-term health risks.

Another ethical dilemma within the field of DOHaD is posed by the use of *assisted reproductive technologies* (ART), which are any fertility-related treatments in which eggs or embryos are manipulated (Jain & Raju, 2013; Jain & Singh, 2022). Using ART evokes questions at the crossroads of the medical responsibilities, ethical considerations, and epigenetic modifications (Roy et al., 2017). ART has been used in the
U.S. since 1981 and its use is becoming more common (Center for Disease Control and Prevention, 2022b). The Centers for Disease Control and Prevention (CDC) estimated that nearly 5% but as high as 11.4% of all preterm births in the U.S. in 2019 were ART infants (Center for Disease Control and Prevention, 2022a). Some researchers suggest that ART can alter epigenetic programming, contributing to later-life disease (Ismaili M’hamdi et al., 2018). Morally, this calls into question the responsibility of the epigenetic disease risk of the ART-conceived individual—specifically, whether the mother or the medical professional bears responsibility for the risk of the epigenetic disease in the fetus.

An ethical dilemma akin to that found within ART is in the field of neonatology. The use of advanced medical treatments and technology may stretch the limits of neonatal viability, which must be balanced against potential, unknown long-term health risks. As DOHaD research unfolds, medical communities must share findings with prospective parents, so they understand potential long-term consequences for their infants, and can make informed decisions (Roy et al., 2017). It seems unprofessional, if not unethical, that immeasurable time and resources have been allocated to reducing preterm birth rates and improving preterm birth survival rates, while the knowledge gained through DOHaD research has not been fully investigated or has had limited results.

Enrollment in research that evaluates long-term health outcomes of prematurity may be difficult, stressful, or even painful for some participants. Educating a prospective participant or parent of a preterm-born individual can increase anxiety and worry because most parents and preterm-born individuals themselves are unaware of emerging disease risks. On the contrary, it is hoped that increased awareness will lead to closer follow-up
and possibly healthier lifestyles. Conveying the importance of this research may benefit the long-term health of individuals who were born prematurely.

**DOHaD Synopsis**

After more than a decade, the DOHaD theory, supported by the emergent themes of fetal programming and epigenetic modification, is recognized as a framework in adult phenotyping (Barker, 1998; Dalziel et al., 2007; Vehaskari, 2007). The DOHaD was used as a framework for this dissertation to depict that multiple elements such as maternal factors, organ development, epigenetic modifications, environment, and the timing of fetal insults can influence the health outcomes of individuals born preterm (de Boo & Harding, 2006; Gluckman et al., 2016; Vehaskari & Woods, 2005). The particular focus of this dissertation was altered organ development and broad social environments rather than epigenetic aspects. The potential long-term effects of altered fetal nutrition on fetal organ growth and development as an example is depicted in Figure 3.
Figure 3

*The Effects of Altered Fetal Nutrition on Growth and Maturation of Fetal Organ Systems*

Note. This figure represents the effects of altered fetal nutrition on growth and maturation of fetal organ systems and their links with adult disease. Reprinted from “The developmental origins of adult disease (Barker) hypothesis” by H.A. de Boo & J.E. Harding, 2006, *The Royal Australian and New Zealand College of Obstetricians and Gynaecologists*; 46, p. 6.

The DOHaD theory was a helpful framework for analyzing the long-term health trajectories of adult women enrolled in the WHI-OS who were born preterm. The specific outcomes analyzed were hypertension, RA, and hypothyroidism. Exploring environmental and lifestyle factors helped differentiate optimal health from diseased health in women born preterm. Statistical modeling helped identify cardiovascular
phenotypes that were pivotal for investigating disease patterns, risk factor determinations, and ultimately, health outcomes in WHI-OS enrolled women born preterm.

Scientific evidence and application of the DOHaD theory illuminate the necessity of initiating health promotion and disease prevention in individuals born preterm. Manuscripts II and III in this dissertation endeavor to expand our understanding of the lifelong implications of preterm birth using the DOHaD lens on adult women in the WHI-OS database. The challenge is translating what was learned into actionable clinical health practices. Manuscript I, a state-of-the-science publication, is a step toward this translation.

The following sections address specific conditions examined in this dissertation. The literature supporting the associations between preterm birth, cardiovascular comorbidities, and cardiovascular health of women is presented.

**Hypertension**

Hypertension is the most important risk factor for CVD and is among the leading contributors to CVD morbidity and mortality worldwide (Center for Disease Control and Prevention, 2021c; NCD Risk Factor Collaboration, 2021; World Health Organization, 2021). The clinical consequences of elevated blood pressure have been studied since the 1920s (Whelton et al., 2018). The well-known Framingham Heart Study corroborated the relationship between blood pressure levels and CVD mortality in the 1960s. By the late 1960s into the early 1970s, the Veteran’s Administration Cooperative Study Group was exploring the effectiveness of treatment modalities for lowering blood pressure (Dawber, 1980; Whelton et al., 2018). The first national guideline for the detection, evaluation, and management of hypertension was published in 1977 under the direction of the National
Heart, Lung, and Blood Institute (NHLBI; Moser, 1977; Whelton et al., 2018). The guideline has been updated approximately every four years with the continued goal of presenting the most current, relevant clinical and scientific evidence to inform and support the healthcare community in improving the prevention, awareness, treatment, and control of hypertension (Whelton et al., 2018).

Hypertension is a complex, multifactorial, multigenetic, progressive vascular condition (Armani et al., 2011). A direct linear relationship has been established between blood pressure levels and CVD (Rapsomaniki et al., 2014; Wang & Liu, 2018; Whelton et al., 2018). Observational studies of more than one million adults have shown that CVD morbidity and mortality double for every systolic reading increased by 20 mmHg or diastolic reading increased by 10 mmHg above baseline, beginning with blood pressures as low as 115 mmHg systolically and 75 mmHg diastolically (Chobanian et al., 1988; Whelton et al., 2018). The Framingham Heart Study also discovered that participants without a history of hypertension or CVD had up to a six-fold increase in developing CVD with blood pressures ≥ 130/85 mmHg compared to those with blood pressures < 120/80 mmHg (Levy et al., 1996; Oh & Cho, 2020; Vasan et al., 2001). The most recent landmark blood pressure study with over 9,000 participants, the Systolic Blood Pressure Intervention Trial (SPRINT), demonstrated that intensive blood pressure control (SBP < 120 mmHg) compared to routine management control (SBP < 140 mmHg) resulted in significantly less CVD events (5.2% vs. 6.8%, hazard ratio (HR) 0.75, 95% confidence interval (CI) [0.64, 0.89], p < 0.0001) in adults 50 years of age and older (Lewis et al., 2021). The trial concluded early due to favorable findings. The NHLBI determined it was
necessary to communicate the beneficial findings to participants, investigators, healthcare community, and the public (Lewis et al., 2021).

In the U.S., hypertension contributes to more CVD deaths than any other modifiable risk factor (Danaei et al., 2009; Whelton et al., 2018). Countless epidemiological studies have substantiated the linear relationship between blood pressure levels and CVD risks and events (Whelton et al., 2018). In a follow-up study of 23,272 National Health and Nutrition Examination Survey (NHANES) participants, more than 50% of the cardiovascular and cerebrovascular deaths were attributed to elevated blood pressure (Ford, 2011; Whelton et al., 2018). Twenty-five percent of the cardiovascular events in the Atherosclerosis Risk in Communities (ARIC) study participants were attributed to hypertension (Whelton et al., 2018).

Surprisingly young adults have a high prevalence of hypertension (Pleis et al., 2009). While this is likely multifactorial, hypertension is often undetected or overlooked in this population due to lack of interaction with healthcare professionals and age-based health assumptions (Niiranen et al., 2017; Wang et al., 2020). Hypertension in young adults aged 18–30 years is evidenced by the findings of the longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) study. The CARDIA study (1985-1986) enrolled 5,115 young adults between the ages of 18-30 years. Findings indicated that one in eight young adults is hypertensive (De Venecia et al., 2016; Hinton et al., 2020; Yano et al., 2018). Leeson (2017) found that one in five young adults less than 40 years of age have blood pressures above the recommended thresholds. Any increase in blood pressure increases the relative risk for CVD in young adults, whereas the absolute risk is higher in adults 50 years of age and older. The point is that elevated blood pressure is not typically
addressed until after a cardiovascular event or it becomes a critical concern. The evaluation of early-onset hypertension, as with the WHI-OS women who self-reported their age at diagnosis, provided the opportunity to assess co-existing risk factors, evaluate indiscernible target organ damage, and define cardiovascular and cerebrovascular mortality risk (Leeson & Lewandowski, 2017; Melgarejo et al., 2021; Niiranen et al., 2017; Wang et al., 2020).

**Hypertension in Women**

**Epidemiological Evidence.** A common misconception is that men and women develop and experience cardiovascular conditions equally (Brewer et al., 2015; Crea et al., 2015; Maas & Appelman, 2010; Melgarejo et al., 2021; Taqueti, 2018; Westerman & Wenger, 2016). Research in the last two decades has determined that CVD manifests differently in males and females, specifically concerning disease onset and clinical symptoms (Crea et al., 2015; Maas & Appelman, 2010; Taqueti, 2018; Westerman & Wenger, 2016). Analyzing blood pressure trends is the most accessible measure of evaluating vascular aging and cardiovascular status. Ji et al. (2020) conducted gender-specific analyses of 43 years of blood pressure measurements from 32,833 participants (ages 5 to 98 years) from four research cohorts, including the Framingham Heart Study (FHS), the Atherosclerosis Risk in Communities Study (ARIC), the Coronary Artery Risk Development in Young Adults Study (CARDIA), and the Multi-Ethnic Study of Atherosclerosis (MESA). Analyses of blood pressure trajectories revealed that blood pressure elevation began earlier in life and progressed faster in women than men over the course of their lives (Ji et al., 2020). Blood pressure markedly increased as early as the third decade for women and persisted throughout their lives, even after adjusting for
CVD risk factors such as weight, cholesterol levels, diabetes, and smoking (Ji et al., 2020). Similarly, hypertension was the more potent risk factor for CVD mortality in women between the ages of 40–50 years compared to same-aged males in Lewington’s (2002) 61-study meta-analysis.

In the NHANES data from 1999 to 2006, 36.3% of healthy adults had “borderline” hypertension or were in the “prehypertension” stage (SBP 120–139 mmHg or DBP 80–90 mmHg) with a greater prevalence in men (45% men versus 27% women; Gupta et al., 2010). These data strengthened the presumption that young women (ages 20–44 years) were shielded from hypertension and CVD because of the cardioprotective properties of estrogen (Murphy et al., 2011; Ramirez & Sullivan, 2018). Although these differences appear seemingly low, 20% of the women (ages 20–44 years) were still hypertensive. Subsequently, the WHI determined that hormone replacement therapy not only failed to reduce cardiovascular events but augmented them, questioning the cardioprotective properties of female hormones (Murphy et al., 2011; Rossouw et al., 2002). The importance of gaining a better understanding of blood pressure trends among women remains a priority. A critical evaluation of conclusions drawn in clinical studies on hypertension should be evaluated with an emphasis on recognizing gender differences.

Male participation has traditionally dominated cardiovascular clinical trials (Jin et al., 2020). Furthermore, in cardiovascular clinical trials that include both genders, findings are rarely analyzed or reported separately (Ramirez & Sullivan, 2018). It is therefore challenging to infer the effect of hypertension on CVD outcomes in women as well as the efficacy of antihypertensive treatments for controlling women’s blood pressure and reducing their CVD risk (Ramirez & Sullivan, 2018). To illustrate this point,
three national, innovative hypertension trials vastly underrepresented women (39.5%, 40%, and 36%, respectively) including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH), and Systolic Blood Pressure Intervention Trial (SPRINT; Abramson, 2018; Jin et al., 2020; Wenger et al., 2018). An analysis of cardiovascular studies registered with ClinicalTrials.gov determined that the overall participation rate of women was 38.2% (Jin et al., 2020). A cross-sectional analysis of 20,020 U.S.-based clinical trials by Steinberg et al. (2021) determined that gender bias was evident by disease category. Women were the most underrepresented in research trials in two top medical specialties, cardiology and infectious disease (Steinberg et al., 2021). The lack of gender-specific analyses and low enrollment of women in clinical trials calls into question the reliability of treatment methods for hypertensive women and warrants acute attention to a condition that most women will develop during their lifetime. Equal representation in CVD research is clinically necessary to develop gender-specific practices and treatment modalities that are most effective for women.

Gender Differences in the Regulation of Blood Pressure. Research studies have been designed to explain why women have a higher prevalence of hypertension and identify gender-specific blood pressure differences (Gudmundsdottir et al., 2012; Wenger et al., 2018; Wenger et al., 2022). Biologically, women have smaller hearts, smaller ventricular cavities, thinner ventricular walls, smaller and stiffer coronary arteries, develop more diffuse atherosclerotic plaque patterns, and have greater hormonal influences than men (Beale et al., 2018; Brahmbhatt et al., 2019; Ji et al., 2021; Maas &
Appelman, 2010). Gender-specific research shows that sex steroids and hormone levels, particularly androgens, estradiol, and progesterone in premenopausal and postmenopausal women, play a significant role in blood pressure regulation (Brahmbhatt et al., 2019; Gerdts et al., 2022; Gudmundsdottir et al., 2012; Reckelhoff, 2018). Women have unique, hormonally-related hypertensive patterns depending on their life stage or condition, such as pregnancy, menopause, and polycystic ovarian disease (Ahmad & Oparil, 2017; Brahmbhatt et al., 2019; Reckelhoff, 2018). A pregnancy complicated by preeclampsia, for instance, portends a four-fold increase in long-term hypertension, doubling the 15-year risk of CVD mortality compared to women without a pregnancy complicated by hypertension (Gerdts et al., 2022; Wenger et al., 2018). On the other end of the spectrum, menopause, which includes the loss of estrogen and progesterone, is associated with a two-fold increased risk of hypertension, accounting for 75% of all postmenopausal women in the U.S. (Abramson, 2018).

Emerging hypertension research has identified lower plasma renin levels in hypertensive women compared to normotensive women and hypertensive men (Medina et al., 2020). This suggests that the renin-angiotensin system (RAS) may respond differently in hypertensive women (Gerdts et al., 2022). Renin is an enzyme produced by the kidneys to regulate blood pressure through a series of complex reactions. When low circulating plasma renin levels are detected, a cascade of chain reactions ultimately causes an increase in circulating angiotensin II. Angiotensin II causes vasoconstriction and triggers the release of vasopressin, an antidiuretic hormone from the pituitary gland. The result is elevated blood pressure (Gudmundsdottir et al., 2012; Pacurari et al., 2014).
Another essential factor in blood pressure regulation that has been found to differ among genders is the **baroreflex** or blood pressure response loop (Fu & Ogoh, 2019; Gudmundsdottir et al., 2012; Sevre et al., 2001). The baroreflex feedback loop consists of two main components – the cardiovagal component, which is responsible for heart rate control, and the sympathetic component, which is responsible for vasculature control (Fu & Ogoh, 2019; Karvonen et al., 2019; Matthews et al., 2019; Sevre et al., 2001). Cardiovagal and sympathetic baroreflex sensitivity (BRS) has been found to be significantly reduced, with greater magnitude, in hypertensive women compared to age-matched hypertensive males and normotensive women (Gerdt et al., 2022; Sevre et al., 2001). This inverse relationship between reduced BRS and higher blood pressure, significantly evident in women, may contribute to the unique type of hypertension found in females (Fu & Ogoh, 2019). Furthermore, low BRS has been reported to be an independent factor associated with developing cardiac arrhythmias and sudden death following a myocardial infarction (Sevre et al., 2001). Emerging research on BRS activity provides evidence that hypertensive women have an increased risk of CVD morbidity and mortality (Matthews et al., 2019).

**Gender Differences in Cardiac Structural and Functional.** Adverse consequences of cardiac pathophysiology appear to be more prevalent in hypertensive women compared to hypertensive men (Gerdt et al., 2022; Taqueti, 2018; Wenger et al., 2018). **Left ventricular (LV) hypertrophy** (LVH) is the clinical manifestation of hypertension and a powerful prognostic indicator of hypertension severity and duration (Gerdt et al., 2022). Hypertensive LVH is more prevalent in women compared to age-matched men and less responsive to antihypertensive treatment (Gerdt et al., 2008;
Gerdts et al., 2022; Okin et al., 2008). The Strong Heart study found that hypertensive women were 36% more likely to have LVH than age-matched hypertensive men (de Simone et al., 2013).

The left atrium (LA) dilates with persistent hypertension. In healthy individuals, the LA is larger in males than females; however, LA dilatation is more prevalent in women than men with hypertension (Gerdts et al., 2022). A dilated LA is associated with increased CVD, particularly atrial fibrillation, heart failure, and ischemic stroke (Gerdts et al., 2002; Gerdts et al., 2007; Gupta et al., 2013; Sardana et al., 2018). Hypertension increases the risk of heart failure three-fold for women but only two-fold risk in men (Gerdts et al., 2022; Virani et al., 2021).

Anatomical changes due to hypertensive heart disease lead to functional alterations (Hayward et al., 2001). Hypertensive women have lower ventricular stroke volumes than hypertensive men, even after adjusting for body surface area (Hayward et al., 2001). Persistent LVH causes lower left ejection fraction and reduced cardiac output, resulting in a downstream effect that contributes to arterial stiffness and a higher incidence of CVD events or mortality (de Simone et al., 2013; Gerdts et al., 2008; Gerdts et al., 2022).

**Gender Differences in Coronary Vasculature.** Differences in coronary vascular structure and function exist among genders in response to blood pressure and CVD outcomes (Gerdts et al., 2022; Virani et al., 2021). Women develop coronary microvascular disease more frequently than men (Taqueti, 2018; Virani et al., 2021). *Coronary microvascular disease*, also known as small artery disease or small vessel disease, is a type of coronary heart disease due to alterations in the endothelial lining of
the microvascular coronary arteries (Mehta et al., 2019; Reynolds et al., 2022). This is different from coronary heart disease which typically develops in men. In men, plaques form and adhere to the endothelium of the macrovascular coronary arteries causing a blockage of blood flow (Mehta et al., 2019; Reynolds et al., 2022). In microvascular disease, hypertension destroys the endothelial lining, impairing the physiological mechanisms of the vessels. This non-obstructive endothelial alteration, unable to meet the hemodynamic needs of the heart, causes coronary spasms, resulting in reduced blood flow (Mehta et al., 2019; Reynolds et al., 2022). The result of microvascular (small vessel, non-obstructive disease) and macrovascular (large vessel, plaque obstructive disease) coronary disease is restricted blood flow (Groepenhoff et al., 2020; Looi et al., 2012; Mehta et al., 2019; Mileva et al., 2022; Reynolds et al., 2022; Taqueti, 2018; Virani et al., 2021). It is important to note that microvascular and macrovascular diseases are not isolated to a specific gender. Men can develop microvascular disease, just as women can develop macrovascular disease. However, the predominance of obstructive plaque formation is the more pervasive disease in men, and the strong prevalence of hypertension in women combined with smaller coronary vessels makes microvascular heart disease more common for women (Groepenhoff et al., 2020; Looi et al., 2012; Mileva et al., 2022).

The clinical manifestation of coronary vascular disease also differs (Groepenhoff et al., 2020; Mileva et al., 2022). Women often present with uncharacteristic, transient pain due to hypoxic spasms of the small coronary arteries. Men with macrovascular disease typically present with crushing, substernal chest pain caused by a complete blockage of blood and oxygen of a larger coronary vessel (Mehta et al., 2019; Mileva et
The presentation of symptoms supports the need for gender-specific hypertension care and treatments.

**Gender Differences in Cardiovascular Events and Mortality.** Acute myocardial infarction is the most prevalent CVD event, with hypertension being the most potent determinant of CVD risk (Kringeland et al., 2021). In the Norwegian Tromsø study, hypertension was associated with a greater risk of myocardial infarction for women 35–94 years of age compared to men of the same age range (Albrektsen et al., 2017; Jacobsen et al., 2012; Kringeland et al., 2021). The Interheart Study found comparable results in women compared to age-matched men (Anand et al., 2008; Kringeland et al., 2021; Yusuf et al., 2004). The United Kingdom Biobank study, including 471,998 participants without a history of CVD, found that women with hypertension were 40% more likely to experience a fatal or non-fatal myocardial infarction than men (Millett et al., 2018). Lastly, the Hordaland Health Study found that blood pressure $\geq 130/80$ mmHg in the fourth decade of life doubled a woman’s risk of a midlife CVD event. These findings did not materialize for men of the same age, even after adjusting for other confounding cardiovascular risk factors (Kringeland et al., 2021).

CVD, the leading cause of death in the U.S., affected 448,498 men and 420,164 women in 2018 (Virani et al., 2021). The gender-combined number of CVD deaths increased by 4.8% in 2021, which is the most significant increase in heart disease fatalities since 2012 (Ahmad & Anderson, 2021). Deaths from cerebrovascular disease in the U.S. in 2018 totaled 62,844 men and 84,966 women; women accounted for 57.5% of the U.S. stroke deaths in 2018 (Virani et al., 2021). As a frame of reference, each year, twice as many women die from CVD compared to breast cancer (Wenger et al., 2018).
On average, 55,000 more women than men, equating to one in every five women, experience a cerebrovascular event each year (Virani et al., 2021). Among risk factors, hypertension was and has remained the most significant contributor to stroke and CVD mortality in women (Virani et al., 2021; Wenger et al., 2018). The most effective strategy for reducing stroke risk is to reduce blood pressure (Virani et al., 2021). A meta-analysis by Law et al. (2009) consisting of 147 randomized control trials found stroke incidence decreased by 41% (95% CI [33%, 48%]) when systolic blood pressure was reduced by 10 mmHg or diastolic blood pressure by 5 mmHg. It is an understatement, therefore, to assert that hypertension detection and control are critically important to women’s adult health.

In summary, the regulators of blood pressure, hypertensive structural and functional alterations, vascular responses, and cardiovascular outcomes due to longstanding and/or uncontrolled hypertension differ between women and men (Gerdts et al., 2022; Virani et al., 2021). These differences confer a greater risk of adverse CVD events in women compared to men with the same degree of hypertension (Bello & Cheng, 2022). The greater harm of hypertension for women compared with similarly aged men warrants further research into gender-specific blood pressure thresholds to mitigate CVD risk for women (Beale et al., 2018; Ji et al., 2020; Ji et al., 2021; Wenger et al., 2018).

**Gender Differences in Hypertension Detection, Evaluation, and Management.** Currently, there are no gender-specific recommendations for antihypertensive therapy, but comorbidities may influence choice of treatment. Diuretic medications are commonly prescribed in women based on the assumption that its
treatment effects will result in reduced bone loss and prevention of osteoporosis (Abramson, 2018). Women tend to have more drug-related side effects and adverse effects from antihypertensive medications than men (1.5–1.7-fold higher; Abramson, 2018; Brahmbhatt et al., 2019; Turnbull et al., 2008; Wenger et al., 2018). In the Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE) and Treatment of Mild Hypertension Study (TOMHS) trials, women reported side effects more often than men. For instance, women who were prescribed angiotensin-converting enzyme (ACE) inhibitors developed a cough three times more often than men (Wenger et al., 2018). A meta-analysis of seven randomized clinical trials (RCTs) with 20,802 women and 19,975 men revealed that the efficacy of antihypertension treatment for preventing CVD events did not differ by gender. For maximum effectiveness, treatment options must incorporate gender-specific profiles (Gueyffier et al., 1997; Muiesan et al., 2017; Muiesan et al., 2016).

The most recent hypertension guideline does not differentiate hypertensive treatment recommendations among genders, but advises individualizing treatment based on risk-enhancing factors and comorbid conditions (Ahmad & Oparil, 2017; Whelton et al., 2018). Therefore, future cardiovascular research must use recruitment methods more inclusive of women so that gender-specific blood pressure targets and therapeutic recommendations can elucidate effective blood pressure parameters and positively benefit women’s cardiovascular health (Ahmad & Oparil, 2017; Muiesan et al., 2016). The identification and treatment of hypertension remains suboptimal for women, which impedes gender-specific health promotion efforts.

*Women’s Health Initiative Hypertension Studies*
The Women’s Health Initiative (WHI) is a large-scale, racially and ethnically diverse, well-characterized, longitudinal cohort of postmenopausal women in the U.S. (Women’s Health Initiative, 2021). Valuable data on the prevalence and incidence of hypertension and antihypertensive treatments were available in this landmark study and continue to be collected in extension studies. The blood pressures of WHI participants have been analyzed in numerous settings, among varying ethnicities, and in various concomitant conditions. Concomitant or comorbid conditions include peripheral artery disease, colorectal and breast cancers, heart failure, diabetes, periodontal disease, sickle cell trait, varying dietary patterns, various hormone replacement formulations, and more (Women’s Health Initiative, 2021). Many ancillary studies have evolved from the Women’s Health Initiative Observational Study (WHI-OS) and Clinical Trials (WHI-CT) in which blood pressures have been assessed. The Women’s Health Initiative Memory Study (WHIMS), the Women’s Health Initiative Sight Exam (WHI-SE), and the Objective Physical Activity and Cardiovascular Health (OPACH) study are examples of WHI research studies in which blood pressure was an important measure (Women's Health Initiative, 2021).

Secondary analyses have also emerged. Allison et al. (2008) studied the association between blood pressure readings and coronary artery calcium scores of participants enrolled in the Hormone Replacement Therapy (HRT) clinical trial. Margolis and colleagues (2008) studied the effect of calcium and vitamin D supplementation on blood pressure in a randomized trial. Kosoy et al. (2012) examined the relationship of hypertension in African and Hispanic American women enrolled in the WHI-OS and WHI-CT studies. Visit-to-visit blood pressure variability, various physical performance
measures, and urinary sulfatoxymelatonin levels have been studied as potential markers to measure the prevalence and incidence of hypertension in WHI participants (Laddu et al., 2022; Pérez-Caraballo et al., 2018; Shimbo et al., 2014). A vast number and array of research on blood pressure has stemmed from the WHI studies, but none have compared birth history of preterm birth versus full-term birth.

Three studies from the WHI database have focused directly on blood pressure. The first study of interest, published by Wassertheil-Smoller et al. (2000), assessed patterns of antihypertensive treatment and the effectiveness of blood pressure control. A total of 90,755 women from the WHI-OS and the WHI-CT were included in the analysis. Hypertension was detected in 34,339 (37.8%) of the women. Among the hypertensive women, 64.3% were treated with antihypertensive medications, but only 36.1% had systolic blood pressures < 140 mmHg and diastolic blood pressures < 90 mmHg. Therefore, almost 12,000 women had untreated hypertension, and 64% of the women had uncontrolled hypertension. Furthermore, of the total number of hypertensive women, over 62% had experienced a prior CVD event, portending a poor level of control and management. Uncontrolled hypertension that contributed to CVD events may be attributed to ineffective treatment; 61% of the women were treated with monotherapy (Wassertheil-Smoller et al., 2000).

A second analysis confirmed Wassertheil-Smoller’s findings and determined that hormone therapy did not influence blood pressure (Oparil, 2006). The oldest participants and black American women had the highest blood pressures. Obesity (BMI > 27.3 kg/m²) was the most predominant CVD risk factor associated with hypertension. Treatment recommendations for hypertension were based on the guidelines at the time of data
collection, which were the Fourth (1988) through Sixth (1997) Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 4 Writing Group, 1988; JNC 5 Writing Group, 1993; JNC 6 Writing Group, 1997). All three guidelines advised individuals with diabetes to maintain stricter blood pressure control, aiming for a blood pressure goal of < 130 mmHg and < 85 mmHg; only 21% of diabetic women in the WHI were at goal (Oparil, 2006).

Lastly, the most recent research to explicitly examine blood pressures involved WHI-OS participants. Smith et al. (2016) explored birth weight as a risk factor for CVD. A sample of 63,815 women self-reported their birth weight, categorized as < 6 pounds, 6-7 pounds 15 ounces, 8-9 pounds 15 ounces, and ≥ 10 pounds. Unexpectedly, over 7,000 women reported a birth weight of < 6 pounds. Study findings associated the co-existence of low birth weight and hypertension with a significant increase in CVD events (Smith et al., 2016). This was the first study to examine the association of hypertension and CVD risks with birth weight in the WHI-OS cohort of women (Smith et al., 2016). Although birth status (preterm versus full term) has never been investigated in the WHI-OS cohort, a study that focuses on birth status could contribute substantially to the present understanding of women’s cardiovascular health and outcomes.

In conclusion, hypertension is a common cardiovascular condition that affects women during all phases of the lifecycle (Wenger et al., 2018). The incidence of hypertension increases more precipitously in women than men after 50 years of age (Wenger et al., 2018). The awareness, treatment, and particularly the control of hypertension in women remains suboptimal despite the magnitude of its detrimental impact on health and mortality (Abramson, 2018; Wenger et al., 2018). Gender-specific
hypertensive preventive measures and sophisticated risk factor stratification integrating gender-specific comorbidities can guide healthcare providers in the most effective treatment modalities for women. Among the many large U.S. studies of hypertension and CVD, few have incorporated prematurity as a factor in adult studies.

**Hypertension and Prematurity**

**Historical Foundation.** From his observations and subsequent studies, the British epidemiologist David Barker (1938-2013) discovered that maternal undernutrition during pregnancy correlated with higher risks of CVD for their offspring when they reached adulthood (Barker & Osmond, 1986). From 1921–1925, infant mortality rates were high in England and Wales. The infants who survived had high mortality rates from heart disease 40–50 years later, from 1968-1978. Barker hypothesized that during that era, maternal malnutrition during pregnancy and concurrent poor nutrition in early life was associated with the high neonatal mortality rate in infants born early as well as later-life heart disease in those who grew into adulthood (Barker & Osmond, 1986; Huxley et al., 2002). Additional epidemiological observations and recent epigenetic studies have supported Barker’s hypothesis that the perinatal environment strongly influences susceptibility to cardiac disease later in life (Arima & Fukuoka, 2020). As discussed earlier in this chapter, the Barker hypothesis, originally referred to as Fetal Origins and Disease, has expanded and is now known as the Developmental Origins of Health and Diseases (DOHaD).

Using the lifelong observational framework of the DOHaD theory, consistent and robust evidence was found to support the hypothesis that birthweight and later-life blood pressure are associated (Arima et al., 2018). In alignment with Barker’s hypothesis,
Johansson (2005) embarked on research to determine whether gestational age was linked with increased risk of hypertension later in life. The population-based cohort of 32,495 men born from 1973–1981 who served in the Swedish military found that an increased risk of hypertension was associated with small-for-gestational age (SGA) infants who were born at 33 weeks gestation or later. Small-for-gestational age in this study was defined as a birth weight > 2 standard deviations (SDs) below the mean reference weight for gestational age according to the Swedish reference curve for normal fetal growth (Johansson et al., 2005). Men born even earlier, between 24–28 weeks gestational age, displayed a two-fold increased risk of hypertension. This analysis supported Barker’s work and established that the risk of high blood pressure correlated with gestational age to a greater extent than previously thought (Johansson et al., 2005). Dalziel (2007) enrolled 147 30-year-olds who were full term born and 311 who were preterm born in his study on birth status and systolic blood pressure. Dalziel (2007) found that preterm birth was associated with higher systolic blood pressures in the third decade of life. Dalziel’s findings were significant in that gestation duration/gestational age rather than poor fetal growth was the critical element for increased risk of hypertension (Cocco et al., 2018; Dalziel et al., 2007).

Research that followed Dalziel et al. (2007) reported conflicting findings. For example, Bonamy (2008) and Pyhala (2009) determined that low birth weight due to poor fetal growth, not gestation duration, was associated with hypertension in later adulthood (Bonamy et al., 2008; Pyhala et al., 2009). Researchers de Jong et al. (2011) conducted a systematic review of 27 observational studies and a meta-analysis of 10 studies comparing systolic blood pressure between adolescents of the same age who were born
preterm, very low birth weight (VLBW), or full term (6.3-22.4 years, median age 17.8 years). Samples of adolescents totaled 1,324 preterm (28.8-34.1 weeks gestational age, mean gestational age of 30.2 weeks), and VLBW adolescents (1,098-1,958 grams, with a mean birth weight of 1,280 grams) were compared with 1,738 adolescents born full term of the same ages. Results revealed that adolescents born preterm or VLBW had systolic blood pressures 2.5–3.8 mmHg higher than the adolescents born full term (de Jong et al., 2012).

Since this first meta-analysis, research on the association between preterm birth and hypertension has advanced. Another meta-analysis by Parkinson et al. (2013) found that prematurity was associated with 2.8–5.7 mmHg higher systolic blood pressure (mean systolic blood pressure difference of 4.2 mmHg) for young adults who were born preterm. Parkinson’s meta-analysis also found that women born preterm were at greater risk of developing hypertension than men born preterm, with 4.6 mmHg higher systolic blood pressures and 2.9 mmHg higher diastolic blood pressures (Hovi et al., 2016; Parkinson et al., 2013). These differences are significant because a 2 mmHg decrease in diastolic pressure is predicted to reduce CVD mortality by up to 14% and cerebrovascular events by 19% (Hovi et al., 2016). Thus, the research to date has been on adolescents and young adults, not middle-aged or older adults.

**Anatomical and Physiological Cardiac Findings.** Rapid fetal cardiac development occurs during the third trimester of pregnancy. Approximately 3 billion cardiomyocytes shape the human heart, with nearly 40% proliferating during the first few postnatal weeks (Bergmann et al., 2009; Lázár et al., 2017; Tirziu et al., 2010). The *cardiomyocytes*, which are the functional cells of the heart muscle responsible for
initiating contractility and controlling rhythmic beating, undergo robust growth and proliferation during this time. These cells form the ventricular trabeculations and myocardial walls in preparation for the increased workload of the systemic system (Bensley et al., 2010; Woodcock & Matkovich, 2005; Zhao et al., 2020).

Cardiomyocyte count is relatively consistent over the human lifespan but slowly diminishes < 1% per year, beginning around age 25 (Parmacek & Epstein, 2009). Examining the myocardium of preterm infants who died shortly after birth (23–36 weeks of gestation) compared to stillborn full-term infants revealed a significant reduction in the number of proliferated cardiomyocytes in the preterm infants (Bensley et al., 2018). Sudden disruption of cardiomyocyte proliferation due to preterm birth accentuated the reduction in cardiomyocyte endowment and potentially the adverse cardiac growth trajectory during preterm-birth infants’ neonatal period (Bensley et al., 2018; Zhao et al., 2020).

Bensley et al. (2010) used ovine models in the first experimental study designed to investigate the effects of premature birth on myocardial structure and function. Distinct myoarchitectural changes were measured in cardiac size (diameter), mass (hypertrophy), geometry (wall thickness and chamber shape), which also changed cardiac function in the preterm hearts (Bensley et al., 2010). Many of the cardiomyocytes were underdeveloped, functionally immature, and hypertrophied. Furthermore, halted postnatal cellular proliferation was assumed to be responsible for the lower cardiomyocyte endowment count (Bensley et al., 2010).

Large collagen deposits, up to a seven-fold increase, and lymphocytic infiltration were detected in the myocardium of preterm infant sheep (Bensley et al., 2010). Collagen
deposits diminish elastic recoil of the myocardium, resulting in impaired diastolic function (Bensley et al., 2018; Bensley et al., 2010; Cowling et al., 2019). Lymphocytic infiltration is indicative of myocardial injury (Bensley et al., 2010). It was inferred that physiological remodeling of cardiomyocytes occurred as the result of disrupted cardiogenesis due to preterm birth. Potentially irreversible, cardiac remodeling clinically manifests as biventricular hypertrophy and intraventricular septal hypertrophy. These alterations were suggested to possibly result in long-term cardiac dysfunction in adults born preterm (Bensley et al., 2010).

The first studies recognizing unique cardiac phenotypes of prematurity in humans included 102 young adults, 23–28 years of age, born preterm (mean gestational age of 30 weeks) and 132 same-aged young adults born full term (Lewandowski, Augustine, et al., 2013). Echocardiography and cardiac magnetic resonance imaging (cMRI) found that compared to full-term born young adults, their peers born preterm exhibited smaller left ventricular (LV) end-diastolic volumes, smaller LV cavities, thicker LV walls corresponding to reduced internal cavity size, and greater LV mass. LV mass was increased by as much as 20% even after indexing for body surface area and blood pressures. See Figure 4. Structural and Functional Changes in Young Adults Born Preterm. Lower contractility and relaxation of cardiac ventricles between cycles, measured as LV systolic and diastolic strain rates, led to lower ventricular stroke volume in young adults born preterm compared to their peers full-term born. Yet, LV ejection fractions remained within the clinically normal range (Lewandowski, Augustine, et al., 2013). Like the LV, right ventricular (RV) systolic and diastolic strain rate was reduced in young adults born preterm. An important difference in ventricular findings was that
21% of the young adults born preterm had ejection fractions on the lower limits of normal, and 6% of young adults born preterm had clinically significant decreased ejection fraction levels indicative of RV systolic impairment (Lewandowski, Bradlow, et al., 2013). Degree of prematurity correlated directly with myocardial alterations such that each shortened week of gestation corresponded to a 1.5% relative increase in LV mass, 2.7% relative increase in RV mass, and 2.5% lower RV ejection fraction (Lewandowski, Bradlow, et al., 2013). These findings have escalated the need for defining this unique cardiac remodeling process and distinct cardiac phenotype in individuals born preterm (Bertagnolli et al., 2014; Bertagnolli et al., 2016; Mohamed et al., 2020).

**Figure 4**

*Structural and Functional Changes in Young Adults Born Preterm*


The RV is the dominant pumping chamber *in utero*, responsible for over 60% of cardiac output during fetal circulation (Gardiner, 2005). At birth, a complex and rapid physiological shift occurs, with the RV becoming the low-pressure circuit responsible for
the pulmonary circulation and the LV taking over the high-pressure circuit responsible for systemic circulation (Bensley et al., 2016; Gardiner, 2005; Tan & Lewandowski, 2020). In the early postnatal period, physiologic adaptations that the ventricles undergo differ in premature infants compared to infants born full term (Belfort & Sacks, 2021). The exact mechanisms responsible for adaptive ventricular remodeling of the RV, for example, are essentially unknown but are thought to be based on two phenomena—hemodynamic instability and abnormal cardiomyocyte development (Lewandowski, Bradlow, et al., 2013; Mohamed et al., 2018; Mohamed et al., 2021; Tan & Lewandowski, 2020).

The first phenomenon is hemodynamic instability of the cardiopulmonary system associated with prematurity (de Boode, 2020). Changes in hemodynamic pressures in an underdeveloped, functionally immature cardiopulmonary system increase the functional demands of the RV. As pressure builds from a dysfunctional LV that is unable to meet the body’s demands, hemodynamic pressure backflows to the RV (Bates et al., 2020). In the immature pulmonary system, backflow from the LV encourages structural adaptations, which may eventually result in maladaptive RV remodeling, which in turn leads to hemodynamic instability (Bates et al., 2020; de Boode, 2020; Erickson et al., 2019).

The second phenomenon coincides with the loss of third trimester cardiomyocyte development or lack of functional cardiomyocytes expressed earlier (Erickson et al., 2019). Cardiomyocyte mitosis is inhibited, resulting in diminished RV function and reserve (Erickson et al., 2019). Antenatal and postnatal experiences and environments, including medical therapies and medical conditions like pulmonary hypertension and
bronchopulmonary dysplasia that often develop in compromised preterm infants, can further stress the adaptive remodeling of the ventricle. Subsequently, ventricular changes due to physiological impairments yield maladaptive changes in the RV’s functional ability (Belfort & Sacks, 2021; Erickson et al., 2019).

One last noteworthy meta-analysis that investigated ventricular modifications in the preterm population noted that anatomical and physiological cardiac alterations were evident and persisted across all developmental life stages, from neonatal life to young adulthood (Telles et al., 2020). Understanding that morphological and functional cardiac alterations were detected in almost 2,000 preterm-born individuals lends credence to the notion that the preterm heart has unique, persistent phenotypes. It is unknown but speculated that this unique phenotype predisposes the preterm-born individual to early CVD risk (Telles et al., 2020).

**Implications of Anatomical and Physiological Cardiac Findings.** There are many potential contributing variables to the remodeling process of the immature heart; just a few are discussed. A deeper understanding of phenotype variability in the premature heart’s ventricular cavities, walls, and function may facilitate or prohibit the use of specific treatments and interventions (Abushaban et al., 2020). It is unknown whether developmental programming effects on organ development and function are latent and/or not clinically apparent for possibly years after birth. The meta-analysis by Telles (2020) supports discernable modifications in the premature heart from birth to young adulthood. However, large-scale prospective study on clinical phenotyping with preterm infant cohorts is needed. Longitudinal health outcome studies are essential to advance our knowledge about the interrelations between disrupted organogenesis and
lifelong health outcomes. It is necessary to broaden the focus of preterm research from reducing neonatal mortality to understanding the long-term sequelae of prematurity.

**Complimentary Organ Systems.** Renal and vascular systems are also responsible for developmental programming of hypertension in adults born preterm (Dasinger et al., 2016). Studies have noted microvascular and macrovascular structural differences and dysfunction in both organ systems in individuals born preterm, which may influence the development of hypertension (Bensley et al., 2016; Ligi et al., 2010).

**Vascular System.** Disrupted vasculogenesis and vascular remodeling, like cardiogenesis and ventricular remodeling, can result from premature birth (Lazdam et al., 2012). The *endothelium*, or thin membrane of cells lining the inside wall of all blood vessels, is responsible for the overall vascular tone of the vessel as well as vasomotor functions like vasodilation and vasoconstriction (Norman, 2008). Proper physiological function of the vascular system is vital for uninterrupted blood flow (Norman, 2008). An early systematic review of low birth weight and premature individuals found evidence of narrowing in the aorta, coronary arteries, retinal arteries, and carotid arteries, likely resulting from dysfunctional or inadequate elastin synthesis (Norman, 2008).

The production of *elastin*, the connective tissue protein responsible for vascular flexibility, increases significantly after the 25th week of gestation and continues maturing for a few weeks into the postnatal period (Crisafulli et al., 2020). Preterm birth disrupts elastogenesis, yielding inadequate elastin production and impaired elasticity (Berry & Looker, 1973; Crisafulli et al., 2020; Tauzin, 2015). Emerging literature has identified a second vascular component in vasomotor function and maintenance called “endothelial progenitor cells.” Chehade et al. (2018) reported fewer progenitor cells in the endothelial
lining of individuals born preterm, with impeded proliferation in existing cells. Clinically, fewer progenitor cells may play a role in diseases marked by abnormal vascular development, such as bronchopulmonary dysplasia and retinopathy of prematurity (Bertagnolli et al., 2017). These cells may also accelerate vascular aging; a prognosticated process in preterm-born individuals (Bertagnolli et al., 2017).

In addition to impaired endothelial cellular structure and function, Bensley et al.’s (2010) ovine study detected that more than half of the premature sheep exhibited injury to the arterial wall of the ascending aorta. Exposure of the immature aorta to the sudden increase in blood pressure at the time of birth was likely the cause of aortic wall damage (Bensley et al., 2016). Moreover, the lumen of the descending thoracic and abdominal aorta has also been determined to be as much as 20% smaller in the preterm born human population, even after adjusting for body surface area (Boardman et al., 2016; Odri Komazec et al., 2016; Tauzin, 2015). Damage to and smaller size of lumen in the main blood vessel is alleged to have adverse cardiovascular and cerebrovascular consequences over time (Bensley et al., 2016; Boardman et al., 2016; Norman, 2008).

Boardman et al. (2016) performed a comprehensive analysis of cardiac vasculature using ultrasound, doppler imaging, and magnetic imaging to measure cardiovascular structure and stiffness. The study included 102 young adults 23–28 years of age born premature (gestational mean of 30.3 weeks) and 102 full-term peers of the same age. The thoracic and abdominal aorta exhibited smaller aortic lumens and reduced distensibility in preterm infants. Structural and functional findings were manifested as higher systolic blood pressure (121 mmHg +/- 10.9 mmHg versus 112.9 mmHg +/- 10.1
mmHg) and diastolic blood pressure (73 mmHg +/- 7.2 mmHg versus 68.8 mmHg +/- 7 mmHg) in young adults born preterm versus those born full term (Boardman et al., 2016).

In addition to Boardman’s findings, studies using similar technologies have identified generalized increased arterial stiffness, impaired vasomotor responses, reduced elasticity, and altered endothelial compliance in individuals born preterm (Bensley et al., 2016; Bonamy et al., 2005; Lazdam et al., 2012; Martyn & Greenwald, 1997; Rossi et al., 2011; Sutherland et al., 2014; Tauzin, 2015). These structural and functional changes in the endothelium and impaired endothelial responses are evident throughout the central and peripheral circulation (Bensley et al., 2016; Bonamy et al., 2005; Lazdam et al., 2012; Tauzin, 2015). Impaired peripheral vasomotor responses result in elevated peripheral resistance, which leads to substantially higher blood pressures (Lazdam et al., 2012). Reduced aortic elasticity and reduced lumen diameter have also been intricately linked to increased LV mass in adults born preterm (Lazdam et al., 2012; Martyn & Greenwald, 1997).

A final consideration is based on the premise that small babies have small vessels. If the vessels do not grow and develop in proportion to the rest of the body, vascular alterations can have adverse outcomes later in life, particularly in terms of raising blood pressure (Bensley et al., 2016; Norman, 2008).

In summation, impaired vasculogenesis due to the abrupt cessation of endothelial cell proliferation is recognized as a contributor to higher blood pressures noted in individuals born preterm (Chehade et al., 2018; Ligi et al., 2010). More research is needed to understand the complexities of vascular tree development and the mechanisms underlying the development of hypertension. Growth processes of the arterial system and
pathological conditions emanating from adaptive responses associated with early birth are complicated because multiple mechanistic pathways and measurement methods are undefined (Ligi et al., 2010; Tauzin, 2015; Tauzin et al., 2006).

Maladaptive endothelial development is accelerated when elastin maturation is halted and with medical interventions such as antenatal corticosteroids (Bensley et al., 2016; Chehade et al., 2018). The reversibility of these vascular deficiencies is unknown. It is necessary to conduct further studies to substantiated and strengthen the cardiovascular findings that have already been found.

**Renal System.** The kidneys are essential for blood pressure regulation (Brenner et al., 1988; Gurusinghe et al., 2017). Groundbreaking work by Dr. Barry Brenner (1988) demonstrated the association between the role of the kidneys in hypertension, identifying the strong inverse relationship between high blood pressure and low nephron count and function (Brenner et al., 1988; Gurusinghe et al., 2017).

Nephrogenesis begins in the first trimester of pregnancy and continues for up to six weeks after birth, with more than half of the total nephrons developing in the last four weeks of pregnancy (Heo & Lee, 2021; Starr & Hingorani, 2018). The non-regenerative nature of these filtering units makes the nephron number at birth lifelong (Crump, Sundquist, et al., 2019; Heo & Lee, 2021; Starr & Hingorani, 2018). Physiologically, nephron endowment is less in women (Bertram et al., 2011). Preterm birth occurs at a critical stage of nephron development and maturation and may predispose the individual born preterm to kidney complications later in life (Crump, Sundquist, et al., 2019).

Disruption of the nephrogenic process has yielded smaller kidney size, lower nephron count, altered glomerular filtration, and impaired renin-angiotensin function.
(Brenner & Mackenzie, 1997; Crump, Sundquist, et al., 2019; Heo & Lee, 2021; Kanda et al., 2020; Paquette et al., 2018; Starr & Hingorani, 2018). Furthermore, incomplete maturation of the nephrons, together with strained hemodynamic functioning from other organ systems, may result in dysfunctional and unstable nephrons (Hughson et al., 2003). Nephrotoxic medications, including many medications used as treatments during the postnatal period, can also impede postnatal maturation of the nephrons, producing suboptimal renal phenotypes (Crump, Sundquist, et al., 2019). See Figure 5. *Factors Influencing Kidney Endowment.*

**Figure 5**

*Factors Influencing Kidney Endowment*

![Diagram of Factors Influencing Kidney Endowment]

*Note.* This figure depicts the interplay between the DOHaD concepts of environmental exposures and impaired development resulting in low nephron endowment.

The Brenner Adaptive Hypothesis established the inverse association between blood pressure and nephron count (Brenner et al., 1988; Starr & Hingorani, 2018). Mature nephrons must compensate for low nephron count by increasing their surface area to maintain a constant filtration rate (Brenner et al., 1988). This adaptive process leads to
a series of progressive and detrimental structural changes within the functioning nephrons, and over time, the overworked nephrons hypertrophy and become sclerosed (Starr & Hingorani, 2018). Simultaneously, sodium retention from compromised renin-angiotensin mechanisms and reduced filtration surface area of nephrons leads to development of hypertension (Brenner et al., 1988). This vicious cycle of nephron enlargement, coupled with dysfunctional filtration mechanisms and maladjusted renal systems over time, can result in nephron death, advanced hypertension, and renal failure (Brenner et al., 1988; Brenner & Mackenzie, 1997; Kanda et al., 2020).

The relationship between kidney function, hypertension, and premature birth is more complicated than described here. Essentially, hypertension and premature birth are the strongest risk factors for developing kidney disease (Crump, Sundquist, et al., 2019). Elevated blood pressure is often the first indication of renal system dysfunction (Crump, Sundquist, et al., 2019). Treatments to lower blood pressure have been found to preserve renal function and slow the progression of kidney disease. Therefore, early recognition and control of blood pressure is crucial for the population of adults born preterm (de Jong et al., 2012).

There are no known prospective cohort studies of adults born prematurely that reinforce or contradict the association between preterm birth and later-life kidney disease, although animal experiments and autopsies of infants born preterm substantiate the lower nephron count reported in some research (Starr & Hingorani, 2018). In young children and young adults, a national cohort study found that those born preterm (< 37 weeks) and extremely preterm (< 28 weeks) had a two-fold and three-fold risk of kidney disease, respectively (Crump, Sundquist, et al., 2019). Of interest, individuals born early term
(37–38 weeks) were also at increased risk for developing kidney disease (aHR 1.3, 95% CI [1.2, 1.4], \( p < 0.001 \)). Laboratory biomarkers and blood pressure are conventional measures used to evaluate kidney function. Use of the WHI-OS database to evaluate blood pressure in adult women born prematurely provides further insight into the development of hypertension as well as risk factors that may have accelerated the progression of their hypertension. Future analysis of epigenetic factors that could potentially influence nephron endowment, which ultimately contributes to the development of hypertension, must be researched.

**Summary: Hypertension and Prematurity Research.** Research on the health outcomes after preterm birth and the association between preterm birth and higher blood pressure has doubled over the past decade. The literature described earlier in this chapter provided the foundation for the association between preterm birth and hypertension. The anatomical and physiological research described provides a basis for the link between hypertension and preterm birth. Additional important studies include the large Swedish cohort study of 636,552 young adults, 25–37 years of age, with 28,220 born preterm (<37 weeks), that determined that preterm birth was associated with increased use of antihypertensive medication (Crump et al., 2011b). Almost 4% of young adults born between 23–27 weeks gestation took at least one antihypertensive medication, while 1.7% were on four or more antihypertensive medications (Crump et al., 2011b). Two-thirds of the preterm cohort were born late preterm (between 35–36 weeks gestation), and 2% of these young adults took at least one antihypertensive agent per year (Crump et al., 2011b).
As extensive evidence revealed higher systolic blood pressures in adults born preterm, research evolved to explore various factors that could possibly contribute to the development of hypertension in this population. For example, the postnatal environment became an area of focus. Alexander & Intapad (2012) concluded that accelerated postnatal growth directly influenced the development of hypertension, indicating that the postnatal environment was instrumental in the developmental programming of hypertension. Sipola-Leppanen et al. (2015), advancing the “higher systolic blood pressure” literature, tested the hypothesis that young adults born preterm exhibited greater blood pressure variability over 24 hours. Findings demonstrated that those born preterm had a four-fold risk of elevated daytime blood pressures and a six-fold risk of higher 24-hour (sleep and awake) blood pressures. The 24-hour systolic blood pressure of young adults born early was 5.5 mmHg higher than those born full term and 6.4 mmHg higher during daytime blood pressure than young adults born full term. These blood pressure increases correlate to an 18% higher risk of a cardiovascular event and a 21% higher risk of a cerebrovascular event. Young adults born preterm demonstrated greater variability in awake and asleep blood pressures, as depicted by higher individual standard deviations (Sipola-Leppanen, Karvonen, et al., 2015). These findings, replicated by Haikerwal et al. (2020), are highly suggestive of target organ damage, atherosclerosis, and cardiovascular mortality (Mena et al., 2017; Sipola-Leppanen, Karvonen, et al., 2015).

Another study evaluated blood pressures in young adults born preterm at very low birth weights (VLBW; < 1500 g) to ascertain whether higher blood pressures resulted from an early birth or whether another condition accompanying the premature birth was
responsible. Among many risk factors investigated, maternal preeclampsia and female gender of the infant were the only factors to reach significance (Hovi et al., 2016). One study determined that exposure to a hypoxic intrauterine environment due to maternal preeclampsia resulted in a thickened aortic wall, the loss of nitric oxide vessel synthesis, and left ventricular remodeling (Tan & Lewandowski, 2020).

A recent examination of cardiovascular risk factors recognized that 38% of adults born preterm were living with two or more comorbidities compared to 22% in adults born full term (Flahault et al., 2020). Heart failure is a highly prevalent comorbid condition in adults born preterm who have hypertension, and is estimated to carry as high as a 17-fold increased risk for adults born extremely premature (Carr et al., 2017; Crump et al., 2021; Leeson & Lewandowski, 2017; Telles et al., 2020). The etiologic process that leads to the high incidence of heart failure is likely decreased myocardial functional reserve that develops from left ventricular systolic dysfunction (Burchert & Lewandowski, 2019).

**Current Hypertension Treatments.** Determining the unique mechanisms that influence the development of hypertension in individuals born preterm is still ongoing (Flahault et al., 2019). Presently, there is little research that specifies different treatment modalities for hypertensive adults who were born preterm, though data suggests that some neonatal risk factors are modifiable. For example, a few studies have evaluated the effects on cardiac morphology and performance in preterm infants who were fed breast milk compared to formula (El-Khuffash et al., 2021; Lewandowski, 2018; Lewandowski et al., 2016). Lewandowski et al. (2016) assessed the association between early postnatal nutrition and later-life cardiac structure and function. He found that regardless of whether infants were exclusively fed breast milk versus formula-fed, all preterm infants exhibited
comparable LV mass index and ejection fractions. However, formula-fed preterm infants showed significantly shorter LV and luminal narrowing (Lewandowski et al., 2016). Importantly, preterm infants who exclusively received breast milk showed normalization of the LV (9.73%, \( p = 0.04 \)) and RV (18.2%, \( p < 0.001 \)) end-diastolic volume index and biventricular stroke volume index (9.79%, \( p = 0.05; 22.1\%, \( p = 0.01 \), respectively) compared to preterm infants who were formula-fed (Lewandowski et al., 2016). A similar cross-sectional evaluation of 80 infants born preterm (23–28 weeks gestation, breastmilk-fed) and 100 infants born full term (whose postnatal nutrition varied) were evaluated by echocardiogram at one-year post-birth. Preterm infants who received breast milk had LV and RV cavities, function, and pulmonary pressures that were approaching measures comparable to the full-term infants at one year of age (El-Khuffash et al., 2021).

Later-life cardioprotective effects of breast milk given in early life corresponds with the DOHaD philosophy that an infant’s early life environment can influence their health in later life (Barker & Fall, 1993). Unfortunately, common postnatal treatments and interventions for infants born preterm have demonstrated a relationship with impaired vascular compliance and may contribute to permanent, adverse cardiovascular remodeling (Lewandowski & Leeson, 2014). While beneficial for survival, medications and other interventions for preterm infants pose a long-term risk for their cardiac health later in life (Lewandowski & Leeson, 2014). Further research is necessary to understand the impact of early life interventions on cardiac remodeling and cardiovascular risk. For example, the medical community supports the use of breast milk versus formula in infants born full term, yet long-lasting cardiovascular benefits are unknown in this population (Center for Disease Control and Prevention, 2021a; El-Khuffash et al., 2021).
This begs the questions: Are there other interventions that are cardioprotective? Are there additional factors that enhance or modulate maladaptive structural remodeling? Can the progression of elevated blood pressure be eliminated or reduced with aggressive therapy? If so, when and with what treatment interventions? Anatomic and physiologic mechanisms that contribute to the unique cardiovascular phenotype of prematurity have been researched and identified, as depicted in Figure 6. *Organogenesis Disrupted by Preterm Birth.* Research should now focus on preventing hypertension and CVD morbidity and mortality from the perinatal period through adulthood.

**Figure 6**

*Organogenesis Disrupted by Preterm Birth*

*Note.* This figure depicts the primary pathways that contribute to the development of hypertension in preterm-born individuals.
Summary

Emerging evidence demonstrates that structural and physiological changes occur in the cardiovascular and renovascular systems of infants who were born preterm. Premature birth confers a higher risk of hypertension because organogenesis is disrupted or even permanently arrested (Bertagnolli et al., 2016). Mechanistic causes are not entirely understood. However, disrupted organogenesis has been hypothesized to be one underlying process that could potentially influence development of the adverse cardiovascular phenotype detected in individuals who were born preterm.

Cardiovascular outcomes and the significance of altered cardiovascular phenotypes in adults born preterm are largely unknown. In the literature, gaps exist regarding later-life cardiac health in individuals who were born preterm. Knowledge gaps on disrupted cardiovascular development are primarily grouped into the three principal areas discussed: cardiac remodeling; cardiac adaptation, including the extent and duration; and an altered cardiac phenotype (Bates et al., 2020; Le et al., 2018; Lewandowski et al., 2020). Research has been encouraged to resolve these gaps in knowledge. For instance, Harris et al. (2020) encouraged research to determine if the altered cardiac phenotype of prematurity is associated with an increased cardiovascular risk independent of genetic and other traditional risk factors. Le et al. (2020) recommended the investigation of cardiac remodeling as a contributing risk factor for early-onset heart failure. Carr et al. (2017) suggested research to question the relationship between reduced myocardial functionality with reserve and exercise tolerance in adolescents who were born preterm.
Disrupted nephrogenesis and impaired renal development, leading to reduced nephron endowment due to preterm birth, is another important, inextricable link to hypertension. Avoiding accelerating nephron loss throughout life may help avert the development of hypertension and contribute to improved long-term renal health outcomes. More research into nephroprotective strategies, beginning with interventions that may improve postnatal nephrogenesis and continuing over the life course for preterm-born survivors is needed.

The first step in closing these knowledge gaps may be recognizing preterm birth as a risk factor for later-life cardiovascular disease (D'Agata et al., 2022; Kelly et al., 2021; Leeson & Lewandowski, 2017; Lewandowski et al., 2020). Healthcare providers must inquire about birth history. Parents of those born preterm and the individuals themselves who were born preterm must share their birth history with their healthcare providers, especially as they approach adulthood (Brewer et al., 2022; Manuscript I). Best practice guidelines must be developed that recommend providers inquire about birth history and implement acute screening and preventive measures from early childhood through adulthood.

For years, experimental animal models have been the mainstay for studying the sequelae of premature birth (Lewandowski et al., 2020). Hypertension is the most extensively studied CVD risk factor supported by the DOHaD theory (Gluckman et al., 2016). The study of blood pressure trajectories, age at diagnosis and onset of hypertension, treatment strategies, and the effects of poorly controlled hypertension among women in the WHI-OS database, specifically of the women born preterm, was a focus of this research. The goal of analysis was to discover how birth histories influenced
development of hypertension and contribution to later-life CVD outcomes. Results could offer a greater understanding of the most effective timing and type of CVD prevention strategies, especially in adults who were born prematurely.

Evaluation of CVD outcomes in preterm-born women addresses some of the present knowledge gaps and identifies areas for future research. Consideration of living environments and lifestyle choices of the women in the WHI-OS database, particularly those born prematurely, could possibly deepen our understanding of the unique cardiac phenotypes associated with prematurity. The WHI-OS database provided a valuable description of longitudinal disease and health events and enabled the comparison of differences in lifetime health trajectories between birth cohorts. This dissertation research adds to the existing knowledge of disease onset and health outcomes by extending the study to postmenopausal adult women who were born prematurely. Participants self-reported their health status over their lifetimes, being followed since midlife. The longitudinal perspective was critical to understanding risk factors that contributed to later-life disease and health outcomes. Analysis of these data can close the knowledge gap about pathways of non-communicable disease development in the preterm population.

Hypertension rarely presents in isolation, commonly occurring with CVD comorbidities as well as non-communicable diseases (Virani et al., 2021; Whelton et al., 2018). The high prevalence of non-communicable diseases and unrecognized or untreated hypertension presents a healthcare challenge. The following section introduces two non-communicable conditions associated with hypertension that are more prevalent in women and may be more problematic in women born preterm.
Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a progressive, multi-system autoimmune disorder that affects roughly 1.5 million Americans, or 1% of the adult population (American College of Rheumatology, 2022). Complex interactions among the mechanisms that underlie this chronic condition result in tissue and joint destruction as well as the breakdown of the skeletal system, which profoundly and adversely alters individuals’ functional ability and quality of life (Favalli et al., 2019; Saxena et al., 2014). RA, a disabling disorder, is the most common type of inflammatory arthritis that has an elevated risk for premature cardiovascular mortality (Anyfanti et al., 2021; Favalli et al., 2019; Strait et al., 2019).

The immune-mediated inflammatory disorder of RA is significantly more prevalent in women than men (3:1). Women account for 75% of all individuals with RA. RA is an insidious disorder that typically begins between the third and fourth decade of life in 80% of women and in the sixth decade for men (Agca et al., 2021; Carlens et al., 2009; Favalli et al., 2019). Disease presentation appears to be gender-specific. Women have more distal joint involvement with joint space narrowing, while RA in men mainly affects the large joints and stimulates joint erosion (Favalli et al., 2019). The Consortium of Rheumatology Researchers of North America (CORRONA) network has determined that RA is more aggressive and more debilitating in women than men, based on higher scores on two instruments: the Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire Disability Index (HAQ-DI) [(16.6 vs. 15.8, \( p = 0.02 \) and 0.42 vs. 0.35 ± 0.43, \( p < 0.0001 \), respectively] (Favalli et al., 2019; Jawaheer et al., 2012). The Better Anti-Rheumatic FarmacOTHERapy (BARFOT) study found that significantly
fewer women achieved disease remission despite treatment at two years (32.1% vs. 48%; \( p = 0.001 \)) and five years compared to men (30.8% vs. 52.4%; \( p = 0.001 \); Favalli et al., 2019; Tengstrand et al., 2004).

Individuals with RA have a 1.5-fold higher mortality rate than individuals of similar age who do not have RA (Kuller et al., 2014). RA has been estimated to shorten life expectancy by approximately seven years (Lassere et al., 2013). Interplay between physiological complexities, the progressive and incurable nature of RA, and lack of recognition and control of hypertension in females with RA highlights the importance of gender-specific research for this population (Favalli et al., 2019). Despite the high prevalence of RA, understanding of the pathology and pathophysiology responsible for increased mortality from this condition is not well delineated. Neither are effective treatment strategies for RA (Kuller et al., 2014).

**Hypertension and Rheumatoid Arthritis**

The relationship of hypertension and RA is multifactorial. An understanding of the many risk factors and their relationship in the development of hypertension is evolving as RA research continues (Bartoloni et al., 2018). The prevalence of hypertension in individuals with RA has substantially increased over the past 25 years (Agca et al., 2021; Bartoloni et al., 2018; Jafri et al., 2017). There is debate whether hypertension causes the systemic inflammation associated with RA or whether inflammation from RA triggers hypertension. The latter is the favored association (Bartoloni et al., 2018). Nonetheless, numerous studies report prevalence of hypertension as high as 80% in individuals with RA (Bartoloni et al., 2018; Panoulas et al., 2010). The etiological basis for the high prevalence of hypertension is due to immune-mediated
mechanisms that damage the endothelium of vascular walls, causing increased arterial stiffness and reduced arterial distensibility (Nus & Mallat, 2016). The relationship between arterial stiffness and elevated blood pressure is complicated. Stated simply, arterial stiffening leads to restricted blood flow, causing increased systemic pressure (Mitchell, 2004, 2014, 2021; Mitchell et al., 2004).

Pathogenetically, high levels of C-reactive protein (CRP), a pro-inflammatory biomarker, are detected in individuals with RA (Anyfanti et al., 2021; Cozlea et al., 2013; Manavathongchai et al., 2013; Nus & Mallat, 2016; Panoulas et al., 2008). Persistently elevated circulating CRP levels play a role in endothelial damage by (1) directly contributing to and enhancing vascular inflammation, (2) altering nitric oxide synthesis, thereby impeding the vasodilatory properties of the arterial vessel walls, and (3) increasing oxidative stress, which increases vasoconstriction, vascular remodeling, and vascular wall fibrosis (Cozlea et al., 2013; Manavathongchai et al., 2013; Pope & Choy, 2021). Concurrently, additional pro-inflammatory cytokines, specifically interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) disrupt lipid synthesis, spurring plaque destabilization and rupture (Chodara et al., 2017; Dayer, 2002; Panoulas et al., 2008). This immune-mediated inflammatory cascade results in persistent vasoconstriction, endothelial dysregulation, impaired vasomotor function, and accelerated plaque development and thrombogenesis instability (Anyfanti et al., 2021; Cottone et al., 2006; Cozlea et al., 2013; Willerson & Ridker, 2004). The culmination of this complex inflammatory cascade results in elevated blood pressure and development of atherosclerosis (Cottone et al., 2006).
In systemic autoimmune disorders like RA, the kidneys also play a role in the development of hypertension (Bartoloni et al., 2018; Taylor & Ryan, 2016). Various pathological renal mechanisms contribute to the high prevalence of hypertension (Bartoloni et al., 2018; Taylor & Ryan, 2016). The first mechanism is impaired glomerular filtration due to autoimmune damage to the kidneys. The Kansai Consortium for the Well-Being of Rheumatic Disease Patients (ANSWER) study is the latest research to provide evidence of renal dysfunction, specifically lower glomerular filtration rates in individuals with RA (Ebina et al., 2020; Onishi et al., 2021). When glomerular filtration rate drops, the juxtaglomerular apparatus responds by releasing renin. *Renin*, a crucial component of the renin-angiotensin system, is an enzyme secreted by the kidneys to aid in fluid and blood pressure regulation (Taylor & Ryan, 2016). Through a series of complex reactions, renin splits angiotensinogen into angiotensin I and angiotensin II. The most active of the two is angiotensin II. *Angiotensin II*, a potent systemic vasoconstrictor that increases blood pressure, is also a pro-inflammatory cytokine that simulates production of CRP (Agca et al., 2021; Anyfanti et al., 2021; Bahramali et al., 2014; Chodara et al., 2017; Taylor & Ryan, 2016).

A 2015 meta-analysis of 4,388 individuals who had been diagnosed with RA for < 5 years determined that when hypertension co-existed with RA, the risk of a CVD event was increased by 84% (Baghdadi et al., 2015). In the same meta-analysis of individuals with RA, hypertension was the most prevalent of all comorbid conditions, occurring at a higher rate than diabetes mellitus, smoking, hypercholesterolemia, and obesity (RR 2.24, 95% CI [1.42, 2.06]; Baghdadi et al., 2015). A small echocardiography study of 134 individuals with RA and hypertension and 102 normotensive controls of
similar age found that, independent of age, gender, diabetes, and inflammatory markers, the co-existence of hypertension and RA presented a three-fold higher prevalence of LV hypertrophy (OR 2.89, 95% CI [1.09, 7.63], p = 0.03), LV diastolic dysfunction (OR 2.92, 95% CI [1.14, 7.46], p = 0.03), and lower systemic arterial compliance (Midtbo et al., 2016). Together, the two destructive inflammatory disorders of RA and hypertension create an endless loop of accelerated disease progression and significant management challenges, resulting in a poor prognosis for either condition (Bartoloni et al., 2018). See Figure 7. Rheumatoid Arthritis and Hypertension.

Figure 7

Rheumatoid Arthritis and Hypertension

Note. Representation of mechanisms that contribute to hypertension. CRP = C-reactive protein; NO = nitric oxide; AT II = angiotensin II; PVR = peripheral vascular resistance; CVD = cardiovascular disease.

In the general population, hypertension is considered the most important modifiable risk factor for CVD. However, for individuals with autoimmune diseases, hypertension may be more than a “traditional” risk factor (Panoulas et al., 2008). Hypertension often goes undiagnosed and untreated in individuals with autoimmune disorders (Manavathongchai et al., 2013; Panoulas et al., 2008). Treating hypertension in
individuals with RA can significantly and positively affect their CVD outcomes (Agca et al., 2021). Chodara et al. (2017) determined that for every 11 hypertensive individuals with RA whose blood pressure was controlled, one CVD event was averted each year. Another study determined that hypertension control in individuals with RA could reduce their annual stroke and CVD event rates by more than 2,000 occurrences compared to either condition alone (Panoulas et al., 2008). Treating hypertension in individuals with RA can be challenging (Bartoloni et al., 2018). Antirheumatic medications, joint pain, restricted physical activity, and weight gain complicate treatment strategies and can further increase blood pressure (Chodara et al., 2017).

A variety of drug classes exist to treat RA, including immunosuppressive therapies, biologic agents, non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase (COX) 1 and 2 enzyme inhibitors, disease-modifying antirheumatic drugs (DMARDs), and glucocorticoids. Some RA treatments improve blood pressure while others exacerbate it (Bartoloni et al., 2018; Manavathongchai et al., 2013; White, 2004). Agents like methotrexate (an immunosuppressant) and NSAIDs can worsen kidney function and contribute to higher blood pressure (Bartoloni et al., 2018). Currently there are no treatment guidelines for managing hypertension in individuals with RA. The union of these two concomitant conditions significantly multiplies the risk for CVD, making the development of treatment guidelines an urgent priority.

**Women’s Health Initiative Rheumatoid Arthritis Studies**

The WHI was not designed to study RA. However, health conditions, diagnostic information, medication data, physical activity, and general well-being were self-reported by all participants. RA is a female-predominant condition, with most diagnoses occurring
between the ages of 25- and 45 years (Kobak & Bes, 2018). The predominance, age of disease onset, and life course of the disease have supported numerous ancillary and post hoc analyses, including the prevalence and incidence of RA.

The Women’s Health Initiative Rheumatoid Arthritis (WHI-RA) Study (2009-2011) is the most noteworthy study of women with RA. This study evaluated the prevalence of anti-cyclic citrullinated peptide (anti-CCP), an extremely sensitive biomarker for RA, in 9,988 participants (Kuller et al., 2014; Walitt et al., 2013). The study’s objective was to compare the presence of inflammatory biomarkers with CVD biomarkers and the incidence of CVD. As a follow-up, Kuller et al. (2014) evaluated the mortality rate of individuals with RA over 10 years. A total of 1,325 (13%) participants with RA died. The median time to death was eight years for those who self-reported RA at enrollment and 6.4 years for those who reported RA during follow-up years (Kuller et al., 2014). CVD was the most common cause of death (Kuller et al., 2014).

Two additional WHI studies of RA examined the association between tea and coffee intake and their interaction with anti-rheumatic medications (DMARDs) and fractures (Carbone et al., 2020; Lamichhane et al., 2019). In the Lamichhane et al. (2019) study, a cohort of 76,853 women in the WHI-OS completed questionnaires about their coffee and tea intake. Coffee intake was not associated with RA, but non-herbal, non-decaffeinated tea was associated with incident RA (1.40, 95% CI [1.01, 1.93], p = 0.04; Lamichhane et al., 2019). Carbone et al.’s (2020) study included 1,201 women with a history of RA from the WHI-CT and WHI-OS database. After six years of follow-up, they found that medications used to treat RA, like methotrexate, sulfasalazine, and
hydroxychloroquine, alone or in combination, did not increase the risk of bone fractures (Carbone et al., 2020).

**Rheumatoid Arthritis and Prematurity**

Literature on autoimmune disorders like RA is plentiful; however, research on RA in adults born preterm and in the context of DOHaD is limited. The central premise of Manuscript III is that a higher prevalence of RA in adults born preterm compared to adults born full term might be due to disrupted organogenesis and epigenetic modifications that occurred because of prematurity (Vehaskari & Woods, 2005; Wadhwa et al., 2009). Accordingly, three body systems—the immune, vascular, and renal—and their roles, independently or conjointly, are likely responsible for the developmental programming of RA. Genetic predispositions and environmental factors are also likely contributors to the pathogenesis of RA. In addition to epigenetic regulation, autoimmunity modifications must be considered as influencing the susceptibility or development of RA (Araki & Mimura, 2016).

The first system important in the development of RA is the immune system. An unfavorable intrauterine environment may profoundly and negatively affect the developing fetal immune system (Chen et al., 2016). Maternal behaviors, prenatal exposures, and prenatal stressors influence immune deficiencies in the developing immune system. Especially when coupled with an early birth, maternal stressors may result in permanent physiological alterations in the preterm infant’s immune system (Anyfanti et al., 2021; Chen et al., 2016). Elevated levels of circulating pro-inflammatory cytokines, namely CRP and interleukin-1B and -6 (IL-1B & IL-6), have been detected in the serum of mothers who have high stress/anxiety levels during their second and third
trimesters (Coussons-Read et al., 2007). Not only can these cytokines trigger preterm birth, but they can also cause dysregulation of immune pathways, which can predispose the infant to developing an autoimmune disorder later in life (Anyfanti et al., 2021; Coussons-Read et al., 2007; Yockey & Iwasaki, 2018).

In the immune system, the earliest organ to develop is the thymus (Chen et al., 2016). Development begins in the sixth week of gestation. It continues through late childhood and puberty, when it slowly shrinks and loses its ability to produce T-cells, the primary immune cells that fight infections (Chen et al., 2016; Gordon & Manley, 2011). Maternal stress and exposure to medications such as betamethasone during pregnancy can cause T-cell death and atrophy of the fetal thymus (Diepenbruck et al., 2013). Furthermore, an early life environment permeated with neonatal infections, stressors, and medical therapies can accentuate the pathophysiologies found in an immature immune system, biasing the preterm-born survivor to an autoimmune condition like RA later in life (Carlens et al., 2009).

Within the vascular system, impaired vasculogenesis causes increased susceptibility to autoimmune conditions (Simard et al., 2010). Premature birth disrupts the development of blood vessels and the vascular system, then prenatal and postnatal insults trigger the cytokine-responsive cascade. The complex interplay between an underdeveloped, dysfunctional vascular system with inflammation and pro-inflammatory cytokines can promote vasculopathy, long-term endothelial dysfunction, and the development of inflammatory disorders (Bertagnolli et al., 2016; Chehade et al., 2018; Chen et al., 2016; Ueda et al., 2014). See Figure 8. Disrupted Organogenesis of the Immune and Vascular Systems in Individuals Born Preterm.
**Figure 8**

*Disrupted Organogenesis of the Immune and Vascular Systems in Individuals Born Preterm*

![Diagram of disrupted organogenesis](image)

**Note.** A simplified illustration of the pathway to inflammatory and immune disorders in preterm individuals. IL-6 = interleukin-6; CRP = C-reactive protein; WBC = white blood cells; PTB = preterm born. This chart is a modified version from “Developmental origins of inflammatory and immune diseases” by T Chen, H. Liu, D. Wu, and J. Ping, 2016, *Molecular Human Reproduction, 22*(8), p. 562.

When development is disrupted, the kidneys are the third system that predispose adults born preterm to a condition like RA. The Arthritis Foundation states that individuals with RA have a one-in-four chance of developing kidney disease, compared to the one-in-five likelihood found in the general population (Arthritis Foundation, 2021). The increased risk of kidney dysfunction in individuals with RA is potentially attributed to chronic inflammation, ongoing renal stress from chronic comorbid conditions like...
hypertension, and the nephrotoxic properties of antirheumatic drugs (Chiu et al., 2015). Physiologic research on the preterm population has identified smaller kidneys, lower nephron endowment, altered glomerular filtration rates, and impaired renin-angiotensin function, presumably the result of impaired nephrogenesis (Brenner & Mackenzie, 1997; Heo & Lee, 2021; Kanda et al., 2020). Brenner et al. (1988) proposed that intrauterine and extrauterine stress and impaired nephrogenesis were responsible for kidney malformations and dysfunctions that contributed to the higher prevalence of kidney disease in preterm-born individuals (Starr & Hingorani, 2018).

The heritability of RA is estimated at 60% (Araki & Mimura, 2016; Dedmon, 2020). Aside from an unalterable genetic predisposition, perinatal factors and early infant life may also influence RA development in preterm-born individuals (Araki & Mimura, 2016; Colebatch & Edwards, 2011; Dedmon, 2020). A Finnish study determined that maternal smoking during pregnancy was associated with increased odds of developing RA in female offspring (Jaakkola & Gissler, 2005). Mandl et al. (2009) found that high birth weight was associated with an increased risk of RA development, while others found that low birth weight reduced the risk of RA development later in life (Carlens et al., 2009; Edwards et al., 2006; Jacobsson et al., 2003; Mandl et al., 2009). Findings on breastfeeding have been inconsistent, likely due to variability in how long this form of nutrition was provided (Jacobsson et al., 2003; Simard et al., 2010; Young et al., 2007). Numerous environmental factors have been studied and likely influence the development of RA, including inhaled allergens and pollutants, dust exposure, ultraviolet light, poor or shared living conditions, nutrition, hygiene practices, and infections like cytomegalovirus, hepatitis A, and Escherichia coli (Colebatch & Edwards, 2011;
Edwards & Cooper, 2006; Gluckman et al., 2008). These perinatal and environmental influences may also encourage the expression of epigenetic abnormalities that lead to RA (Arika & Mimura, 2016). Arika & Mimura (2016) reported abnormalities in histone modifications, DNA methylation, and microRNA activate synovial fibroblasts, which exacerbates joint damage and inflammation. An over-proliferation of synovial fibroblasts promotes joint destruction and inhibits T-cell production and suppression of T-cell function, ultimately weakening immune responses in the individual with RA (Araki & Mimura, 2016; Ospelt, 2017). Suppression of an already immature immune system supports the rationale behind Manuscript III.

Mechanisms of programming or reprogramming and the development of the immune system are complex and beyond the scope of this dissertation. However, using the DOHaD paradigm as a basis for understanding the pathogenesis of RA is beneficial. The DOHaD theory is not limited to the in utero period but includes early-life environmental influences like those found in RA development. To date, there is no known research to support the premise that adults born preterm are prone to RA. One study in a similar sized population of women to the WHI was the evaluation of women with RA and self-reported preterm birth history in the Nurses’ Health Study (Simard et al., 2010). Simard et al. (2010) reported there was no correlation between preterm birth and RA. These results must be interpreted with the following caveats: (1) preterm birth was defined as being born two or more weeks early, which did not align with the WHO’s definition, and (2) women with RA may have been underrepresented because (a) they were not nurses, or (b) they were less likely to initially participate in the Nurses’ Health Study because they had an existing diagnosis of RA at enrollment (Sparks et al., 2016).
Summary

In summary, a gap in the literature exists regarding adults who were born preterm and have autoimmune conditions such as RA. The primary reason for lack of research is because the study of common conditions in adults born preterm primarily includes young adults. The symptoms of RA may not present until mid- to later adulthood; therefore, the study of RA in preterm-born adults is still emerging.

For this study, it was reasonable to hypothesize the possible relationship between prematurity and later development of RA because of the high prevalence of RA in women, the greater likelihood in preterm-born individuals, and the strong link to CVD. The DOHaD principles of disrupted development and epigenetic modifications support the hypothesis that an association could exist between preterm birth and later development of RA. Notably, preterm-born women enrolled in the WHI-OS were born before neonatal intensive care was established. Their postnatal environment is largely unknown. When health outcomes were analyzed, exploration and differentiation of their living environments and lifestyle choices had to be considered. This dissertation research studied the prevalence and incidence of RA and the RA-hypertension connection to understand more about the common health occurrences in women born preterm and explore how the triad of their birth history, environment, and lifestyle impacted their health outcomes later in life.

Hypothyroidism

Hypothyroidism, or an underactive thyroid, is a clinical condition that occurs when the thyroid gland produces insufficient amounts of thyroid hormones (Jonklaas et al., 2014). Hypothyroidism affects approximately 10% of the U.S. population, with
another 5% or more who are undiagnosed or unaware that they have thyroid dysfunction (Chiovato et al., 2019; Udovcic et al., 2017). Although there are several causes of hypothyroidism, the two most common causes are inflammation and medical treatments. Hashimoto’s disease, an autoimmune thyroid condition, is the most common cause of thyroid inflammation. Radiation therapy and partial or complete surgical removal of the thyroid gland are the most common medical treatments that cause hypothyroidism (Chiovato et al., 2019; Shahid et al., 2022; Udovcic et al., 2017). Other less common causes of hypothyroidism include dysfunction of or damage to the pituitary gland; iodine deficiency, which is rare in the U.S.; medications; congenital hypothyroidism; and rare infiltrating conditions such as sarcoidosis and hemochromatosis (Chiovato et al., 2019; Jonklaas et al., 2014; Shahid et al., 2022; Udovcic et al., 2017).

Two important iodinated hormones produced by the thyroid are thyroxine (T4; chemically known as tetraiodothyronine) and triiodothyronine (T3). The pituitary gland controls the production of these two thyroid hormones. The pituitary gland, which is regulated by the hypothalamus, produces thyroid stimulating hormone (TSH). TSH tells the thyroid gland how much T4 and T3 to produce and secrete (Shahid et al., 2022). Thyroxine (T4), the primary hormone produced by the thyroid, which accounts for approximately 85% of the gland’s production, is deiodinated and converted to T3 by two deiodinase enzymes (Klein & Danzi, 2007). T3 plays a vital role in the development and function of almost every human cell and organ system in the body (Klein & Danzi, 2016; LaFranchi, 2021). A thyroid hormone deficiency can slow down the body’s metabolism and cause conditions such as osteoporosis, dyslipidemia, obesity, hypertension, and CVD (Shahid et al., 2022; Udovcic et al., 2017). The symptoms of hypothyroidism are vague,
develop gradually, and may be challenging to differentiate from other conditions. Weight gain, fatigue, changes in digestion and bowel habits, dry skin, and muscle aches and weakness are typical symptoms of hypothyroidism but can be easily confused with other conditions (Chiovato et al., 2019; Shahid et al., 2022). Diagnosis is based on clinical presentation and positive blood tests for T3, T4, and TSH. Reversal of symptoms and additional organ involvement can be minimized with prompt diagnosis and treatment (Shahid et al., 2022; Wilson et al., 2021).

Hypothyroidism is the second most common endocrine disorder in women following diabetes (Dunn & Turner, 2016). Women are nearly 10% more likely than men to develop hypothyroidism. One of every eight women will develop the condition during her lifetime (American Thyroid Association, 2022; Dunn & Turner, 2016; Garber et al., 2006). The peak age of disease onset is between 30–50 years of age and is most prevalent in white women compared to women in Black or Hispanic populations (American Thyroid Association, 2022; Dunn & Turner, 2016; Garber et al., 2006). Hypothyroidism is a lifelong condition and can be life-threatening if untreated or poorly managed (American Thyroid Association, 2022; Aoki et al., 2007; Dunn & Turner, 2016; McLeod et al., 2014).

**Early Thyroid Function**

During the first trimester, the placenta is the sole source of T4, which is critical for fetal neurodevelopment (Obregon et al., 2007). The thyroid gland is visible by seven weeks gestation and begins T4 production in the second trimester (LaFranchi, 2021; Patel et al., 2011). Growth of the thyroid gland and most fetal T4 production occurs during the third trimester. For example, T4 concentration is approximately 2 ug/dl in early term and
significantly increases to 10 ug/dl at term. TSH production gradually increases until birth. Triiodothyronine (T3) remains relatively low due to the placenta’s role in inactivating type 3 deiodinase. Despite its low level, T3 plays a crucial role in the production of thermogenin. *Thermogenin* is an uncoupling protein exclusive to brown adipose tissue (Obregon, 2014; Patel et al., 2011). Through a series of complex mechanisms, brown adipose tissue is responsible for generating *thermogenesis*, or heat production at birth, which is essential for neonatal body temperature regulation (Fisher, 2008; Thorpe-Beeston et al., 1991; Zaletel & Gaberšček, 2011).

The hypothalamic-pituitary-thyroid (HPT) axis, which maintains normal circulating levels of thyroid hormones, materializes during the latter part of gestation (Obregon, 2014; Obregon et al., 2007). However, the HPT’s complex feedback loops are not developed until term (Patel et al., 2011). During the last trimester, the thyroid gland increases in size and volume by eight- to ten-fold, leaving enough room for iodine and thyroglobulin reserves, which are necessary for T3 and T4 synthesis (Fisher, 2008). Shortly after birth, TSH markedly increases, causing T4 and T3 to increase, but then steadily drops during the first few weeks of life (Kim et al., 2019; LaFranchi, 2021; Thorpe-Beeston et al., 1991; Zaletel & Gaberšček, 2011).

In infants born preterm, the TSH surge is less dramatic, resulting in lower T4 and T3 levels, often directly proportional to the level of prematurity (LaFranchi, 2014, 2021). See Figure 9. *Thyroid Function in Infants*. Two other processes that directly influence the reduction of T4 levels include (1) the loss of maternal thyroxine transfer; roughly one third of maternal T4 crosses to the fetus at term, and (2) the liver’s decreased production of *thyroxine-binding globulin*, which is the protein responsible for transferring T4 to
appropriate endpoints. This unique paradigm of thyroid dysfunction in infants born preterm has been labeled “hypothyroxinemia of prematurity” (LaFranchi, 2021).

**Figure 9**

*Thyroid Function in Infants*

![Graph showing changes in TSH, T4, and T3 levels following birth in infants born preterm versus infants born full term.](image)

Note. This figure compares changes in TSH, T4, and T3 levels following birth in infants born preterm versus infants born full term. From “Thyroid function in preterm/low birth weight infants: Impact on diagnosis and management of thyroid dysfunction” by S.H. LaFranchi, 2021, *Frontiers in Endocrinology, 21*, 1-9, p. 3.

In addition to the loss of maternal T4, preterm-born infants are likely to have difficulty maintaining body temperature. Fluctuations in body temperature can result from (1) impaired thyroid metabolism leading to compromised thermogenesis, hypotension, and hypoglycemia, (2) hypothalamic-pituitary immaturity, and (3) non-thyroidal illnesses (Fisher, 2008). Comorbidities commonly treated in premature infants include infection, patent ductus arteriosus, necrotizing enterocolitis, and hypoxia. Such
illnesses can further stress the immature thyroid for increased production of thyroid hormones, overtaxing the thyroid gland (Fisher, 2008).

Impaired development of the thyroid, other organs and systems, and comorbidities can result in epigenetic modifications. One area of ongoing research focus is determining long-term consequences from hypothalamic-pituitary-adrenal (HPA) axis dysfunction, a separate neuroendocrine pathway from HPT. For example, altered programming of the HPA axis due to either disrupted organogenesis or a stressful neonatal environment may have long-term physiological health consequences (Sullivan et al., 2019). Associations between HPA function and diabetes, obesity, autoimmune-inflammatory syndromes, cognitive disorders, and CVD have been noted in the general population (Sheng et al., 2020). Long-term consequences and the downstream impact of an immature thyroid is unknown. Although research is evolving, much remains to be learned about how an underdeveloped thyroid gland in preterm infants affects later-life outcomes.

The Effects of Hypothyroidism on the Cardiovascular System

The cardiovascular system is one of the body systems most impacted by hormone deficiencies (Klein & Danzi, 2007, 2016). Cardiomyocyte contractility is greatly reliant on and altered by low T3 concentrations, thereby influencing cardiac chronotropy or heart rate and inotropy or contractility (Klein & Danzi, 2007; Udovcic et al., 2017). Physiological manifestations of thyroid hormone deficiencies are bradycardia, decreased or impaired cardiac contractility, and reduced cardiac output (Berta et al., 2019; Dunn & Turner, 2016; Klein & Danzi, 2016; Toft & Boon, 2000; Udovcic et al., 2017). See Figure 10, Proposed Pathways of Hypothyroidism to Hypertension. Impaired cardiac contractility results in reduced ventricular function and vulnerability to cardiac
arrhythmias. Additionally, case study analyses have detected prolonged QT intervals in individuals with hypothyroidism, which are presumably influenced by low T3 concentrations (Fredlund & Olsson, 1983; Kandan & Saha, 2012; Klein & Danzi, 2016). QT intervals are defined as the measure of time between the start of the Q-wave of the QRS complex and the end of the T-wave in an electrocardiogram. Prolonged QT intervals can predispose an individual to a potentially fatal ventricular arrhythmia.

Vascularly, low T3 levels decrease endothelial-derived relaxation factor and nitric oxide (NO) production, resulting in impaired arterial compliance and endothelial dysfunction in the peripheral circulation (Udovcic et al., 2017). Hemodynamic consequences include elevated systemic vascular pressure and arterial stiffness (Berta et al., 2019; Marchiori et al., 2015; Udovcic et al., 2017). Pro-inflammatory cytokines such as interleukin-6 (IL-6), CRP, and homocysteine also increase with thyroid hormone deficiencies. Cytokines increase oxidative stress, which exacerbates endothelial injury and endothelial dysfunction (Klein & Danzi, 2016; Zhang et al., 2015).

**Figure 10**

*Proposed Pathways of Hypothyroidism to Hypertension*

Note. The effects of hypothyroidism leading to hypertension. CO = cardiac output; NO = nitric oxide; SVR = systemic vascular resistance; IL-6 = interleukin 6; CRP = C-reactive protein; CVD = cardiovascular disease.
Cardiovascular risks and outcomes are also influenced by alterations in lipid metabolism due to hypothyroidism (Marchiori et al., 2015; Udovcic et al., 2017; van Tienhoven-Wind & Dullaart, 2015). Hypothyroidism can reduce the liver’s production of low-density lipoprotein (LDL) cholesterol receptors and cholesterol monooxygenase, the enzyme responsible for breaking down cholesterol. The result is increased levels of circulating cholesterol and LDL-cholesterol (Marchiori et al., 2015; Udovcic et al., 2017; van Tienhoven-Wind & Dullaart, 2015). Increased LDL cholesterol is the main component in the composition of coronary plaque that contributes to macrovascular coronary artery disease.

The cumulative outcomes of physiological alterations due to hypothyroidism include increased blood pressure, increased atherosclerotic plaque formation, and increased hyperlipidemia, which increase the risk for heart failure, cardiac arrhythmias, and CVD events (Klein & Danzi, 2007; Udovcic et al., 2017). Reactive processes, such as arterial vasoconstriction and increased production of pro-inflammatory cytokines, exacerbate both hypertension and progressive atherosclerosis (Berta et al., 2019; Marchiori et al., 2015).

A well-established association between higher blood pressure and hypothyroidism has been recognized. However, hypothyroidism is rarely considered a causative factor for hypertension (Berta et al., 2019; Saito & Saruta, 1994). Higher prevalence of hypertension in women with hypothyroidism parallels the higher rate of CVD events in women compared to men (Klein & Danzi, 2007). Many of these adverse hemodynamic responses can be averted, managed, or lessened with timely treatment of hormone imbalances (Berta et al., 2019; Pearce, 2004; Saito et al., 1983). A meta-analysis of 10
randomized clinical trials and 19 observational studies found that systolic and diastolic blood pressure improved with thyroid hormone replacement therapy in individuals with hypothyroidism (He et al., 2018). When hypothyroidism was appropriately managed with pharmacologic treatments, systolic blood pressure was significantly reduced by 4.8 mmHg (95% CI [-6.5, -3.1], \( p < 0.001 \)) and diastolic blood pressure by 2.7 mmHg (95% CI [-4.06, -1.43], \( p < 0.001 \); He et al., 2018). In order to positively alter cardiac health outcomes, awareness about the increased risks for CVD in individuals who were born preterm is necessary. Further, identification and early treatment of hypothyroidism and hypertension independently or jointly is important for preterm-born individuals. The evidence supports further research of hypothyroidism in preterm-born individuals, especially in women.

**Women's Health Initiative Hypothyroidism Studies**

The study of hypothyroidism in the WHI cohort is not as common as the study of RA. One study obtained thyroid biomarkers from 3,663 women without a self-reported history of hypothyroidism in 2005 and 2006 (LeGrys et al., 2013). A total of 282 women (8%) met the criteria for *sub-clinical hypothyroidism*, an elevated TSH level with a normal/within-limit T4 level, which is presumed to be an indication of deteriorating thyroid function. LeGrys et al. (2013) further evaluated this relationship between sub-clinical hypothyroidism and myocardial infarction risk over a seven year period and determined that there was no correlation. Giri et al. (2014) studied the same cohort of women, looking for an association between sub-clinical hypothyroidism and cerebrovascular events. It was hypothesized that women with sub-clinical hypothyroidism would exhibit more cerebrovascular events because of altered
atherogenic lipid profiles, diastolic hypertension, endothelial dysfunction, and elevated homocysteine and CRP levels. No correlation was found (Giri et al., 2014).

Weng et al. (2020) studied 19,735 women from the WHI-OS ($n = 11,921$) and WHI-CT ($n = 7,814$) with a history of hypothyroidism to look for an association with breast cancer. Women with hypothyroidism had a 9% lower risk of breast cancer than women without a self-reported history of thyroid disease (Weng et al., 2020). The use of levothyroxine, a common medication for hypothyroidism, appeared to have a protective effect, since women who took it had an 11% lower risk of breast cancer. A sub-analysis of women on hormone replacement therapy who took estrogen or estrogen plus progestin found that women with hypothyroidism and without hormone replacement therapy had an even lower risk of breast cancer (HR 0.08, 95% CI [0.69, 0.93]) compared to those on hormone replacement therapy and with hypothyroidism (Weng et al., 2020).

The most recent study of hypothyroidism in women enrolled in the WHI explored the association between birth weight and thyroid dysfunction (Monahan et al., 2022). The sample consisted of 76,087 women. Birth weight, specifically < 6 pounds and 8 pounds and greater at birth, were linked with a higher prevalence of hypothyroidism (< 6 pounds: OR 1.13, 95% CI [1.04, 1.22]; 8–9 pounds: OR 1.09, 95% CI [1.03, 1.15]; > 10 pounds: OR 1.14, 95% CI [1.02, 1.28]). Women born at lower birth weights were presumed to be at a greater risk for thyroid dysfunction due to potential hypothalamic-pituitary-thyroid (HPT) dysfunction and impaired immunity (Monahan et al., 2022). It was concluded that the smallest and the largest birth weights correlated with a higher occurrence of thyroid dysfunction. These results must be interrupted with three caveats. First, birth weight, as well as most medical histories, were self-reported; there was no
documentation of objectively measured birth weight. Secondly, since approximately 60% of individuals with hypothyroid disease are unaware of their condition, it is possible that the incidence of hypothyroidism was higher, but not diagnosed, which would have led to an inaccurate sample size in this study. Thirdly, the study did not consider maternal exposures during pregnancy, pregnancy complications and conditions like gestational diabetes and hypertension, childhood iodine levels, and family history of autoimmune disorders. Results of this study align with the DOHaD theory, supported by the concept that early life phenotypes impact later-life health outcomes (Monahan et al., 2022).

**The Hypothyroid-Rheumatoid Arthritis Connection**

A growing body of literature supports the link between thyroid disease and RA (Fukui et al., 2021; Huang et al., 2022; Li et al., 2021; Mahagna et al., 2018; McCoy et al., 2012; Monahan et al., 2022; Nazary et al., 2021; Raterman et al., 2008). It is difficult to discern if there is a causal pathway and if so, which condition is the precipitating variable. Raterman et al. (2008) investigated the occurrence of hypothyroidism in 236 women and determined that hypothyroidism was three times more prevalent in women with RA than women in the general population. Additionally, those with hypothyroidism and RA had a four-fold higher risk of CVD than individuals with RA and normal thyroid function (Raterman et al., 2008).

Findings from a retrospective medical review did not concur. McCoy et al. (2012) reviewed the medical records of 650 individuals with RA and 650 without a documented RA diagnosis (mean age 55.8 years, 69% of the cohort female). They found no significant difference between the two cohorts in terms of prevalence or incidence of hypothyroidism. However, a significant association with CVD (HR 2.0, 95% CI [1.1,
3.6]) was noted in participants who had both hypothyroidism and RA (McCoy et al., 2012). This association persisted after adjusting for traditional CVD risk factors such as smoking, hypertension, dyslipidemia, diabetes, and obesity. Incidentally, an analysis of comorbidities in individuals with RA found that individuals with a history of atrial fibrillation were also more likely to have hypothyroidism (HR 3.1, 95% CI [1.3, 7.7]). The limitations of this study, namely its observational design and small sample population, prohibit the ability to draw any causal relationships (McCoy et al., 2012).

A larger cross-sectional database analysis of 11,782 individuals with RA found that RA was an independent predictor of thyroid dysfunction (Mahagna et al., 2018). Compared to age- and gender-matched peers without an RA diagnosis, individuals with RA had a 16% higher prevalence of hypothyroidism and a 2.3% higher prevalence of hyperthyroidism. These findings were and continue to be consistent with the literature (Mahagna et al., 2018). Additional meta-analyses and case-control studies have reinforced the association between RA and hypothyroidism (Fukui et al., 2021; Huang et al., 2022; Li et al., 2018; Nazary et al., 2021). Moreover, it has been estimated that 15–35% of individuals with RA will develop hypothyroidism over the course of their lives (Cardenas Roldan et al., 2012; Przygodzka & Filipowicz-Sosnowska, 2009).

**Thyroid and Prematurity**

Beyond the newborn period, few studies exist about thyroid status in individuals born preterm, because the current belief is that their thyroid condition is transient (Fisher, 2008; Yilmaz et al., 2021). A study of 180 infants born before 32 weeks gestational age found that one fifth of the infants exhibited thyroid dysfunction (Kim et al., 2019). Furthermore, pregnancy-induced maternal hypertension was significantly noted in
preterm infants who had thyroid dysfunction. Because maternal hypertension can cause placental insufficiency, it was surmised that passage of T4 from the placenta to the fetus may have contributed to the preterm infants’ hypothyroidism (Kim et al., 2019).

Thyroid hormone levels were compared in 82 school-age children born preterm (5 years of age) with 31 age-matched, full-term born children. Independent of neonatal comorbidities, children born preterm had lower free-T4 levels (16.1 pmol/l vs. 17.0 pmol/l) and higher TSH levels (3.0 µU/l vs. 2.3 µU/l) compared to the children born full term (Posod et al., 2017). Clinically, this is important because it shows that thyroid dysfunction may not be transient as hypothesized in preterm-born individuals.

A national registry study of 629,806 individuals aged 25–37 years, of which 27,935 were born preterm, reported that preterm-born individuals were almost two times more likely to have hypothyroidism that required treatment (OR 1.7, 95% CI [1.29, 2.23]) compared to their age-matched peers who were born full term (Crump et al., 2011a). Additionally, female gender was the strongest predictor of the need for thyroid hormone supplementation therapy (adjusted OR 7.29, 95% CI [6.9, 7.71]) after adjustments for potential confounders and shared familial (genetic or environmental) factors (Crump et al., 2011a).

Premature birth can have serious implications for the thyroid system, including potential loss of maternal T4, impaired thermogenesis, immaturity of the HPA axis, limited thyroid gland reserve, impaired hormone synthesis and metabolism, and predisposition to a host of neonatal illnesses (Fisher, 2008). A logical conclusion would be that individuals born preterm are prone to long-standing hypothyroidism; however,
this area is not well-studied. The research on hypothyroidism in adults born preterm is scant.

**Summary**

Hypothyroidism is a common condition, particularly for women. The condition is associated with dyslipidemia, atherosclerosis, and increased risks for CVD events, which are also common in aging women (Posod et al., 2017). It is extremely challenging to determine the course of hypothyroidism as it evolves from transient to permanent (Lee et al., 2015). The implications of elevated TSH levels in long-term cardiovascular health are unknown, particularly for a vulnerable population like those born prematurely (Crump et al., 2011a). The evaluation of hypothyroidism in adult women born preterm in the WHI cohorts is pragmatic and novel. Like RA, inductive logic supported the hypothesis that women born preterm would exhibit a higher prevalence and incidence of hypothyroidism compared to women born full term, which follows the DOHaD principles that adult health disorders result from fetal origins.

**A Trilogy of Chronic Conditions**

Research that links the association between hypothyroidism and RA is consistently emerging, with the majority reported in the last few years. Evidence to date of the co-existence of RA and hypertension is strong. The physiological effects of hypothyroidism on the cardiovascular system, specifically on the development of hypertension, are well-established. The physiological pathways of RA, hypothyroidism, and prematurity are well founded. However, the literature on the co-existence of these three conditions is limited in general and non-existent for the preterm population. A retrospective cohort study of 16,714 individuals with RA and 66,856 individuals without
RA found that hypertension was the most prevalent comorbidity in both cohorts. When stratified by RA and hypothyroidism, hypertension was the third most common comorbidity, behind previous stroke and diabetes (Huang et al., 2022). Given the DOHaD framework, it is reasonable to hypothesize that prevalence of this trilogy would be greater in a vulnerable population like adults born preterm. If the susceptibility to each condition exists independently for preterm-born individuals, inferring a higher prevalence among all three conditions jointly is logical. The principles of the DOHaD framework align with and support this conceptual paradigm. Manuscript III addressed this potential trilogy of conditions in adult women who were born prematurely in the WHI-OS.

**Summary**

The DOHaD theory and the two primary pillars of the framework, disrupted organogenesis and epigenetic modifications, have been discussed and explained in detail for each disease. The historical evaluation of the DOHaD theory as it pertains to prematurity was outlined. A cursory review of initial studies and its transformation from a fetal hypothesis to a theoretical framework of health outcomes for individuals born preterm was provided.

Premature birth disrupts the development and maturation of all body systems, such that the function of affected body system(s) may be altered. Disruption of organogenesis may or may not inhibit complete development of the affected body systems. There is also the possibility that a body system matures over time, while another remains impaired, affecting the hemodynamic stability of the developed system. Phenotypes of prematurity are unpredictable and studies that have attempted to discern their patterns of development are inconclusive. Research is needed to explore epigenetic
modifications in preterm infants and how significantly their early and ongoing environmental exposures impact their long-term health, which is a key tenet of the DOHaD theory.

In this chapter, the common condition of hypertension and two chronic conditions, RA, and hypothyroidism, were defined, described, and evaluated guided by the DOHaD theory. The selection of these three conditions was based upon (1) the evidence of higher prevalence and incidence in adult women, prematurity, and the interrelationship among them, (2) the existence of scientific evidence demonstrating a lack of screening, detection, and management of these conditions in women; and (3) the potential for poorer health outcomes for women with these conditions who were born prematurely. The cellular and molecular interplay between hypertension, RA, and hypothyroidism place women at a greater risk of CVD morbidity and mortality. The weighted risk to adult women born prematurely with one, two, or all three of these conditions is unknown and has never been studied in this population.

As more infants born prematurely survive the early infancy period and reach adulthood, more data are required to understand the long-term consequences of prenatal, perinatal, and postnatal influences, as well as determinants and characteristics of subsequent health conditions over their life course. Cohorts of adults born preterm are rare, especially in the U.S. The ability to explore such determinants in an older population of women who were born prematurely is extraordinary. Conducting the research in this dissertation was made possible by the remarkable opportunity to access the longitudinal WHI-OS database of U.S. postmenopausal adult women. Findings from
this examination of the lifelong health of U.S. women who were born prematurely can inform current prospective studies of individuals born preterm.

A review of the supporting literature concerning women’s health and health outcomes, particularly those born premature, has been presented. The uniqueness of studying a common condition in women by comparing birth status (preterm birth vs. full term birth) and the opportunity to identify differences in disease onset, impact on overall health, treatment success, and ultimate health outcomes is innovative. The WHI database provides a plethora of health data, including age of disease onset, comorbidities, medical treatments and consequences, and morbidity and mortality outcomes for select conditions and cohorts. The WHI is noted for its inclusion of diversity with respect to geography, socioeconomic status and race/ethnicity. The breadth and richness of the longitudinal data allow for the explorations and investigation of many clinical outcomes and exposures. A comprehensive health overview of common conditions and associated or predisposing conditions in adult women born preterm has never been investigated in this cohort of the WHI. Dissemination of the findings are presented in the following three manuscript chapters.
Chapter 3: Methodology

This chapter begins with a review of the aims and hypotheses of each manuscript. The methodology for the two empirical studies follows, including the research design, a description of the national Women’s Health Initiative (WHI) database, and an overview of WHI’s initial vision and structure. Data collection methods and measurements, data analysis techniques, and methodological limitations are presented. A concise summary concludes the chapter.

Aims

This dissertation is focused on prematurity and adult health outcomes associated with CVD. Specifically, the purpose of this research was to investigate the association between preterm birth, cardiovascular comorbidities, and cardiovascular health in a U.S. cohort of postmenopausal adult women.

The specific aims for each manuscript were:

Manuscript I

- To synthesize the growing evidence about disrupted organogenesis, specifically cardiogenesis, due to prematurity.
- To inform clinicians who provide health care to individuals of all ages and in all clinical settings that they may be caring for people born preterm, who potentially have increased CVD risks associated.

Manuscript II

- To determine the effects of prematurity on blood pressure in an adult population born preterm.
To investigate whether prematurity-related alterations in blood pressure predisposed preterm born women to a greater incidence of CVD events.

**Manuscript III**

To investigate the development of multimorbidity and determine if there is an association between three female-predominant, chronic cardiovascular-associated conditions (hypertension, rheumatoid arthritis (RA), and hypothyroidism) in women who were born prematurely.

**Methodology**

**Research Designs**

Manuscript I is a brief report on state-of-the-science research of cardiovascular health in individuals born preterm. The most current research evidence, emerging trends, and research priorities were presented. This comprehensive overview identified areas for further investigation. The critically important roles of clinicians who care for adult patients were emphasized. The lifetime risk for adverse cardiovascular health associated with prematurity was explicitly described, as was the need for early intervention in this vulnerable population. The manuscript was published in the *Journal of the American Association of Nurse Practitioners* [December 2022, Vol. 34, No. 12, 1252-1257, doi: 10.1097/JXX.0000000000000784].

Manuscripts II and III employed a longitudinal research design of a closed U.S. cohort of women enrolled from 1993 to 1998 in the Women’s Health Initiative (Women's Health Initiative, 2021). The observational arm (WHI-OS) is a correlational research design, often described in epidemiology as an observational study. In Manuscripts II and III, the population studied was postmenopausal adult women who enrolled in the WHI-
OS. Specifically, investigations included the primary exposure of preterm birth with later-life health outcomes, such as disease prevalence and incidence. Risk factors for hypertension and its related sequelae, as well as RA and hypothyroidism, were identified. Both manuscripts are secondary analyses of follow-up data and provided longitudinal group comparisons from a large and unique cohort of postmenopausal adult women in the U.S.

The women in this well-designed, well-powered, and well-conducted longitudinal study were racially, ethnically, and geographically diverse. An extensive database that tracked their medical histories and health habits provided the opportunity for multivariable modeling, including socioeconomic data like region of birth, income level, and marital status, as well as lifestyle modifiers such as physical activity, diet, obesity, smoking, and alcohol use. Validity and reliability of data were fostered by the well-designed research protocol of annually collecting health updates via medical questionnaires and by the Fred Hutchinson Cancer Research Center in Seattle, Washington, which continues to function as the coordinating center responsible for data management, monitoring, communications, and oversight of clinical activities of the WHI, WHI-CT, and WHI-OS (Women's Health Initiative, 2021).

**Sample**

**Women's Health Initiative.** In 1991, the National Heart, Lung, and Blood Institute (NHLBI), a division of the National Institutes of Health (NIH), launched the WHI to understand how some of the most common diseases affected postmenopausal adult women. Clinical investigations of preventive strategies for CVD, the leading cause of death among U.S. women at the time; breast and colorectal cancer, the second-and
third-leading cause of cancer deaths in U.S. women; and osteoporotic fractures, the leading cause of bone fracture in U.S. women, were investigated (ClinicalTrials.gov identifier: NCT00000611, U.S Department of Health and Human Services).

From 1993 to 1998, postmenopausal adult women \( (n = 161,808) \) between the ages of 50 and 79 years (birth years 1920–1940s) across the U.S. were enrolled in the WHI. Women were randomized into one, two, or three sub-trials in the partial factorial WHI-CT \( (n = 68,132) \) or enrolled in the WHI-OS \( (n = 93,676) \). Sub-trials included the Dietary Modification Trial \( (n = 48,835) \); the Hormone Replacement Trial \( (n = 27,347) \), which was further subdivided into an Estrogen plus Progestin (E+P) arm \( (n = 16,608) \) and an Estrogen-alone (E-alone) arm \( (n = 10,739) \); and the Calcium and Vitamin D Supplement Trial \( (n = 36,282) \). Study close-out occurred between October 2004 and March 2005 (Women's Health Initiative, 2021).

Since its inception, the WHI has collected valuable data as Extension Studies (ES), in which women completed yearly updates about their socioeconomic and lifestyle status and health outcomes. All participants of the initial WHI study (WHI-CT and WHI-OS) were invited to enroll. The first ES (ES-1) ran from 2005-2010, the second ES (ES-2) ran from 2010-2015, and the third ES (ES-3) ran from 2015-2020; a fourth Extension Study (ES-4) is planned through 2028 (WHI, 2021). A total of 115,406 women agreed to participate in ES-1, 82% of WHI-CT participants \( (n = 52,176) \) and 73% of WHI-OS participants \( (n = 63,230) \). ES-2 had 93,567 participants–41,499 from the WHI-CT and 52,068 from the WHI-OS. Noteworthy, 87% of the women consented to follow-up for life when asked during ES-2. As of February 2020, 63,557 women remain in active follow-up, 18.8% of whom are 90 years of age or older (Women’s Health Initiative,
2021). See Figure 11. *Evolution of the Women’s Health Initiative Study.* The WHI is one of the most significant studies on the health of postmenopausal adult women in U.S. history. The large sample of postmenopausal adult women enrolled ensured high statistical power for hypothesis testing in this dissertation.

**Figure 11**

*Evolution of the Women’s Health Initiative Study*

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Findings derived from the data-based manuscripts in this dissertation may result in new research areas, particularly in cohorts of adults born prematurely. The non-directional nature of the analysis aided in depicting distinct characteristics among cohorts, such as socioeconomic variables like education level, region of birth, and income. The large sample of both birth status (preterm vs. full term) cohorts allowed for differentiation of these variables. The odds ratios, or the relative odds of occurrence, were calculated to determine the association between the exposure (preterm birth) and outcomes of interest. This research structure also allowed for analyses of multimorbidity.

See Figure 12. *The Cross-Sectional Design of the Women’s Health Initiative Observational Study*. Secondary analysis of the cross-sectional data from WHI-OS participants was an economical and practical approach to study health trajectories.

**Figure 12**

*The Cross-Sectional Design of the Women’s Health Initiative Observational Study*

![Diagram](image)

*Note.* This figure depicts the cross-sectional design as it pertains to this dissertation.

WHI-OS = Women’s Health Initiative Observational Study; HTN = hypertension; RA = rheumatoid arthritis; CVD = cardiovascular disease; OR = odds ratio.
**WHI Eligibility Criteria (1993).** Eligibility was defined broadly for all WHI studies (WHI-CT and WHI-OS) with specific exclusion criteria for the clinical trials. Criteria were purposely liberal to enhance generalizability of the results. The WHI study inclusion criteria included:

- age 50-79 years at the time of enrollment,

- postmenopausal,
  - if age ≥ 55 years, no menstrual period for at least six months
  - if age 50–54 years, no menstrual period for at least 12 months

- intention to maintain residence within the same geographic area for three years,

- willing and able to provide written informed consent (Women's Health Initiative, 2021).

Exclusion criteria included conditions with a predicted survival time < 3 years; competing risks for cancer or CVD; adherence or retention issues, such as alcohol or drug dependency; mental illness such as severe depression, dementia; participation in an outside trial; the inability to complete questionnaires and clinical visit(s); and/or an unwillingness to participate in follow-up components. There were no additional exclusion criteria for the WHI-OS (Women's Health Initiative, 2021).

A total of 93,676 women were enrolled in the WHI-OS between 1993 and 1998. This sample population was used for the two database manuscripts in this dissertation—Manuscript II and Manuscript III. The baseline descriptive characteristics of WHI-OS participants are shown in Table 2.
### Table 2


<table>
<thead>
<tr>
<th>Age at screening (y)</th>
<th>N=93,676</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>50-54</td>
<td>12,386</td>
<td>13.2</td>
</tr>
<tr>
<td>55-59</td>
<td>17,319</td>
<td>18.5</td>
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<tr>
<td>60-69</td>
<td>41,197</td>
<td>44.0</td>
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<tr>
<td>70-79</td>
<td>22,774</td>
<td>24.3</td>
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<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
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<th>%</th>
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<tbody>
<tr>
<td>American Indian</td>
<td>422</td>
<td>0.5</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>2,671</td>
<td>2.9</td>
</tr>
<tr>
<td>Black</td>
<td>7,639</td>
<td>8.2</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3,623</td>
<td>3.9</td>
</tr>
<tr>
<td>White</td>
<td>78,013</td>
<td>83.3</td>
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<td>Unknown</td>
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<tr>
<th>Education</th>
<th>N=93,676</th>
<th>%</th>
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<tr>
<td>0-8 years</td>
<td>1,560</td>
<td>1.7</td>
</tr>
<tr>
<td>Some high school</td>
<td>3288</td>
<td>3.5</td>
</tr>
<tr>
<td>High school diploma/GED</td>
<td>15,121</td>
<td>16.3</td>
</tr>
<tr>
<td>School after high school</td>
<td>33,933</td>
<td>36.5</td>
</tr>
<tr>
<td>College degree or higher</td>
<td>39,002</td>
<td>42</td>
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<th>Family Income</th>
<th>N=93,676</th>
<th>%</th>
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<tr>
<td>&lt;$10,000</td>
<td>3,916</td>
<td>4.5</td>
</tr>
<tr>
<td>$10,000-19,000</td>
<td>10,100</td>
<td>11.7</td>
</tr>
<tr>
<td>$20,000-34,999</td>
<td>20,226</td>
<td>23.3</td>
</tr>
<tr>
<td>$34,000-49,999</td>
<td>17,429</td>
<td>20.1</td>
</tr>
<tr>
<td>$50,000-74,999</td>
<td>17,486</td>
<td>20.2</td>
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<tr>
<td>$75,000 +</td>
<td>17,608</td>
<td>20.3</td>
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<tr>
<th>Marital Status</th>
<th>N=93,676</th>
<th>%</th>
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<tbody>
<tr>
<td>Never married</td>
<td>4,390</td>
<td>4.7</td>
</tr>
<tr>
<td>Divorced/Separated</td>
<td>14,727</td>
<td>15.8</td>
</tr>
<tr>
<td>Widowed</td>
<td>16,290</td>
<td>17.5</td>
</tr>
<tr>
<td>Presently married/Living as married</td>
<td>57,805</td>
<td>62</td>
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<table>
<thead>
<tr>
<th>Body Mass Index (BMI), kg/m²</th>
<th>N=93,676</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>1,107</td>
<td>1.2</td>
</tr>
<tr>
<td>Normal (18.5-24.9)</td>
<td>36,687</td>
<td>39.6</td>
</tr>
<tr>
<td>Overweight (25-29.9)</td>
<td>31,463</td>
<td>34</td>
</tr>
<tr>
<td>Obesity I (30.0-34.9)</td>
<td>14,578</td>
<td>15.8</td>
</tr>
<tr>
<td>Obesity II (35.0-39.9)</td>
<td>5,451</td>
<td>5.9</td>
</tr>
<tr>
<td>Obesity III (≥ 40)</td>
<td>3,282</td>
<td>3.6</td>
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<table>
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<tr>
<th>Perceived Health Status</th>
<th>N=93,676</th>
<th>%</th>
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<tbody>
<tr>
<td>Excellent</td>
<td>16,577</td>
<td>17.8</td>
</tr>
<tr>
<td>Very good</td>
<td>37,686</td>
<td>40.5</td>
</tr>
<tr>
<td>Good</td>
<td>29,670</td>
<td>31.9</td>
</tr>
</tbody>
</table>
Measurements

Upon initial enrollment in the WHI-OS, all participants answered structured questionnaires about their demographic characteristics, lifestyle behaviors, and medical and family histories. Many variables were collected repeatedly during the core study (1993-2005). Study variables, the WHI data collection form, and the frequency of data collection are shown in Table 3 (Women's Health Initiative, 2021).

Table 3

*WHI-OS Data Collection Documents, Corresponding Form Number, and Collection Year*

<table>
<thead>
<tr>
<th>Topic</th>
<th>Demographics</th>
<th>Observational Study Collection Year (1993-2005)</th>
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<tbody>
<tr>
<td></td>
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<td>BL 1 2 3 4 5 6 7 8 9</td>
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Note. Adapted from the Women’s Health Initiative (Women's Health Initiative, 2021).
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<td>Living assistance</td>
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On the enrollment questionnaire, women of the WHI-OS were asked about details of their birth (Form 42 - Observational Study Questionnaire, V1.1, 12/1/94, Women’s Health Initiative, 2021). The questionnaire asked, “When you were born, were you:

- Full term (pregnancy, lasted about 9 months),
- 4 or more weeks premature,
- Don’t know” (WHI Form 42, Observational Study Questionnaire, Ver. 1.1, 12/01/94).

Women who were aware of their birth status totaled 88,343 (93%). Among these women, 86,040 women (97.4%) reported being born full term, 2,303 women (2.4%) reported being born four or more weeks premature, and 5,333 women (5.7%) did not know their birth status. See Figure 13. *Women’s Health Initiative Birth Status Flow Diagram.*
Figure 13

*Women’s Health Initiative Birth Status Flow Diagram*

Note. Participants highlighted in the red box identify the sample population for Manuscript II and Manuscript III. GA = gestational age.

At the enrollment visit, certified staff obtained participants’ anthropometric measures and blood pressure using standardized procedures and instruments. An inventory of current medications, including over-the-counter supplements, was conducted.
at the enrollment visit. At an in-person follow-up visit conducted in Year 3, blood pressure measurements were obtained and medications were inventoried again.

**Outcome Measurements (Manuscripts II and III).** In Manuscript II, the primary outcome was prevalent hypertension, measured at enrollment, or incident hypertension, measured at any point during study years through 2021. Secondary outcomes that were analyzed included individual components of hypertension, such as age at diagnosis and level of blood pressure control as determined by antihypertensive medication use. Hypertension was defined as the self-reported physician diagnosis of hypertension at enrollment or on any annual medical history questionnaire during follow-up years; being treated for hypertension with antihypertensive medications; or if systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg (treated or untreated) was identified at enrollment or the Year-3 visit. The blood pressure parameter of ≥ 140/90 mmHg followed the JNC guidelines (JNC IV-JNC VI) at the time of data collection (JNC 4 Writing Group, 1988; JNC 5 Writing Group, 1993; JNC 6 Writing Group, 1997).

Incident coronary heart disease (CHD) and CVD were also collected as important outcomes in Manuscript II. For incident CHD, adjudicated outcomes included myocardial infarction (MI); cardiac revascularization, including percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG); and CHD death. Incident CVD was a composite of physician-centrally-adjudicated fatal or nonfatal MI, cardiac revascularization (PCI, CABG), CVD death, stroke (of any type), heart failure, and peripheral artery disease.
In Manuscript III, the primary outcome was the development of one, two, or three selected female-predominant, chronic conditions - hypertension, RA, and/or hypothyroidism. Beginning at enrollment (1993-1998) and continuing throughout the core study (ending in 2005), disease occurrence was analyzed by birth status. For Manuscripts II and III, all relevant outcomes were collected by participants’ self-reported answers to annual medical history and follow-up questionnaires.

**Statistical Analysis**

**Manuscript II.** Analyses for Manuscript II were performed by birth status (preterm vs. full term) using baseline data. Descriptive statistics were used (mean and standard deviation for continuous variables; counts and percentages for categorical variables) to summarize socio-demographic characteristics and CVD risk factors. Potential confounders were set apriori, based on a directed acyclic graph (DAG) and literature review. See Figure 14. Directed Acyclic Graph for Hypertension.
Note. A conceptual representation of known or assumed to be true causal relationships between birth status and hypertension development. BMI = body mass index; Hx = history; DM = diabetes mellitus.

Person-years of follow-up for each participant was based on time from enrollment to outcome of interest, loss to follow-up, or death. Multivariable logistic regression models were used to estimate odds ratios (OR) and their associated 95% confidence intervals (95% CI) to model prevalent hypertension at enrollment by birth status, age at hypertension diagnosis, and antihypertensive medication use by preterm and full-term birth status. Multivariable Cox proportional-hazards regression models were used to estimate hazard ratios (HR) and 95% CI for the development of incident hypertension, incident CHD, and incident CVD by preterm and full-term birth status. Both models adjusted for age, race/ethnicity, education, smoking status, physical activity, body mass
index (BMI), and diabetes. A stratified analysis to examine interaction of hypertension groupings and birth status on incident CHD and incident CVD was conducted. An interaction $p$ value of $\leq 0.10$ was considered significant. Covariates selected for inclusion of modeling were standard CVD risk factors including age (continuous), race/ethnicity (categorical), education (categorical), smoking status (categorical), physical activity (continuous), BMI (continuous), and diabetes (categorical). A post hoc supplementary analysis was conducted to examine for potential confounding by low birth weight. Joint effect associations between birth status (preterm vs. full term) and birth weight were evaluated by creating four categories and using full-term normal birth weight as the reference. Analyses were conducted using SAS v9.4 (Schoenfeld, 1983). A significance level of $p \leq 0.05$ was used for all analyses unless otherwise noted.

**Power Calculation.** WHI analysis cohort has median follow-up time 12.6 years with a maximum of 25.5 years. As of March 2020, the overall number of CVD events in the analysis sample was 8,072. Using preterm status to determine the necessary sample size, a total number of events equal to 7,423 with a 0.05 two-sided significance level will have 80% power to detect a constant hazard ratio of 1.21 (Schoenfeld, 1983).

**Manuscript III.** Analyses were performed by birth status (preterm vs. full term) using baseline data. Descriptive statistics were used (mean and standard deviation for continuous variables; count and percentage for categorical variables) to summarize socio-demographic characteristics. Covariates selected for inclusion in modeling were known risk factors for hypertension, RA, and hypothyroidism. Demographic variables included education level, income level, marital status, and region of birth. Lifestyle variables incorporated smoking status, physical activity, alcohol intake, and BMI. Risk factor
covariates were defined as short stature, diabetes, hyperlipidemia, and breastfed as an infant. Initially, individual diseases were analyzed using logistic regression models and included the other diseases as covariates.

Modeling of the combined diagnosis outcome was configured in two ways. The first outcome configuration summed the presence of the three diagnoses under examination per participant and ranged from 0 to 3 (no disease to all 3 diseases). The second outcome configuration examined the actual disease combinations present in each participant (none, RA only, hypothyroidism only, hypertension only, hypothyroidism and RA, RA and hypertension, hypertension and hypothyroidism, and all three - hypertension, RA, and hypothyroidism. Both configurations of the outcome variable were modeled with multinominal logistic regression using ‘no disease’ as the reference. Odds ratio and their associated 95% confidence intervals estimated the association of disease by birth status. The first model included age, race/ethnicity, education level, income level, marital status, and region of birth. The second model included age, smoking status, physical activity, alcohol intake, and BMI. The third model included age, short stature, diabetes, hyperlipidemia, and breastfed as an infant. Building on the previous models, the fourth model included those from model 1 without marital status, model 2 and model 3. Marital status was removed from model 4 because it did not have a significant effect in the modeling. This was performed after adjusting for potential confounders such as age and race/ethnicity. Analyses were conducted using SAS v9.4 (Schoenfeld, 1983). A significance level of $p \leq 0.05$ was used for all analyses unless otherwise noted.

**Power Calculation.** WHI analysis cohort has median follow-up time 12.6 years with a maximum of 25.5 years. As of March 2020, the overall number of incident RA,
hypothyroid disease, and hypertension cases in the sample were 4,283, 6,958, and 34,696, respectively. Using preterm status to determine the necessary sample size, a total number of events equal to 4,160 with a 0.05 two-sided significance level will have 80% power to detect a constant hazard ratio of 1.29 (Schoenfeld, 1983). Using proportions for prevalence estimates, the minimum detectable risk ratio for the sample cohort with a 0.05 two-sided significance level and 80% power is 1.11 for RA and 1.19 for hypothyroidism (Fleiss, 2003).

**Model and Diagnostics in Logistic Regression**

Logistic regression is the most suitable modeling approach for analyzing a data set with one or more explanatory variables to determine a binary event or outcome (Munro, 2001; Polit & Beck, 2017). The goal is to find the best fitting model to describe this relationship accurately. Before a model is deemed reliable to make inferences (e.g., predict outcomes), it is necessary to verify that the data do not conflict with the model assumptions. Logistic regression assumptions include (1) the outcome is binary, (2) linearity exists in the logit for continuous variables, (3) there are no outliers, (4) there is no multicollinearity, and (5) no important variables or observations are omitted (Munro, 2001). Once it is determined that the data do not conflict with the assumptions made by the model, diagnosing how well the model fits the data can be achieved by goodness-of-fit tests (Polit & Beck, 2017). Various goodness-of-fit tests exist (e.g., Chi-square goodness of fit tests and deviance, Hosmer-Lemeshow test, ROC curves [c-statistics], and the Wald statistic), yet there is no consensus on which approach is best since each test affords a different view of the model’s performance. Using more than one test may be beneficial (Polit & Beck, 2017).
In the analyses performed in Manuscripts II and III, collinearity among covariates were examined using Spearman correlations due to the categorical nature of the variables. A correlation $> 0.6$ was considered problematic. No two independent variables were deemed collinear. Covariates were added to the models sequentially based on their Wald Chi-square statistics. Model performance was assessed by changes in negative 2 Log Likelihood statistic (-2 Log L), Akaike Information Criteria (AIC), and Bayesian information criterion (BIC). Goodness-of-fit was assessed by changes in c-statistic value. The Wald statistics and the OR with 95% confidence interval were included to determine the magnitude, precision, robustness, and direction of the estimates (Munro, 2001; Polit & Beck, 2017).

**Methodological Limitations**

Cross-sectional data analysis is common in observational studies (Gordis, 2014). A shortcoming of this type of study design is that associations between exposure and the outcome cannot predict causation (Gordis, 2014). For instance, prevalent disease, such as hypertension, was identified in the preterm cohort; however, a conclusion based on birth history cannot be derived with certainty. This one-time measurement does not support the cause-and-effect relationship. Additional limitations with the research design include incomplete or missing data which could impact trends, recall bias in terms of selective memory and questionnaire completion, attrition, participants lost-to-follow up, the inability to verify diagnoses, the accuracy of prematurity/birth status, and the inability or inaccuracy of pertinent prenatal data and neonatal illnesses. These limitations influence the primary explanatory variable. Furthermore, the findings are only generalizable to
women and may not apply to younger preterm-born cohorts due to medical improvements.

Limitations were identified in each manuscript. An example of limitations noted in Manuscript II included the limited number of clinical blood pressure measurements that may have affected blood pressure sequencing and diagnosis. The use of unclassified, less common antihypertensive medications, the chronology of medications, co-existing CVD comorbidities, and the inability to control for confounding by indication to rule out unmeasurable factors that would cause a healthcare provider to prescribe one drug over another as first-line therapy were all limitations that may have altered the interpretations of the hypertension data. Another important limitation in Manuscript II was the potential bias of left censored data. The one-time measurement of disease incidence (e.g., hypertension or CVD) precluded women with prevalent disease prior to study entry. Inaccurate conclusions can occur (Hernández-Herrera et al., 2022). The fact that missing data is marginal in the WHI-OS database helps offset the inefficient estimates.

Limitations noted in Manuscript III, aside from recall bias, social desirability bias, and response bias, include the cautious interpretation of data when the preterm cohort sample was small, the lack of disease confirmation or adjudication by a physician, and the inability to adjust for covariates that may have been significant in the pathophysiology of the selected conditions. Additionally, various conditions can resemble RA, contributing to an incorrect self-reported condition.

Other Variables as Methodological Limitations

The DOHaD theory provided a framework for organizing confounders and variables, disease processes, and environmental influences. An overview of these
variables related to each manuscript and disease process is presented in Table 4. The variable breastfed as an infant is included as a confounder and a mediator. The third variable effects are subject to sampling variability, and in any given sample such as this, may appear to act as a mediator, confounder, or suppressor simply due to chance (MacKinnon et al., 2000). Calculating the confidence interval for a mediated effect is often used to differentiate between the two (MacKinnon et al., 2000).

Table 4
Confounders, Covariates, and Potential Mediators: Manuscripts II and III

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<th>Manuscript III</th>
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<td>Preterm birth, 4 weeks or more preterm</td>
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<td>TIA</td>
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<td>Treated hyperlipidemia</td>
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<td>Atrial fibrillation</td>
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Note. This table lists the pertinent variables, confounders, covariates, and potential mediators in Manuscripts II and III.
Protection of Human Subjects

The University of Rhode Island (URI) Office of Research Integrity approved this secondary data analysis titled “Hypertension, Rheumatoid Arthritis, and Hypothyroidism in Women Born Preterm of the Women's Health Initiative” (Institutional Review Board [IRB] Reference #: 1847843-1; Local Reference #: IRB2122-106) on 12/17/2021. The WHI-OS data had already been collected and de-identified. Permission to access and use the data for the two data-based manuscripts (Manuscripts II and Manuscript III) was approved by the Women’s Health Initiative Publications & Proposals Committee. Analysis support was available through the Center for Primary Care and Prevention, the Rhode Island recruiting location for the WHI. The biostatistician familiar with the Women’s Health Initiative data was readily available. These important documents are included in Appendix A, A1, B, and B1.

Summary

The broad inclusion and limited exclusion criteria of the WHI enhanced the population size and the generalizability of the data in this dissertation. Population-based surveys (in this case, annual medical health histories and health follow-up questionnaires) were the mainstay methods used to determine disease prevalence and incidence. Often viewed as a limitation, the one-time snapshot or measurement enabled the analysis of the primary exposure comparisons (birth status) between associated characteristics and health outcomes (development of the selected health condition or CVD). The case numbers of the preterm-born cohort compared to the full-term born cohort were appropriate. Aside from the apparent cost and time saving benefits of the research design, the ability to longitudinally analyze multiple outcomes by birth status (preterm vs. full term) and at
various time intervals were advantages. The uniqueness of these analyses included the variables and the opportunities to examine relationships among variables never analyzed in the national sample of women.
Chapter 4: Manuscript I

A New Cardiovascular Disease Risk Factor for Young Adults: Preterm Birth

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**Conflicts**: We have no known conflicts of interest to disclose.

**Ethical Conduct of Research**: The project has been approved by the University of Rhode Island Institutional Review Board # IRB2122-106.

**Abstract word count**: 195

**Text word count**: 2971

**Figures**: 2
Abstract

Adults born preterm (birth <37 weeks gestation) have a two-fold increased risk of early cardiovascular mortality. With 10% of the U.S population born prematurely and perinatal advancements dramatically improving survival rates, millions of survivors are now reaching adulthood. This phenomenon has introduced a whole new population of individuals with a history of preterm birth. Although the prevailing notion has been that preterm birth is a condition confined only to infancy and early childhood, we now know preterm birth is a risk for lifelong chronic health conditions. Despite almost a decade of epidemiological evidence showing increased cardiovascular risk for those born preterm, this has not yet been translated into clinical practice. As a result, clinicians are caring for adults born prematurely without screening and treatment guidelines for this at-risk population and few inquire about birth history during clinical encounters. This brief presents growing evidence about disrupted cardiogenesis and consequential structural and functional modifications. By asking the question “Were you born preterm?”, nurse practitioners can take the first step of increasing their awareness of this at-risk population and mitigate adverse cardiovascular outcomes by utilizing preterm birth as a risk factor when determining health promotion and treatment decisions.

Keywords: Adults; cardiovascular risk; hypertension; nurse practitioner; preterm birth.
Introduction

Individuals who survive shortened gestation because of preterm birth (birth <37 weeks gestation) are at increased risk of cardiovascular disease (CVD) and other chronic conditions as adults (Raju, Buist, et al., 2017). Preterm birth continues to affect approximately 10% of U.S. births and perinatal advancements have dramatically improved survival rates (Martin et al., 2021). Millions of individuals who were exposed to this early life adversity are now faced with possible long-lasting health consequences as they enter adulthood (Raju et al., 2017).

Preterm birth occurs during critical organ development. Distinct anatomical and physiological modifications have been found in the heart, kidneys, and blood vessels of those born prematurely from infancy through young adulthood (Lewandowski et al., 2020). The structural and functional cardiovascular effects of an abrupt transition from a low-pressure intrauterine to a high-pressure extraterine environment is an area of recent study. Experimental animal and human preterm birth studies have found evidence of cardiac remodeling, that result in increased bi-ventricular mass, smaller ventricular cavities and volumes, and altered cardiac shape (more spherical than elliptical; Tan & Lewandowski, 2020). These anatomical remodeling changes influence ventricular function, causing lower ejection fraction, stroke volume, and cardiac output (Lewandowski, 2022). These changes have also been found to persist beyond childhood, predisposing those born prematurely to an increased risk of CVD conditions like hypertension, heart failure, and coronary artery disease as young adults (Crump, 2020a; Crump et al., 2021; Lewandowski, 2022).
In contrast to historical perceptions, preterm birth does not resolve with intensive neonatal care or by a specific age (Kelly et al., 2021). Research evidence about the long-term health risks for those born preterm has prompted a shift of attention from early neonatal management to chronic health management across the lifecourse (Raju et al., 2017). Regrettably, many of today’s adult clinicians caring for this at-risk population are unaware of their long-term vulnerability (Kelly et al., 2021). Although unique cardiac alterations and higher blood pressure have been identified, neither have been recognized as risk factors in clinical practice (de Jong et al., 2012). The purpose of this brief is to review research evidence important to clinical practice so that clinicians are aware of the impact preterm birth may have on long-term cardiovascular health.

Anatomical and Physiological Alterations

The Early Cardiovascular System

Rapid fetal cardiac development occurs during the third trimester of pregnancy. Approximately 3 billion cardiomyocytes shape the human heart with nearly 40% proliferating during the first few postnatal weeks. The cardiomyocytes, or the functional cells of the heart muscle responsible for initiating contractility and controlling rhythmic beating, undergo robust growth and proliferation during this time. These cells form the ventricular trabeculations and myocardial walls in preparation for the increased workload of the systemic system (Zhao et al., 2020).

The right ventricle (RV) is the dominant pumping chamber, responsible for over 60% of cardiac output during fetal circulation. At birth, a complex and rapid physiological shift occurs with the RV becoming the low-pressure circuit responsible for the pulmonary circulation and the left ventricle (LV) taking over the high-pressure
systemic circulation. A premature birth abruptly forces this transition, causing the immature heart to remodel due to the functional demands of neonatal life (Tan & Lewandowski, 2020).

Animal experiments have found distinct myoarchitectural adaptations in cardiac size (diameter), mass (hypertrophy), geometry (wall thickness and chamber shape), and function in preterm hearts. The cardiomyocytes have been found to be underdeveloped, functionally immature, and hypertrophied (Bensley et al., 2018). Furthermore, the halted postnatal cellular proliferation results in reduced cardiomyocyte count. The remaining immature cardiomyocytes and adaptive structural remodeling can lead to the occurrence of biventricular hypertrophy and a thickened interventricular septum, proportional to the degree of prematurity and early environmental conditions (Bensley et al., 2018). These morphological changes have been found in infants born preterm and persisting into young adulthood (Tan & Lewandowski, 2020). The adaptive remodeling process, vital for survival, is ultimately a maladaptive response with long-term consequences for those born prematurely.

**First Human Studies**

The first studies identifying the unique cardiac phenotypes of prematurity were in 2013 and included 102 young adults born preterm and 132 young adults term born (23-28 years of age) (Lewandowski, Bradlow, et al., 2013). As shown in Figure 1, preterm hearts showed distinct LV and RV changes. Of concern, the RV ejection fractions were significantly lower for the young adults born preterm. The degree of prematurity at birth correlated directly with myocardial alterations such that, each shortened week of
gestation corresponded to 1.5% relative increase in LV mass, 2.7% relative increase in RV mass, and 2.5% lower RV ejection fraction (Lewandowski, Bradlow, et al., 2013).

Numerous studies since the findings of Lewandowski et al. (2013) have confirmed the ventricular differences in the preterm population (Huckstep et al., 2018; Mohamed et al., 2021). Recent studies have further explored LV ejection fraction with exercise (Haraldsdottir et al., 2020). Young adults born preterm have been found to have reduced exercise capacity compared to age-matched term-born peers, with up to 7.3% lower LV ejection fractions (Haraldsdottir et al., 2020; Huckstep et al., 2018). These findings coincide with a 56% lower myocardial functional reserve (or cardiac output reserve). With exercise, the preterm heart was unable to meet the hemodynamic demands (increase cardiac output) during exercise, resulting in lower ejection fractions and delayed blood pressure and heart rate recovery times (Haraldsdottir et al., 2020; Huckstep et al., 2018). Consequently, the structural changes and geometrical reshaping are believed to contribute to the higher prevalence of arrhythmias (due to electrical remodeling), congestive heart failure (due to ventricular hypertrophy and systolic dysfunction because of ventricular remodeling), hypertension (due to diastolic dysfunction and ventricular adaptations), and poor exercise tolerance detected in later-life of individuals born preterm (Raju, Buist, et al., 2017; Schuermans & Lewandowski, 2022).

**Epidemiological Research**

The most extensively researched CVD risk factor and well-established link to preterm birth is elevated blood pressure, based on international epidemiological research (Raju et al., 2017). The first meta-analysis derived from preterm cohort studies published between 1998 to 2011 from 10 countries, identified elevated systolic blood pressure (up
to 4.2 mmHg higher) in children and young adults (6-23 years of age) born prematurely compared to term-born counterparts (de Jong et al., 2012). A meta-analysis by Parkinson et al. (2013) found similar results; however, the differences in systolic and diastolic blood pressures were more pronounced in women born preterm compared with men born preterm and term-born counterparts. A Finish study evaluating 24-hour ambulatory blood pressure in young adults ≥18 years of age also found higher SBP differences of 3.1 mmHg in the preterm population (Sipola-Leppanen, Karvonen, et al., 2015). Regarding antihypertensive treatment, a Swedish cohort analysis of hypertensive young adults (25-37 years of age) found the adults born preterm required more antihypertensive agents for blood pressure control than their hypertensive term-born peers (Crump, 2020).

Unmanaged hypertension has been estimated to correlate with a 25% higher risk of cardiovascular morbidity and a 32.2% higher risk of a cerebrovascular event for the preterm population (Risnes et al., 2021).

The increase in blood pressure may appear small; however, it is clinically significant and imparts clinical consequences over a life course. The degree and duration of blood pressure elevation are important, but even slight elevations over long durations can lead to hypertension-related target organ damage to the kidneys, brain, arterial vasculature, and the heart (Brenner et al., 1988; Sipola-Leppanen, Karvonen, et al., 2015).

Other Epidemiological Outcomes

Aside from higher hypertension prevalence, preterm birth has been associated with an increased risk of metabolic biomarkers and comorbidities. Comorbidities include higher occurrences of obstructive lung disease, diabetes, sleep apnea, kidney disease, and
depression (Raju et al., 2017). Flahault (2020) found 38% of adults born preterm were living with two or more comorbidities compared to 22% in adults term born. Research supports higher fat mass, fasting glucose, insulin resistance, low-density lipoproteins, and total cholesterol levels in adults born preterm compared with term-born adults (Markopoulou et al., 2019).

Early-onset heart failure is an emerging, highly prevalent comorbid condition among adults born preterm with hypertension. One study found individuals 18–43 years of age born prematurely had a 1.4- to 4.7-fold increased risk of new-onset heart failure compared to age-matched term born peers (Crump et al., 2021). Another study concluded children and young adults born <28 weeks gestation had a 17-fold increased risk of developing heart failure and those born between 28 and 32 weeks gestation had a 4-fold increased risk (Carr et al., 2017).

An increased risk of premature mortality has also been associated with preterm birth. A Swedish cohort study discovered preterm survivors had nearly a 40% increased CVD mortality risk in young adulthood (18-38 years; Crump, 2020). Another Nordic study of individuals 23–44 years of age found preterm birth of all gestational ages was associated with a two-fold increased risk of premature mortality from CVD. This link between gestational age and all-cause mortality was found to be highest for women (Risnes et al., 2021).

The Hypertension Connection

It is well established that hypertension is the strongest risk factor for all CVDs, contributing to nearly 8.5 million annual adult deaths worldwide (Zhou et al., 2021). Hypertension is an epidemic in the United States, with one in every two adults having
elevated blood pressure. The prevalence has more than doubled in the past 20 years (Zhou et al., 2021). Blood pressure has been extensively investigated and found to demonstrate a direct relationship between the degree of prematurity and elevated blood pressure, diagnosed as early as school-age children (6-12 years of age; de Jong et al., 2012). The pathogenesis of hypertension development along with the remodeling process and mechanisms that lead to increased CVD risk in the preterm population are not fully understood and still evolving (Mohamed et al., 2021). The anatomical alterations discovered in the last decade may not be fully responsible for hypertension development per se but may render the premature heart susceptible to the smallest increases in blood pressure (Lewandowski et al., 2020). For example, a recent evaluation of individuals born prematurely with and without hypertension had greater LV mass, reduced LV function, and smaller LV volumes compared to individuals term born with and without hypertension (Mohamed et al., 2021). Prematurity correlated with a 2.5-fold higher LV mass per 1 mmHg increase in SBP. Increased LV mass, representative of the cumulative effect of elevated blood pressure on the heart, was the strongest independent risk factor for cardiovascular mortality (Mohamed et al., 2021).

**Mechanisms Contributing to Hypertension**

The mechanistic pathways responsible for hypertension development in individuals born preterm are complex, not fully understood, and warrant further study. In addition to the cardiac alterations as mechanistic contributors to hypertension development, impaired nephrogenesis likely plays a major role. It is well-known that the kidneys have an inextricable role in the regulation of blood pressure. Malfunctioned or
diseased kidneys are unable to regulate blood pressure. Uncontrolled, elevated blood pressure, in turn, contributes to further kidney impairment (Starr & Hingorani, 2018).

Nephrogenesis begins in the first trimester of pregnancy and continues for up to six weeks after birth, with more than half of the nephrons developing in the last four weeks of pregnancy (Heo & Lee, 2021). The quantity of nephrons is determined at birth and are nonregenerative; therefore, the number an infant is born with is lifelong (Starr & Hingorani, 2018). Preterm birth disrupts nephrogenesis, causing smaller kidney size, lower nephron count, altered glomerular filtration, and impaired renin-angiotensin function as found in children 2–13 years old born preterm (Heo & Lee, 2021). Incomplete maturation of the nephrons, together with strained hemodynamic functioning of other organ systems, results in dysfunctional and unstable nephrons. Nephrotoxic medications, often used as treatment during the postnatal period, can also impede postnatal maturation, whereby producing suboptimal renal phenotypes (Heo & Lee, 2021).

The Brenner hypothesis established the inverse association between blood pressure and nephron count (Brenner et al., 1988; Starr & Hingorani, 2018). Low nephron count forces hyperfunction of the remaining nephrons. The hyperfunctioning nephrons compensate by increasing surface area to maintain a constant filtration rate. This adaptive process leads to a series of progressive and deleterious structural changes within the functioning nephrons. Over time, the overworked nephrons hypertrophy and become sclerosed. Simultaneously, sodium retention from compromised renin-angiotensin mechanisms and reduced filtration surface area of the nephrons leads to hypertension development (Brenner et al., 1988). This vicious cycle of nephron
enlargement, coupled with the exploitation of dysfunctional filtration mechanisms and maladjusted systems, may result in nephron death, advanced hypertension, and renal failure (Starr & Hingorani, 2018).

The relationship between kidney function, hypertension, and premature birth is complicated; however, hypertension and premature birth are the two strongest risk factors for the development of kidney disease (Figure 2; Heo & Lee, 2021). Elevated blood pressure is often the first indication of renal system dysfunction (Heo & Lee, 2021). The lowering of blood pressure has been found to preserve renal function and slow the progression of kidney disease; therefore, early recognition and control of blood pressure are crucial for the preterm population (de Jong et al., 2012).

**Other Potential Mechanisms for Prematurity-Related Hypertension**

Impaired maturation of autonomic regulation has been suggested as a causative factor in hypertension development (Schlatterer & du Plessis, 2021). The autonomic nervous system (ANS) has a prolonged developmental period that extends after birth, and therefore, incomplete development may result from preterm birth. The immature and unbalanced ANS, which is responsible for regulating the baroreceptor reflex (regulator and controller of rapid blood pressure changes), is unable to control baroreceptor discharges that then lead to higher blood pressure and greater blood pressure variability (Schlatterer & du Plessis, 2021).

Another potential hypertension contributing mechanism is impaired elastin synthesis within the arterial system. The synthesis of elastin, the protein responsible for the extensibility of large arteries, occurs at the end of gestation (Sutherland et al., 2014). Impaired vasculogenesis and disrupted elastin synthesis from preterm birth results in low
elastin production, increased vascular stiffness, and smaller arterial lumens (Sutherland et al., 2014). The cumulative effect of these pathophysiological deficits is increased peripheral resistance. Additionally, insulin resistance, also found to be elevated in individuals born preterm, alters renal tubular sodium reabsorption, exacerbating endothelial dysfunction, and increasing sympathetic activity. These combined factors contribute to higher blood pressure (Sutherland et al., 2014).

Antiangiogenic biomarkers (e.g., soluble endoglin) have been suggested as potential contributors of microvascular abnormalities promoting hypertension. Based on disrupted angiogenesis, elevated levels of antiangiogenic factors that impede blood vessel growth have been found in individuals born preterm compared to term-born peers (Lewandowski et al., 2015). The imbalance between proangiogenic and antiangiogenic biomarkers is suspected to elevate resting and ambulatory blood pressure. Over the life course, this augmented antiangiogenic state contributes to hypertension development and microvascular alterations that increase CVD risk (Lewandowski et al., 2015).

A final mechanistic consideration possibly influencing blood pressure development emanates from early life exposures that may have unfavorable long-term consequences on cardiac structure and function. For example, postnatal therapies like corticosteroid therapy, caffeine administration, surfactant, and various ventilatory methods are being explored as potential factors having a long-term effect on cardiovascular sequelae (Schuermans & Lewandowski, 2021).

**Implications for Practice**

It is increasingly evident that preterm birth causes structural and functional changes in the heart and kidneys that persist into adulthood; yet, the repercussions are not
fully known (Schuermans & Lewandowski, 2021). The association of higher rates of hypertension, congestive heart failure, and coronary heart disease with preterm birth has important implications for clinicians and individuals born preterm. Clinicians are caring for this at-risk populations without knowing it because birth history is rarely ascertained beyond early childhood (D'Agata et al., 2022; Kelly et al., 2021). Education about the risks and potential adverse long-term cardiovascular outcomes is critically needed for all clinicians (students and experienced), parents of individuals born preterm, and preterm born individuals themselves.

Hypertension may not be coupled with other traditional risk factors in the preterm population; therefore, an inquiry of birth history is necessary to fully evaluate cardiovascular risk (Lewandowski et al., 2020). Given the growing segment of the adult population who were born preterm and are seeking healthcare, it is necessary for all healthcare members to be aware of the building evidence about CVD risk, especially the increased risk for higher blood pressures. Preemptively inquiring about birth history, performing targeted screening and frequent monitoring, and promoting healthy lifestyles are essential for this at-risk population (Raju et al., 2017). Preterm birth carries a lifelong risk, yet most clinicians are unaware of the substantiated long-term health effects.

**Conclusion**

Millions of preterm born survivors are entering adulthood, introducing a whole new population at risk for CVD. In light of the anatomical and physiological alteration noted in this population, additional research is needed to determine the effectiveness of traditional lifestyle behaviors, clinical measures, and conventional therapies for management in this population. It is unknown which pathophysiological mechanisms are
most important and which differ for those born preterm. Long-term monitoring of the cardiac remodeling process is needed to increase understanding of its implications. Further study of the mechanistic components and physiological alterations associating prematurity to greater CVD risks is needed to determine the consequences of early life interventions and treatments. This research is critical to CVD risk-reduction in this population. Finally, more research about U.S. adults born preterm is needed to compare to international findings. To facilitate research and increase awareness, nurse practitioners can start with documenting birth history during clinical encounters. This will position nurse practitioners to preemptively and routinely provide long-term follow-up care that can help to avert adverse cardiovascular sequelae of prematurity.

Birth history, unlike lifestyle, is a nonmodifiable risk factor. Nurse practitioners are in a unique position to influence lifelong cardiovascular health. Hypertension is a major contributing factor for increased CVD morbidity and mortality and is responsive to lifestyle modification. A greater awareness of the emerging findings surrounding preterm birth and embracing a life course approach of CVD prevention begins with a simple inquiry, documentation of preterm birth status, and recognition of its relevance to cardiovascular health.

**Figure 1.** *Structural and Functional Changes in Young Adults Born Preterm*

**Figure 2.** *Organogenesis Disrupted by Preterm Birth*
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https://doi.org/10.1161/HYPERTENSIONAHA.120.15574


https://doi.org/10.1001/jamacardio.2021.0961


Figure 15

Manuscript I, Figure 1

Figure 1.

Structural and Functional Changes in Young Adults Born Preterm

Figure 16

Manuscript I, Figure 2

Figure 2.

Organogenesis Disrupted by Preterm Birth

[Diagram showing the relationship between preterm birth and organogenesis, leading to cardiac remodeling, adaptations, unique cardiac phenotype, and hypertension.]
Chapter 5: Manuscript II

Association of preterm birth with prevalent and incident hypertension, early-onset hypertension, and cardiovascular disease in the Women’s Health Initiative

(Submitted for publication, 2022)

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Running Head: Preterm Birth and CVD
Abstract

Increasing evidence suggests preterm birth is a risk factor for hypertension and cardiovascular disease (CVD) in adulthood. Whether there is effect modification by hypertension on CVD risk is unknown. To investigate the associations between preterm birth, hypertension, and incident CVD, we identified 2,303 women aged 50-79 years who self-reported being born preterm from the Women’s Health Initiative. Using multivariable logistic regression, prevalent hypertension at enrollment, age at hypertension diagnosis, and antihypertensive medication use were compared by birth status (preterm, full term). Risk of incident hypertension, coronary heart disease (CHD), and CVD were analyzed using multivariable Cox proportional-hazard models. Both models adjusted for age, race/ethnicity, education, smoking, physical activity, body mass index, and diabetes. Significant associations were found between preterm birth and prevalent hypertension [37% vs. 33.1%, aOR 1.26 (95% CI 1.15, 1.28) \( p = <.0001 \)], early-onset hypertension (<50 years) [14.7% vs. 11.7%, aOR 1.31 (95% CI 1.15, 1.48) \( p = <.0001 \)], and incident hypertension [53.2% vs. 51%; aHR 1.10 (95% CI 1.03, 1.19) \( p = 0.008 \)]. Preterm-born women reported taking more antihypertensive medications (2.9% vs. 2.6%, \( p = 0.04 \)). Preterm birth had a nonsignificant association with CVD risk but, when stratified by prevalent hypertension, women born preterm without hypertension had elevated CVD risk compared to women born full term without prevalent hypertension. Women with prevalent hypertension, preterm and full term, had similar magnitudes of elevations in CVD risk. In conclusion, preterm birth increases the risk for hypertension and CHD. With 10% of the population born preterm, birth history should be assessed as a CVD risk factor.
**Keywords:** Preterm-born adults; hypertension; cardiovascular risk; women’s health.
More women die annually from CVD than all cancers combined (Danaei et al., 2009; Whelton et al., 2018). Hypertension, the main contributor to CVD mortality, is estimated to shorten a woman’s life expectancy by nearly 5 years (Danaei et al., 2009; Engberding & Wenger, 2012; Franco et al., 2005; Lim et al., 2012; Whelton et al., 2018). Epidemiological research involving adults born preterm (<37 weeks gestation) is slowly emerging, and the findings to date support an increased risk of elevated blood pressure (Raju, Buist, et al., 2017; Sullivan et al., 2019). Most studies have focused on very low birth weight infants and systolic blood pressure in childhood and adolescence, with few studies having explored the relationship between aging preterm-born individuals and the risk of developing adult hypertension, age of hypertension onset, and the ability to control blood pressure (Bertagnolli et al., 2016; Doyle et al., 2003; Hack et al., 2005; Jones et al., 2019; Kistner et al., 2000; Mohamed et al., 2021; Sipola-Leppanen, Karvonen, et al., 2015). Using the Women’s Health Initiative Observational Study (WHI-OS), a large-scale, racially and ethnically diverse, longitudinal cohort of U.S postmenopausal women, the associations between a woman’s birth history (preterm vs. full term) and the risk for hypertension and CVD outcomes in adulthood were investigated. To our knowledge, this is the first U.S. study of adults 50 years of age and older who were born preterm, in which the long-term associations with hypertension and CVD risk have been researched.

Methods

The WHI is a prospective longitudinal cohort study of postmenopausal women aged 50-79 years (born 1920s-1940s) designed to investigate the major causes of chronic disease in postmenopausal women, including known risk factors of CVD, breast and
The WHI’s study design, recruitment methods, inclusion and exclusion criteria, and implementation have been described elsewhere (Anderson et al., 2003; Langer et al., 2003). Briefly, a total of 161,608 women were enrolled into 3 overlapping clinical trials (WHI-CT, n = 67,932) or the longitudinal Observational Study (WHI-OS, n = 93,676) (Anderson et al., 2003; Langer et al., 2003). This study is derived from women who enrolled in the WHI-OS between the years of 1993-1998. Of the 93,676 WHI-OS enrolled women, 88,343 women provided self-reported birth history. From the 88,343 responses, 2,303 women (2.4%) self-reported being born preterm. Participants provided written consent at the time of enrollment and ethics approval was granted by each enrolling center’s Institutional Review Board (Anderson et al., 2003; Langer et al., 2003).

Participants completed structured questionnaires on demographic characteristics, lifestyle behaviors, medical and family histories, and their birth history at enrollment. Birth status, the primary exposure variable, was ascertained only from WHI-OS participants. This self-reported measure was defined as a term (9-month pregnancy) or preterm (4 or more weeks premature) birth. Anthropometric measures and blood pressure were obtained at the enrollment visit by certified staff using standardized procedures and instruments.

The primary outcome was hypertension, either at enrollment (prevalent) or any point during the study years (incident). Individual hypertension components (age at hypertension diagnosis and the level of blood pressure control determined as antihypertensive medication use) were analyzed as secondary outcomes. Hypertension was defined following the guideline(s) at the time of data collection (JNC IV [1988]).
Prevalent hypertension was determined based on the “Yes/No” questionnaire response to, “Did a doctor ever say that you had hypertension or high blood pressure?” or systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg (treated or untreated) identified at the enrollment visit. If participants responded “Yes” to the questionnaire, they were then asked to provide their age at diagnosis, if they were ever treated pharmacologically with antihypertensive medications, and if they were presently being treated for hypertension. A medication inventory of current medications including over-the-counter supplements, was conducted at the enrollment visit. The age at hypertension diagnosis was categorized as early-onset (defined as a hypertension diagnosis prior to age 50 years, starting at <20 years of age and continuing in 10-year increments) or hypertension (≥50 years). Difficult to control hypertension was defined as a blood pressure that remained >140/90 mmHg despite 3 antihypertensive agents from different antihypertensive complementary classes or when blood pressure control (<140/90 mmHg) required 4 or more antihypertensive agents (JNC 4 Writing Group, 1988; JNC 5 Writing Group, 1993; JNC 6 Writing Group, 1997; Whelton et al., 2018).^{1,17-19}

Incident hypertension was computed from annual medical history questionnaires that asked, “Since the prior date on this form, has a doctor prescribed for the first time any pills for high blood pressure or hypertension?” An in-person follow-up visit was conducted at Year 3, obtaining blood pressure measurements and medication inventory. Adjudicated outcomes for incident CHD included myocardial infarction (MI), cardiac revascularization (percutaneous coronary intervention (PCI), coronary artery bypass

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grafting (CABG), and CHD death. Incident CVD was a composite of physician centrally adjudicated fatal or nonfatal MI, cardiac revascularization (PCI, CABG), CVD death, stroke (of any type), heart failure, and peripheral artery disease. Health questionnaires were obtained from 1994 through 2021. Lifestyle covariates included smoking history, physical activity, alcohol intake, and cardiovascular comorbidities (e.g., diabetes, hyperlipidemia, heart failure).

Analyses were performed by birth status (preterm, full term) using baseline data. Descriptive statistics were used (mean and standard deviation for continuous variables; counts and percentages for categorical variables) to summarize socio-demographic characteristics and CVD risk factors. Potential confounders were set apriori based upon literature review. Person-years of follow-up for each participant was based on time from enrollment to outcome of interest, loss to follow-up, or death. Multivariable logistic regression models were used to estimate odds ratios (OR) and their associated 95% confidence intervals (95% CI) to model prevalent hypertension at enrollment by birth status, age at hypertension diagnosis, and antihypertensive medication use by preterm and full-term birth status. Multivariable Cox proportional-hazards regression models were used to estimate hazard ratios (HR) and 95% CI for the development of incident hypertension, incident CHD, and incident CVD by preterm and full-term birth status. Both models adjusted for age, race/ethnicity, education, smoking status, physical activity, body mass index (BMI), and diabetes. A stratified analysis to examine interaction of hypertension groupings and birth status on incident CHD and incident CVD was conducted. An interaction p value of ≤0.10 was considered significant. Covariates selected for inclusion of modeling were standard CVD risk factors including age
(continuous), race/ethnicity (categorical), education (categorical), smoking status (categorical), physical activity (continuous), BMI (continuous), and diabetes (categorical). A post hoc supplementary analysis was conducted to examine for potential confounding by low birth weight. Joint effect associations between birth status (preterm, full term) and birth weight were evaluated by creating 4 categories and using full-term normal birth weight as the reference (Supplementary Table 1). Analyses were conducted using SAS v9.4. (Schoenfeld, 1983)\(^\text{20}\) A significance level of \(p \leq 0.05\) was used for all analyses unless otherwise noted.

**Results**

The baseline characteristics of women born preterm compared to women born full term are outlined in Table 1. Women born preterm were more likely to be younger, identify as White, have a higher BMI, and self-report as having diabetes and hypertension (including diagnosis before age 50). The preterm-born women also required more antihypertensive medications for blood pressure management compared to full-term born women (2.9% vs 2.6%, \(p = 0.04\)).

The association of women born preterm compared to full term with prevalent hypertension, early-onset hypertension, incident hypertension, hypertension control, and incident CHD and CVD are presented in Table 2. Preterm birth was associated with a higher risk of prevalent hypertension [aOR 1.26 (95% CI 1.15, 1.38) \(p = <0.0001\)], early-onset hypertension (<50 years) [aOR 1.31 (95% CI 1.15, 1.48) \(p = <0.0001\)], incident hypertension [aHR 1.10 (95% CI 1.03, 1.19) \(p = 0.008\)], and showed a non-statistically significant association with difficult to control hypertension [aHR 1.38 (95% CI 1.03, 1.19) \(p = 0.008\)]. Incident CHD [aHR 1.06 (95% CI 0.90, 1.25) \(p = 0.4\)] and incident
CVD [aHR 1.12 (95% CI 0.97, 1.28) \(p = 0.11\)], fully adjusted for women born preterm, were not significantly increased.

As depicted in Table 3, incident CHD and incident CVD were significantly increased for women born preterm and without prevalent hypertension [aHR 1.28 (95% CI 1.02, 1.60) \(p = 0.03\) and aHR 1.21 (95% CI 1.00, 1.47) \(p = 0.04\)] compared to women born full term and without prevalent hypertension. Women born preterm and with hypertension had similar increases in CHD and CVD risk as those born full term and with hypertension, both 70-80% higher CVD risk than the control group [aHR 1.80 (1.72, 1.88) \(p < 0.0001\) compared to aHR 1.74 (1.43, 2.11) \(p < 0.0001\)].

The results of the effect modification analyses are presented in Table 4. The Cox proportional-hazards models stratified by prevalent hypertension indicated that the risk of incident CHD increased by 29% (95% CI 1.03, 1.62) \(p = 0.02\) and incident CVD by 23% (95% CI 1.02, 1.49) \(p = 0.03\) for women born preterm and without hypertension. As above, among women with prevalent hypertension, birth status did not modify the associations with CVD risk. Preterm birth and prevalent hypertension did show an interaction effect on incident CHD \((p = 0.011)\) but not in the direction hypothesized. All other tested interactions did not meet our statistical criteria \((p \text{ value} \leq 0.10)\).

The post hoc analyses of the associations by birth status and birth weight are depicted in Supplementary Table 1. Women born preterm with normal birth weight had higher odds of developing some outcomes (e.g., prevalent hypertension) compared to those born full-term with normal birth weight. However, this was not at the same level of risk as those born preterm with low birth weight. This was particularly true for difficult to control hypertension, incident hypertension, and incident CVD.
Discussion

In this large, nationally represented U.S. cohort of postmenopausal adult women, we found a significant association between preterm birth and hypertension. Women born preterm had a greater prevalence of hypertension at study enrollment, higher incidence of hypertension, and reported being diagnosed with hypertension at a younger age than women born full term. Hypertensive women born preterm were taking more antihypertensive medications for blood pressure control compared to full-term women yet, only 34% of them were pharmacologically treated ($p < 0.0001$).

We hypothesized that women born preterm and with prevalent hypertension would be at greater risk for CHD and CVD. We saw a similar risk among the women born preterm with hypertension and the women born full term with hypertension in relation to incident CHD and incident CVD. The result of the assessment of effect modification by prevalent hypertension did not show a statistically significant effect by birth status on incident CVD. Coincidently, there was an interaction between birth status and prevalent hypertension on incident CHD. A potential explanation is that prevalent hypertension is such a strong CVD risk factor that it overshadowed the risks that may be associated with preterm birth. The literature supports an increased CVD risk in adults born preterm; yet, in our study, we surmise that the strong association of hypertension dominated the weaker association of preterm birth and CVD (Crump, Howell, et al., 2019).21

International studies have reported SBP 2–8 mmHg higher and greater 24-hour variability in those born preterm starting as young as 6 years of age (de Jong et al., 2012; Parkinson et al., 2013; Sipola-Leppanen, Karvonen, et al., 2015).12,22,23 Others have
reported that preterm-born women have higher blood pressure measurements than preterm-born males (Haikerwal et al., 2020; Mathai et al., 2015; Parkinson et al., 2013). A Swedish cohort analysis of hypertensive young adults (25–37 years of age) found that the preterm-born adults required more antihypertensive agents for blood pressure control than their hypertensive full-term peers (Crump, 2020a). Uncontrolled hypertension has been estimated to correlate with a 25% higher risk of CVD mortality and a 32% higher risk of a cerebrovascular event for preterm-born individuals (Risnes et al., 2021).

Though the increase in blood pressure may appear small, it is clinically significant and appears to impart health consequences over a life course for these preterm-born individuals (Sipola-Leppanen, Karvonen, et al., 2015).

The WHI-OS women born preterm self-reported more hypertension diagnoses at enrollment than women born full term (preterm 37% vs. full term 33.1%) however, the in-person blood pressure readings between the 2 cohorts were not significantly different. We found the age at hypertension diagnosis and number of antihypertensive medications to be statistically significant between birth cohorts, aligning with the literature based on younger adult preterm-born populations (Crump et al., 2011b; Flahault et al., 2020; Haikerwal et al., 2020; Kowalski et al., 2018; Paquette et al., 2018; Skudder-Hill et al., 2019). To our knowledge, this is the first analysis of hypertension, and hypertension-related incident CHD and CVD in a U.S. preterm cohort of women aged 50–79 years.

Studies evaluating CHD and cerebrovascular events in individuals born preterm are less common. There are limited preterm-born individuals at middle to late adulthood, except those from the Nordic countries (Crump, Howell, et al., 2019; Ueda et al.,
One study of a preterm-born cohort with a maximum age of 42 years, reported an increased relative risk of heart disease among women (Crump, Howell, et al., 2019). Conversely, another cohort with a mean follow-up of 67.5 years reported the hazard ratio for CHD was higher among women, although there was no increased risk for CHD or stroke among those preterm born (Kajantie et al., 2015). A possible explanation relating to our findings is that the WHI-OS participants were born before the development of neonatal intensive care; therefore, these women may represent a strong and healthy cohort of late preterm-born women. Furthermore, some of the current neonatal treatments and advancements may have unfavorable long-term consequences that these preterm-born women did not receive as infants (Vrselja et al., 2021).

Anatomical and physiological alterations in the heart, kidneys, and vasculature have been detected in pre-clinical animal models and in studies of children and young adults born preterm (Chehade et al., 2018; Johansson et al., 2005). Smaller ventricular cavities and thicker ventricular walls, possibly the result of newly discovered low cardiomyocyte endowment and impaired cardiac development, may contribute to the systolic and diastolic dysfunction found in preterm hearts (Lewandowski et al., 2020). Decreased vascularity and increased vascular stiffness resulting from reduced vascular endowment and impaired vasculogenesis may be instrumented in the higher systolic pressures found in preterm-born individuals (Lewandowski et al., 2020). Similar findings have been uncovered in the kidneys. Lower nephron counts, decreased kidney volumes, and reduced glomerular filtration are presumably the result of disrupted nephrogenesis, which may further enhance blood pressure (Crump, Sundquist, et al., 2019; Heo & Lee, 2021). These structural and function alterations offer potential
mechanistic insight into the health sequelae related to preterm birth that may promote the development of hypertension and CVD in this at-risk population (Lewandowski et al., 2020).38

Low birth weight, defined as less than 5.5 pounds by the World Health Organization and less than 5.8 pounds by March of Dimes, is inherently linked and almost an unavoidable consequence of preterm birth (March of Dimes, 2021; World Health Organization, 2022a).41,42 The WHI-OS participants were asked at enrollment to select the most appropriate birth weight category, beginning with <6 pounds through 10 or more pounds (Women's Health Initiative, 2021).43 The post hoc analyses revealed that low birth weight partially mediated the association between preterm status and both hypertension and incident CVD. However, given the persistent significant elevation in these risks with preterm status, even when compared to other women with low birth weight, suggests an independent contribution of this risk factor. Therefore, we concluded it was more appropriate to present a stratified analysis by low versus normal birthweight than to simply adjust for birth weight in the main model.

This first investigation into the associations between preterm birth, hypertension, and incident CHD and CVD in the WHI-OS participants is unique. The women born preterm in the WHI-OS did not benefit from current neonatal intensive care, or from current preventive strategies for CVD risk with contemporary technology or research evidence. Despite these differences, the most important clinical implication of our findings is that preterm birth, regardless of gestational age, is associated with an early-onset of CVD risks.
Our findings emanate from the largest known cohort of women across the U.S. who were born preterm. The credibility of the findings is supported by standardized data collection methods, consistent long-term follow-up by a clinical coordinating center, and an exceptional retention rate (only 1-2% of total participation lost to follow-up). Data are strengthened by the collection of phenotypic profiles at enrollment, the prospective design that enhances the determination of disease incidence, and the extensive long-term follow-up data. Of the 88,343 in our analysis, 87.5% of the preterm group and 85.9% of the term group were White. The low frequency counts of women who identified as Black and Hispanic limited our ability to evaluate racial- and ethnic- specific associations. These findings align with what is known in the general population. The full-term born women with hypertension were older, had lower education, lower normalized socio-economic status (NSES), and high BMI (Engberding & Wenger, 2012; Ji et al., 2020; Ji et al., 2021; Lam, 2011; Wenger et al., 2018).

This study’s findings may not be generalizable to younger preterm-born individuals (male and female) due to changes in perinatal care but, the 8 or more years of CVD data provide insight into the long-term health of a generation of women born preterm. These results have important health implications, specifically the need for early identification of preterm birth so that the quantification of CVD risk like hypertension may be recognized and promptly managed.

Limitations of this study include reliance on self-report and recall bias. In the WHI-OS, birth status was self-reported, and the precise degree of prematurity (or gestational birth age) is unknown. As a margin of error exists with self-reported birth measurement and birth records and national registry databases are the most accurate
sources of birth history, self-reported data have been considered reliable proxies for medical history (Jackson et al., 2014). The age at hypertension diagnosis, if years prior or medications not initiated at disease onset, contributes to recall bias. Additionally, some of the medications used to treat hypertension may also be used to treat other cardiac conditions, possibly complicating the exact number of antihypertensive agents. The subsample size of some of the preterm groupings were small, suggesting caution when interpreting the findings. Lastly, fully controlling for confounding by indication is always a potential despite the prospective design of the WHI-OS.

The cross-sectional analysis for incident disease investigating the health of approximately 65-year-old women for the first time may have limited our findings. Prevalent disease had a strong association with preterm birth; therefore, the analysis of incident disease or a disease-free cohort may have been limited given the age of the participants. The search for incident disease essentially included women who didn’t succumb to hypertension, CHD, or CVD before data collection. Women who were most susceptible to the long-term outcomes associated with preterm birth were excluded from the incident disease evaluation, introducing collider bias. Therefore, the investigations into incident hypertension, CHD, and CVD may have been attenuated by left sided censoring and possibly contributed to the nonsignificant difference in incident CHD and CVD in women born preterm compared with full-term women.

The analysis of difficult-to-control hypertension in the preterm population is of clinical interest, though not statistically significant [aOR 1.38 (95% CI 0.98, 1.96), p = 0.06]. This finding was limited by the small sample size (n = 37), but given the trend and borderline p value, this finding warrants further study, particularly for young women born
preterm. Collaboration among researchers of individuals born preterm to pool data may strengthen and better define hypertensive, preterm-born women most at risk.

In conclusion, the findings of this study are clinically relevant for all clinicians, highlighting the importance of opportunistic blood pressure evaluation and CVD risk stratification with early management, beginning in adolescents. Millions of preterm-born survivors are reaching adulthood, introducing a whole new population at risk for CVD (D'Agata et al., 2022). Though the WHI is a U.S. cohort of women, there are similar risks reported for preterm-born men in international studies, suggesting further research is needed in U.S. cohorts of preterm-born men. Routine documentation of birth gestation at clinical encounters may translate into reduced CVD by preemptively engaging in cardioprotective strategies (Crump, 2014, 2021; Kelly et al., 2021). Although the association between preterm birth and elevated blood pressure appears strong, the mechanisms remain unclear (Jones et al., 2019). Further clinical research is needed to expand our understanding of the mechanistic pathways responsible for the structural and functional modifications seen in the preterm-born population. In doing so, targeted risk-modifying interventions, improved neonatal practices, and pharmacologic and/or behavioral modifications may result that may mitigate long-term cardiovascular consequences.
Conflicts of Interest. None

Acknowledgements. We thank the WHI-OS study participants for their long-term dedication to research and for making this study possible, as well as the WHI principal investigators.

Financial support. The WHI is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268001100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the Helsinki declaration of 1975, as revised in 2008. The WHI Publications and Presentations Committee and the University of Rhode Island Institutional Review Board approved this study. Patient consent was not required for this secondary data analysis as women provided written consent at the time of enrollment and ethics approval was granted by each enrolling center’s Institutional Review Board.

Highlights

• Preterm-born postmenopausal women had a higher incidence of hypertension and CVD.

• Women born preterm have greater long-term CVD risk, beginning at younger ages.

• Preterm birth should be considered a CVD risk factor starting in early adulthood.

• Birth history is rarely ascertained during adult clinical encounters.

• Adding birth history to clinical practice standards may reduce adverse CVD health.
References


42. World Health Organization. Low Birth Weight, 2022.


44. Lam CS. The socioeconomic of hypertension: how $50 000 may buy a drop in blood pressure. *Hypertension* 2011;58:140-141.


51. Crump C. Medical history taking in adults should include questions about preterm birth. *BMJ* 2014;349:g4860.

### Table 1. Baseline characteristics of 88,343 WHI-OS participants, by birth status

<table>
<thead>
<tr>
<th>Demographic and lifestyle factors</th>
<th>Full term (n=86,040)</th>
<th>Preterm (n=2,303)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) (mean, sd)</td>
<td>63.5 (7.4)</td>
<td>62.0 (7.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age cohort (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50-59</td>
<td>27576 (32.1)</td>
<td>944 (41.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60-69</td>
<td>37882 (44.0)</td>
<td>949 (41.2)</td>
<td></td>
</tr>
<tr>
<td>70-79+</td>
<td>20582 (23.9)</td>
<td>410 (17.8)</td>
<td></td>
</tr>
<tr>
<td>Race (n, %)</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>American Indian/Alaska</td>
<td>280 (0.3)</td>
<td>9 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2287 (2.7)</td>
<td>45 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian/Other PI</td>
<td>60 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>6750 (7.9)</td>
<td>175 (7.6)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>73926 (85.9)</td>
<td>2014 (87.5)</td>
<td></td>
</tr>
<tr>
<td>More than one</td>
<td>873 (1.0)</td>
<td>18 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Unknown/Not reported</td>
<td>1864 (2.2)</td>
<td>42 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (n, %)</td>
<td>3640 (4.2)</td>
<td>89 (3.9)</td>
<td>0.45</td>
</tr>
<tr>
<td>Education level (n, %)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>&lt; High school graduate/GED</td>
<td>13787 (16.0)</td>
<td>320 (13.9)</td>
<td></td>
</tr>
<tr>
<td>High school graduate</td>
<td>31078 (36.1)</td>
<td>837 (36.3)</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>36257 (42.1)</td>
<td>1041 (45.2)</td>
<td></td>
</tr>
<tr>
<td>College graduate</td>
<td>678 (0.8)</td>
<td>19 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4240 (4.9)</td>
<td>86 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Income level (n, %)</td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>$50,000 or greater</td>
<td>32786 (38.1)</td>
<td>901 (39.1)</td>
<td></td>
</tr>
<tr>
<td>$20,000 - &lt;$50,000</td>
<td>34595 (40.2)</td>
<td>921 (40.0)</td>
<td></td>
</tr>
<tr>
<td>&lt; $20,000 per year</td>
<td>12522 (14.6)</td>
<td>329 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Missing/Don't Know</td>
<td>6137 (7.1)</td>
<td>152 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Neighborhood SES (mean, sd)</td>
<td>76.0 (8.6)</td>
<td>76.0 (8.1)</td>
<td>0.83</td>
</tr>
<tr>
<td>Partnered (n, %)</td>
<td>53417 (62.4)</td>
<td>1477 (64.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Region of birth (n, %)</td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------</td>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>Not born in US</td>
<td>6112 (7.2)</td>
<td>159 (7.0)</td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>23751 (27.8)</td>
<td>616 (26.9)</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>25148 (29.5)</td>
<td>689 (30.1)</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>18726 (22.0)</td>
<td>501 (21.9)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>11574 (13.6)</td>
<td>322 (14.1)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking status (n, %)</th>
<th></th>
<th></th>
<th>0.10</th>
</tr>
</thead>
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<tr>
<td>Never Smoked</td>
<td>43055 (50.7)</td>
<td>1181 (52.1)</td>
<td></td>
</tr>
<tr>
<td>Past Smoker</td>
<td>36537 (43.0)</td>
<td>928 (41.0)</td>
<td></td>
</tr>
<tr>
<td>Current Smoker</td>
<td>5310 (6.3)</td>
<td>156 (6.9)</td>
<td></td>
</tr>
</tbody>
</table>

| Physical activity (mean, sd) | 13.43 (14.50) | 13.35 (15.29) | 0.80 |

| Physical activity level (n, %) |        |        | 0.20 |
| Inactive: 0 - 1.7 MET hrs/week | 18137 (21.2) | 521 (22.7) |
| Low Activity: 1.8 - 8.3 MET hrs/week | 22513 (26.3) | 617 (26.9) |
| Mod. activity: 8.4 - 20 MET hrs/week | 24305 (28.4) | 628 (27.4) |
| High activity: >20 MET hrs/week | 20659 (24.1) | 530 (23.1) |

| Alcohol servings per week (mean, sd) | 2.52 (5.19) | 2.58 (5.31) | 0.58 |

**Medical history**

<p>| Body mass index (mean, sd) | 27.5 (6.8) | 28.0 (6.7) | 0.001 |
| Height (cm) (mean, sd)     | 161.7 (6.8) | 161.3 (6.6) | 0.003 |
| Short stature (height &lt; 5 feet) (n, %) | 6091 (7.1) | 182 (8.0) | 0.12 |
| Systolic blood pressure, mmHg (mean, sd) | 127 (18.0) | 127 (17.8) | 0.49 |
| Diastolic blood pressure, mmHg (mean, sd) | 75 (9.3) | 75 (9.3) | 0.11 |
| Diabetes (n, %) | 3467 (4.0) | 133 (5.8) | &lt;0.001 |
| Hyperlipidemia (n, %) | 12947 (15.1) | 356 (15.5) | 0.58 |
| Hypertension (n, %) | 28462 (33.1) | 851 (37.0) | &lt;0.001 |
| Angina (n, %) | 4966 (5.8) | 159 (7.0) | 0.01 |
| Atrial fibrillation (n, %) | 3992 (4.7) | 113 (5.0) | 0.54 |
| TIA (n, %) | 2014 (2.3) | 61 (2.7) | 0.33 |
| Heart failure (n, %) | 1217 (1.4) | 41 (1.8) | 0.14 |
| HTN age onset (n, %) | | | &lt;0.001 |
| No HTN | 57477 (67.2) | 1447 (63.3) |
| Less than 20 | 243 (0.3) | 19 (0.8) |
| 20-29 | 820 (1.0) | 25 (1.1) |</p>
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total Number</th>
<th>No HTN meds</th>
<th>1 HTN med</th>
<th>2 HTN meds</th>
<th>3 HTN meds</th>
<th>4 HTN meds</th>
<th>5+ HTN meds</th>
<th>Beta blocker</th>
<th>Calcium channel blocker</th>
<th>Diuretic</th>
<th>ACE</th>
<th>ARB</th>
<th>Other HTN medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>2480 (2.9)</td>
<td>60076 (69.8)</td>
<td>16801 (19.5)</td>
<td>6968 (8.1)</td>
<td>1622 (1.9)</td>
<td>436 (0.5)</td>
<td>137 (0.2)</td>
<td>7418 (8.6)</td>
<td>8435 (9.8)</td>
<td>11775 (13.7)</td>
<td>6812 (7.9)</td>
<td>663 (0.8)</td>
<td>1152 (1.3)</td>
</tr>
<tr>
<td>40-49</td>
<td>6454 (7.6)</td>
<td>1524 (66.2)</td>
<td>488 (21.2)</td>
<td>225 (9.8)</td>
<td>45 (2.0)</td>
<td>17 (0.7)</td>
<td>4 (0.2)</td>
<td>220 (9.6)</td>
<td>257 (11.2)</td>
<td>369 (16.0)</td>
<td>207 (9.0)</td>
<td>21 (0.9)</td>
<td>41 (1.8)</td>
</tr>
<tr>
<td>50-59</td>
<td>10037 (11.7)</td>
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<td>312 (13.7)</td>
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<tr>
<td>60-69</td>
<td>6415 (7.5)</td>
<td></td>
<td>160 (7.0)</td>
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<td></td>
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<tr>
<td>70 or older</td>
<td>1614 (1.9)</td>
<td></td>
<td>30 (1.3)</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

Hypertension Medications (n, %)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total Number</th>
<th>No HTN meds</th>
<th>1 HTN med</th>
<th>2 HTN meds</th>
<th>3 HTN meds</th>
<th>4 HTN meds</th>
<th>5+ HTN meds</th>
<th>Beta blocker</th>
<th>Calcium channel blocker</th>
<th>Diuretic</th>
<th>ACE</th>
<th>ARB</th>
<th>Other HTN medication</th>
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</tbody>
</table>

|                                      |              |             |           |            |            |            |             |             |                        |          |     |     |          |
**Table 2. Association of Preterm vs. Full-Term Birth Status with Hypertension Prevalence, Incidence, Onset, Control, and Incident Coronary Heart Disease and Cardiovascular Disease.**

<table>
<thead>
<tr>
<th></th>
<th>Full Term</th>
<th>Preterm</th>
<th>Age-adjusted Ratio (95% CI)</th>
<th>p-value</th>
<th>Fully adjusted Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalent HTN</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>57,578 (66.9)</td>
<td>1,452 (63.1)</td>
<td>(ref)</td>
<td>&lt;.0001</td>
<td>(ref)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>28,462 (33.1)</td>
<td>851 (37.0)</td>
<td>1.28 (1.17, 139)</td>
<td></td>
<td>1.26 (1.15, 1.38)</td>
<td></td>
</tr>
<tr>
<td><strong>Early Onset HTN</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>57,477 (67.2)</td>
<td>1,447 (63.3)</td>
<td>(ref)</td>
<td>&lt;.0001</td>
<td>(ref)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Onset &lt;50y</td>
<td>9,997 (11.7)</td>
<td>337 (14.7)</td>
<td>1.32 (1.17, 1.49)</td>
<td>&lt;.0001</td>
<td>1.31 (1.15, 1.48)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Onset ≥50y</td>
<td>18,066 (21.1)</td>
<td>502 (22.0)</td>
<td>1.24 (1.12, 1.38)</td>
<td>&lt;.0001</td>
<td>1.23 (1.10, 1.37)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Difficult to Control HTN</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HTN</td>
<td>57,514 (66.9)</td>
<td>1,451 (63.0)</td>
<td>(ref)</td>
<td></td>
<td>(ref)</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>27,347 (31.8)</td>
<td>815 (35.4)</td>
<td>1.27 (1.16, 1.39)</td>
<td>&lt;.0001</td>
<td>1.25 (1.14, 1.37)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DTC HTN</td>
<td>1,179 (1.4)</td>
<td>37 (1.6)</td>
<td>1.45 (1.04, 2.02)</td>
<td>0.02</td>
<td>1.38 (0.98, 1.96)</td>
<td>0.06</td>
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<tr>
<td><strong>Incident HTN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>28,217 (49.0)</td>
<td>680 (46.8)</td>
<td>(ref)</td>
<td></td>
<td>(ref)</td>
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<tr>
<td>Yes</td>
<td>29,361 (51.0)</td>
<td>772 (53.2)</td>
<td>1.11 (1.04, 1.20)</td>
<td>0.003</td>
<td>1.10 (1.03, 1.19)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Incident CHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>77,496 (93.2)</td>
<td>2,065 (93.3)</td>
<td>(ref)</td>
<td></td>
<td>(ref)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5,661 (6.8)</td>
<td>148 (6.7)</td>
<td>1.10 (0.94, 1.30)</td>
<td>0.24</td>
<td>1.06 (0.90, 1.25)</td>
<td>0.49</td>
</tr>
<tr>
<td>Incident CVD**</td>
<td>No</td>
<td>74,873 (93.5)</td>
<td>1987 (93.5)</td>
<td>(ref)</td>
<td>0.06</td>
<td>(ref)</td>
</tr>
<tr>
<td>---------------</td>
<td>----</td>
<td>---------------</td>
<td>-------------</td>
<td>-------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>Yes</td>
<td>5,171 (6.5)</td>
<td>138 (6.5)</td>
<td>1.13 (0.99, 1.30)</td>
<td></td>
<td>1.12 (0.97, 1.28)</td>
<td></td>
</tr>
</tbody>
</table>

(ref)=reference group; in all cases, depicts women born full term and without (“No”) outcome of interest; DTC HTN = Difficult to control hypertension; Incident CHD = adjudicated fatal or nonfatal myocardial infarction, revascularization (angioplasty/percutaneous intervention or coronary artery bypass surgery), and coronary heart disease related death; Incident CVD = adjudicated fatal or nonfatal myocardial infarction, revascularization (angioplasty/percutaneous intervention or coronary artery bypass surgery), CVD death, stroke (ischemic, hemorrhagic), transient ischemic attack, peripheral artery disease, and heart failure.

*Prevalence outcomes use Odds Ratios for age-adjusted ratio and fully adjusted ratio.

**Incident outcomes use Hazard Ratios for age-adjusted ratio and fully adjusted ratio.

†Fully adjusted model includes age, race/ethnicity, education, smoking status, physical activity, BMI, and diabetes.
Table 7

*Manuscript II, Table 3*

**Table 3.** Association of Preterm vs. Full-Term Birth Status with Incident Coronary Heart Disease and Cardiovascular Disease.

<table>
<thead>
<tr>
<th>Incident CHD</th>
<th>FULL TERM</th>
<th>PRETERM</th>
<th>PRETERM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Prevalent HTN</td>
<td>Prevalent HTN</td>
<td>No Prevalent HTN</td>
</tr>
<tr>
<td>No (n, %)</td>
<td>53790 (95.2)</td>
<td>23706 (89.0)</td>
<td>1335 (94.4)</td>
</tr>
<tr>
<td>Yes (n, %)</td>
<td>2739 (4.9)</td>
<td>2922 (11.0)</td>
<td>79 (5.6)</td>
</tr>
<tr>
<td>Age-adjusted hazards ratio (95% CI)</td>
<td>(ref)</td>
<td>2.17 (2.06, 2.29)</td>
<td>1.31 (1.05, 1.63)</td>
</tr>
<tr>
<td><em>p</em>-value</td>
<td>&lt;.0001</td>
<td>0.01</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>†Fully adjusted hazards ratio (95% CI)</td>
<td>(ref)</td>
<td>1.89 (1.79, 2.00)</td>
<td>1.28 (1.02, 1.60)</td>
</tr>
<tr>
<td><em>p</em>-value</td>
<td>&lt;.0001</td>
<td>0.03</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

**Incident CVD**

<table>
<thead>
<tr>
<th>Incident CVD</th>
<th>FULL TERM</th>
<th>PRETERM</th>
<th>PRETERM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Prevalent HTN</td>
<td>Prevalent HTN</td>
<td>No Prevalent HTN</td>
</tr>
<tr>
<td>No (n, %)</td>
<td>51018 (92.4)</td>
<td>20822 (83.8)</td>
<td>1263 (92.1)</td>
</tr>
<tr>
<td>Yes (n, %)</td>
<td>4191 (7.6)</td>
<td>4013 (16.2)</td>
<td>109 (7.9)</td>
</tr>
<tr>
<td>Age-adjusted hazards ratio (95% CI)</td>
<td>(ref)</td>
<td>2.02 (1.94, 2.11)</td>
<td>1.21 (1.00, 1.46)</td>
</tr>
<tr>
<td><em>p</em>-value</td>
<td>&lt;.0001</td>
<td>0.04</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>†Fully adjusted hazards ratio (95% CI)</td>
<td>(ref)</td>
<td>1.80 (1.72, 1.88)</td>
<td>1.21 (1.00, 1.47)</td>
</tr>
<tr>
<td><em>p</em>-value</td>
<td>&lt;.0001</td>
<td>0.04</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

**CVD Death**

<table>
<thead>
<tr>
<th>CVD Death</th>
<th>FULL TERM</th>
<th>PRETERM</th>
<th>PRETERM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Prevalent HTN</td>
<td>Prevalent HTN</td>
<td>No Prevalent HTN</td>
</tr>
<tr>
<td>No (n, %)</td>
<td>54575 (98.4)</td>
<td>24154 (95.8)</td>
<td>1355 (98.3)</td>
</tr>
<tr>
<td>Yes (n, %)</td>
<td>874 (1.6)</td>
<td>1050 (4.2)</td>
<td>24 (1.7)</td>
</tr>
<tr>
<td>Age-adjusted hazards ratio (95% CI)</td>
<td>(ref)</td>
<td>2.30 (2.10, 2.51)</td>
<td>1.34 (0.89, 2.01)</td>
</tr>
<tr>
<td><em>p</em>-value</td>
<td>&lt;.0001</td>
<td>0.15</td>
<td>0.0002</td>
</tr>
<tr>
<td>†Fully adjusted hazards ratio (95% CI)</td>
<td>(ref)</td>
<td>1.91 (1.74, 2.10)</td>
<td>1.31 (0.87, 1.99)</td>
</tr>
<tr>
<td><em>p</em>-value</td>
<td>&lt;.0001</td>
<td>0.19</td>
<td>0.005</td>
</tr>
</tbody>
</table>

†Fully adjusted model includes age, race/ethnicity, education, smoking status, physical activity, BMI, and diabetes.
### Table 4. Effect Modification by Prevalent Hypertension on the Association of Preterm vs. Full-Term Birth Status with Incident CHD and CVD.

<table>
<thead>
<tr>
<th>Hypertension Groupings</th>
<th>Outcome</th>
<th>HR (95% CI)(^\dagger)</th>
<th>(p)-value</th>
<th>Total (n)</th>
<th># Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without prevalent HTN</strong></td>
<td>Incident CHD</td>
<td>1.29 (1.03, 1.62)</td>
<td>0.02</td>
<td>57,943</td>
<td>2,818</td>
</tr>
<tr>
<td></td>
<td>Incident CVD</td>
<td>1.23 (1.02, 1.49)</td>
<td>0.03</td>
<td>56,581</td>
<td>4,300</td>
</tr>
<tr>
<td></td>
<td>CHD death</td>
<td>1.36 (0.81, 2.27)</td>
<td>0.24</td>
<td>57,943</td>
<td>567</td>
</tr>
<tr>
<td></td>
<td>CVD death</td>
<td>1.33 (0.88, 2.02)</td>
<td>0.17</td>
<td>56,828</td>
<td>898</td>
</tr>
<tr>
<td><strong>With prevalent HTN</strong></td>
<td>Incident CHD</td>
<td>0.82 (0.64, 1.05)</td>
<td>0.11</td>
<td>27,427</td>
<td>2,991</td>
</tr>
<tr>
<td></td>
<td>Incident CVD</td>
<td>0.97 (0.80, 1.18)</td>
<td>0.74</td>
<td>25,588</td>
<td>4,120</td>
</tr>
<tr>
<td></td>
<td>CHD death</td>
<td>0.70 (0.40, 1.21)</td>
<td>0.20</td>
<td>27,427</td>
<td>749</td>
</tr>
<tr>
<td></td>
<td>CVD death</td>
<td>0.93 (0.62, 1.40)</td>
<td>0.72</td>
<td>25,966</td>
<td>1,075</td>
</tr>
</tbody>
</table>

\(^\dagger\) Fully adjusted model includes age, race/ethnicity, education, smoking status, physical activity, BMI, and diabetes.
Table 9

Manuscript II, Supplementary Table 1

Supplementary Table

Table 1. Associations by Birth Status and Birth Weight

<table>
<thead>
<tr>
<th></th>
<th>Prevalent HTN</th>
<th>Early-Onset HTN</th>
<th>Difficult to control HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N, %</td>
<td>Age-adjusted OR</td>
<td>Fully adjusted OR</td>
</tr>
<tr>
<td>FT-NBW</td>
<td>20190 (30.5)</td>
<td>(ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>FT-LBW</td>
<td>2195 (34.9)</td>
<td>1.27 (1.20, 1.33)</td>
<td>1.21 (1.14, 1.28)</td>
</tr>
<tr>
<td>PT-NBW</td>
<td>98 (33.6)</td>
<td>1.25 (0.99, 1.58)</td>
<td>1.35 (1.06, 1.72)</td>
</tr>
<tr>
<td>PT-LBW</td>
<td>654 (36.3)</td>
<td>1.35 (1.23, 1.48)</td>
<td>1.29 (1.17, 1.43)</td>
</tr>
</tbody>
</table>

|                  | N, %          | Age-adjusted HR | Fully adjusted HR        | N, %          | Age-adjusted HR | Fully adjusted HR | N, %          | Age-adjusted HR | Fully adjusted HR |
| Incident HTN     |               |                 |                          |               |                 |                          |               |                 |                          |
| FT-NBW           | 40792 (61.6)  | (ref)           | (ref)                    | 4192 (6.3)    | (ref)           | (ref)          | 6302 (9.5)     | (ref)           | (ref)           |
| FT-LBW           | 4049 (64.4)   | 1.12 (1.07, 1.17) | 1.11 (1.06, 1.15)       | 455 (7.2)     | 1.21 (1.11, 1.33) | 1.16 (1.05, 1.27) | 671 (10.7)     | 1.19 (1.10, 1.29) | 1.14 (1.05, 1.23) |
| PT-NBW           | 180 (61.6)    | 1.01 (0.84, 1.23) | 1.05 (0.86, 1.27)       | 12 (4.1)      | 0.71 (0.41, 1.22) | 0.76 (0.44, 1.31) | 21 (7.2)       | 0.83 (0.54, 1.28) | 0.88 (0.57, 1.35) |
| PT-LBW           | 1185 (65.8)   | 1.16 (1.07, 1.25) | 1.14 (1.05, 1.23)       | 126 (7.0)     | 1.20 (1.01, 1.43) | 1.13 (0.94, 1.34) | 181 (10.1)     | 1.22 (1.05, 1.41) | 1.16 (1.00, 1.35) |

FT=Full term; PT=Preterm; LBW=Low birthweight; NBW=Normal birth weight
Chapter 6: Manuscript III

The association between preterm birth and the co-occurrence of the cumulative prevalence of hypertension, rheumatoid arthritis, and hypothyroidism in the Women’s Health Initiative

(Submitted for publication, 2022)

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Short title: Preterm Birth and Multimorbidity
Abstract

Studies suggest that preterm-born individuals (<37 weeks gestation) have impaired immunity, sustained inflammation, and disrupted organogenesis, predisposing them to chronic disease in adulthood. This study investigated the associations between preterm birth \((n=2,303)\) and the prevalence of three chronic cardiovascular disease (CVD) risk-related conditions (hypertension, rheumatoid arthritis [RA], and hypothyroidism) among 82,514 U.S. women aged 50-79 years enrolled in the Women's Health Initiative. Logistic regression was used to analyze the association between birth status (preterm, full term) and disease diagnosis. Multinomial logistic regression models analyzed the association between birth status and each condition alone and in combination. Outcome variables using the 3 conditions were created to give 8 categories ranging from no disease, each condition alone, two-way combinations, to having all three conditions. The models adjusted for age, race/ethnicity, and sociodemographic, lifestyle, and other health-related risk factors. Women born preterm were significantly more likely to have any one or a combination of the selected conditions. In fully adjusted models for individual conditions, the adjusted odds ratios (aORs) were 1.14 (95% CI, 1.04, 1.26) for hypertension, 1.28 (1.12, 1.47) for RA, and 1.12 (1.01, 1.24) for hypothyroidism. Hypothyroidism and RA were the strongest correlated conditions \([aOR 1.69, 95\% CI (1.14, 2.51)]\) and the aOR for all three conditions was 1.69 (1.22, 2.35). Perinatal history is pertinent across the life course. Early identification of risk factors and disease in preterm-born individuals is essential to mitigating adverse health outcomes. Preventive measures and early interventions may reduce health risks in this susceptible preterm population.
Keywords: Preterm birth; hypertension; hypothyroidism; rheumatoid arthritis; women’s health.
Introduction

Preterm birth (<37 weeks gestation) affects 10% of U.S. births and up to 18% of all births worldwide (Center for Disease Control and Prevention, 2021d; World Health Organization, 2018). Increasing preterm birth survival rates have introduced a new population of survivors reaching adulthood, making it critically important to understand the long-term health consequences of preterm birth (Greer et al., 2022). Emerging evidence associates an increased risk for the development of hypertension for preterm-born individuals in adulthood (Alexander & Intapad, 2012; Bertagnolli et al., 2016; Bonamy et al., 2008; Crump et al., 2011b; Sipola-Leppanen, Karvonen, et al., 2015). Further, research findings are supporting preterm birth as a risk factor for early-onset chronic disease (Luu et al., 2016). In this study, hypertension and two chronic disease states, rheumatoid arthritis [RA] and hypothyroidism, were examined independently and as comorbidities in an adult population of women born preterm (Carlens et al., 2009; Crump et al., 2011a). The increased risk of chronic disease multimorbidity in adults born preterm is not well-studied (Heikkila et al., 2021).

The above understanding of disease prevalence comes from studies where outcomes were assessed mostly in the youth or early adulthood and in Nordic European countries that have less racial diversity than the U.S. (Crump et al., 2011a; Heikkila et al., 2021; Luu et al., 2016). It is also unknown if the associations remain significant over the life course. Additionally, only a few studies have explored the prevalence of autoimmune diseases in preterm-born individuals (Carlens et al., 2009; Simard et al., 2010).
Hypertension is the strongest CVD risk factor acquired during life in the general population (Wang et al., 2020). Individuals with RA are at a 50-75% higher risk for CVD morbidity and mortality than those without RA (Abou-Raya et al., 2007; Avina-Zubieta et al., 2012; Chodara et al., 2017; Lindhardsen et al., 2011). Hypothyroidism, a common comorbidity of RA, also increases the risk for CVD (Fukui et al., 2021; Huang et al., 2022; Kannan et al., 2018; Raterman et al., 2008; Udovcic et al., 2017). Preterm birth has recently been suggested as a risk factor for CVD. Based on these associations, the risk of chronic disease multimorbidity would hypothetically be more prevalent in individuals born preterm. It was plausible to hypothesize that two chronic disease states, RA and hypothyroidism, would predispose an individual to hypertension in an already hypertensive susceptible population. The strong connection with hypertension and the collective increased risk for CVD supports the rationale for this study (Avina-Zubieta et al., 2012; Kringeland et al., 2021; McCoy et al., 2012). The underpinnings of the Developmental Origins of Health and Disease (DOHaD) theory substantiate the greater likelihood of multimorbidity in preterm-born postmenopausal adult women. Disrupted development of the hypothalamic-pituitary-thyroid (HPT) axis and the innate immune system, together with early-life environmental exposures that precipitate epigenetic modifications to the adaptive immune system, are the basis for the development of RA and hypothyroidism in preterm-born individuals. To evaluate these associations, we leveraged the Women’s Health Initiative Observational Study (WHI-OS), a large-scale, racially and ethnically diverse, well-characterized, longitudinal cohort of U.S postmenopausal adult women (Anderson et al., 2003; Langer et al., 2003).
Methods

Study Design and Participants

The WHI is a prospective longitudinal cohort study of women aged 50-79 years (birth years 1920s–1940s) designed to investigate the major causes of chronic disease in postmenopausal adult women, including risk factors for CVD, breast and colorectal cancers, and osteoporotic fractures. The WHI’s study design, recruitment methods, inclusion and exclusion criteria, and implementation have been described elsewhere (Anderson et al., 2003; Langer et al., 2003). Briefly, 161,608 women were enrolled in three overlapping clinical trials (WHI-CT, \(n = 67,932\)) or the longitudinal Observational Study (WHI-OS, \(n = 93,676\)) (Anderson et al., 2003; Langer et al., 2003).

The present study included women who enrolled in the WHI-OS between 1993 and 1998 \((n=93,676)\). Of the 93,676 women enrolled in the WHI-OS, the following women were excluded: (1) women with missing or unknown personal gestational age data \((n = 5,333)\), (2) women with a self-reported history of prevalent hyperthyroidism \((n = 2,532)\); prevalent thyroid cancer \((n = 470)\); and, prevalent hyperthyroidism and thyroid cancer \((n = 33)\), and (3) women who developed hyperthyroidism \((n = 2,621)\); thyroid cancer \((n = 262)\); or, both conditions \((n = 23)\) during the follow-up years, ending in 2005. The final analytical count after the specified exclusions was 82,514 women.

Exposures

Birth status, the primary exposure variable, was ascertained from WHI-OS participants at enrollment. Women were asked when born, were they “full term (a pregnancy that lasted about 9 months), 4 or more weeks premature (preterm), or don’t know.”
Outcomes

Hypertension was based on the self-reported physician diagnosis of hypertension at enrollment, the annual medical history questionnaires during the follow-up years (Years 1-9), being treated for hypertension with antihypertensive medications, or if systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg (treated or untreated) was identified at enrollment. Further, to make a hypertension diagnosis comparable to RA and hypothyroidism, hypertension incidence was examined through the year 2005 (the end of the core study).

The development of RA and hypothyroidism were determined through questionnaires obtained at enrollment (prevalence at baseline) and the continuing annual WHI-OS follow-up surveys administered from Year 1 through Year 9 of the core study (1994-2005). Although the WHI-OS continued to collect data for years after 2005, information on the development of RA (collected on the annual Medical History Update form) and hypothyroidism (collected on the yearly OS Follow-Up form) was not collected after 2005 due to the removal of RA from subsequent Medical History Update forms and the cessation of OS follow-up. The analyses reflect the cumulation of prevalent disease at study enrollment and as reported each year.

Covariates

Selected covariates were categorized as sociodemographic, lifestyle, and risk factors. Selected sociodemographic covariates included race/ethnicity, education level (4 categories ranging from < high school graduate to college graduate), income level (3 categories from <$20,000 per year to ≥ $50,000 per year), marital status (partnered/not partnered) and region of birth (Northeast, South, Midwest, West, or not born in the U.S.).
Lifestyle covariates incorporated smoking status (never, past, current), physical activity (inactive, low, moderate, high), alcohol intake (servings/week), and body mass index (BMI). Risk factor covariates were short stature (height <5 feet), breast fed as an infant, and the report of diabetes or hyperlipidemia (Langer et al., 2003).27

Ethical Considerations

Participants provided written consent at the time of enrollment, and ethics approval was granted by each enrolling center’s Institutional Review Board (Anderson et al., 2003; Langer et al., 2003).26,27

Statistical Analyses

Analyses were performed by birth status (preterm, full term) using baseline data. Descriptive statistics were used (mean and standard deviation for continuous variables; count and percentage for categorical variables) to summarize socio-demographic characteristics. Covariates selected for inclusion in modeling were known risk factors for hypertension, RA, and hypothyroidism. Demographic variables included education level, income level, marital status, and region of birth. Lifestyle variables incorporated smoking status, physical activity, alcohol intake, and BMI. Risk factor covariates were defined as short stature, diabetes, hyperlipidemia, and breastfed as an infant. Initially, individual diseases were analyzed using logistic regression models and included the other diseases as covariates.

Modeling of the combined diagnosis outcome was configured in two ways. The first outcome configuration summed the presence of the three diagnoses under examination per participant and ranged from 0 to 3 (no disease to all 3 diseases). The second outcome configuration examined the actual disease combinations present in each
participant (none, RA only, hypothyroidism only, hypertension only, hypothyroidism and RA, RA and hypertension, hypertension and hypothyroidism, and all three – hypertension, RA, and hypothyroidism). Both configurations of the outcome variable were modeled with multinomial logistic regression using the no disease as reference. Odds ratio (OR) and their associated 95% confidence intervals estimated the association of disease by birth status. The first model included age, race/ethnicity, education level, income level, marital status, and region of birth. The second model included age, smoking status, physical activity, alcohol intake, and BMI. The third model included age, short stature, diabetes, hyperlipidemia, and breastfed as an infant. Building on the previous models, the fourth model included those from model 1 without marital status, model 2 and model 3. Marital status was removed from model 4 because it did not have a significant effect in the modeling. This was performed after adjusting for potential confounders such as age and race/ethnicity. Analyses were conducted using SAS v9.4 (Cary, NC). A significance level of $p \leq 0.05$ was used for all analyses unless otherwise noted.

**Results**

Results from the baseline characteristics of women born preterm compared to women born full term are outlined in Table 1. Women born preterm were more likely to be younger, identify as White, and self-report as having diabetes, hypertension, and diagnosed with hypertension at a younger age. As shown in Figure 1, hypertension was the most prevalent independent disease (52.3%), followed by hypothyroidism (22.0%), and then RA (9.9%) in the full cohort of participants ($n=82,514$). Hypertension and hypothyroidism were the most common concurrent diseases (11.8%), followed by
hypertension and RA (6.0%). The co-occurrence of all three conditions was 1.4% for the
WHI-OS participants.

The logistic regression model for individual diagnosis determined that women
born preterm were 14% more likely to have hypertension, 28% more likely to have RA,
and 12% more likely to have hypothyroidism compared to their full-term peers (aOR
1.14, 95% CI [1.04, 1.26]; aOR 1.28, 95% CI [1.12, 1.47]; and aOR 1.12, 95% CI [1.04,
1.26], respectively). The odds ratio for each disease entity, corrected for the other
diseases as covariates by birth status, is shown in Table 2.

The cumulative prevalence count of the three diseases for birth status, using full-
term women as the reference is depicted in Table 3. As shown, preterm-born women
were clearly at an increased risk for disease and multimorbidity. The actual disease
combinations in each participant are shown in Table 4. Women born preterm were found
to be at an increased risk for hypertension, RA, and hypothyroidism, alone or
concomitantly, and in any combination compared to women born full term (Table 4 and
Figure 2). Preterm-born women had approximately a 20% greater likelihood of having
any one of the selected conditions (aOR 1.18 hypertension; aOR 1.24 RA; and aOR 1.19
hypothyroidism) compared to women born full term. In terms of disease combinations,
preterm-born women were 69% more likely to have RA and hypothyroidism [aOR 1.69
(1.14, 2.51)] and 48% more likely to have RA and hypertension [aOR 1.48 (1.20, 1.82)].
Further, preterm-born women had a 69% higher risk of having all three conditions
compared to women born full term [aOR 1.69, 95% CI (1.22, 2.35)].
**Discussion**

Hypertension, RA, and hypothyroidism have been studied independently as risk factors for and comorbidities of CVD in the general population (Chodara et al., 2017; England et al., 2018; Pasceri & Yeh, 1999; Ross, 1999; Van Doornum et al., 2002). More recently, the co-occurrence of RA and hypothyroidism as CVD risk factors have been studied. One study found individuals with RA and hypothyroidism had a four-fold increased risk of CVD [OR 4.1 (95% CI 1.2–14.3)] (Raterman et al., 2008). A large, retrospective, population-based cohort study of 16,174 individuals (20 years of age and older) investigating the RA-hypothyroidism connection found a 1.74-fold higher risk of hypothyroidism in individuals with RA, with hypertension being the most prevalent CVD risk factor in these individuals (Huang et al., 2022). To our knowledge, the concurrent investigation of these three conditions has not been previously explored in the preterm-born adult population.

Research in adults born preterm is slowly emerging and the findings to date support an increased risk of elevated blood pressure (Bates et al., 2020; Bertagnolli et al., 2016; Bonamy et al., 2012; Crump et al., 2011b; Dalziel et al., 2007; Haikerwal et al., 2020; Jones et al., 2019; Nuyt & Alexander, 2009; Sipola-Leppanen, Karvonen, et al., 2015). International studies have reported systolic blood pressure (SBP) 2–8 mmHg higher and greater 24-hour variability in those born preterm starting as young as six years of age (de Jong et al., 2012; Parkinson et al., 2013; Sipola-Leppanen, Karvonen, et al., 2015). A Swedish cohort analysis of hypertensive young adults (25–37 years of age) found that the preterm-born adults required more antihypertensive agents for blood pressure control than their hypertensive full-term peers (Crump et al., 2011b).
Uncontrolled hypertension has been estimated to correlate with a 25% higher risk of CVD mortality and a 32% higher risk of a cerebrovascular event for preterm-born individuals (Risnes et al., 2021). Though the increase in blood pressure may appear small, it is clinically significant and may contribute to cardiovascular health consequences over the life course for preterm-born individuals (Sipola-Leppanen, Karvonen, et al., 2015).

The immune system, regulated by the hypothalamic-pituitary-adrenal (HPA) axis, is not fully developed at the time of birth (Melville & Moss, 2013). The DOHaD theory postulates early life exposures (in utero or early childhood), and the developing environment may influence health outcomes in later life (Baird et al., 2017; Barker & Osmond, 1988; Gluckman et al., 2016). Aligning with these tenets, deficiencies in innate and adaptive immunity and the HPA axis have been identified in individuals born preterm (Colebatch & Edwards, 2011; Durandy, 2003; Melville & Moss, 2013; Strunk et al., 2011). Perinatal and environmental exposures, such as exposure to smoke, environmental pollutants, and infectious organisms, have been implicated as contributors to RA (Birru Talabi et al., 2017; Cardenas Roldan et al., 2012; Carlens et al., 2009; Colebatch & Edwards, 2011; Deane et al., 2017; Dedmon, 2020; Edwards et al., 2006; Jaakkola & Gissler, 2005). Such environmental exposures may affect HPA axis functioning and further compromise the development of immune system organs (Colebatch & Edwards, 2011). Evidence suggests autoantibodies, such as rheumatoid factor, develop years before the onset of clinical symptoms (Colebatch & Edwards, 2011). The interaction between dysregulation of the HPA axis, a deficient immune system, and unfavorable environmental exposures may make a vulnerable preterm-born
individual more susceptible to autoimmune responses (Monahan et al., 2022). Although this is a brief description of a complex interplay of systems, it exemplifies the plausibility of higher risk of disease development in adults born preterm.

Contrary to the DOHaD principles, a few studies have found low birth weight and preterm birth to associate with a reduced risk of RA (Carlens et al., 2009; Colebatch & Edwards, 2011; Jacobsson et al., 2003). In one study, the sample size was small (n=15), and the OR was non-significant 1.4 (0.7, 3.0) (Jacobsson et al., 2003). Carlens et al. (2009) found low birth weight (< 3000 g) and preterm birth (gestational age ≤ 37 weeks) were not significantly associated with the development of RA [OR 0.6 (0.7, 1.0)] (Carlens et al., 2009). Simard et al. (2010) found similar results [RR 1.1 (0.8, 1.5)] in women enrolled in the Nurses’ Health Study (Simard et al., 2010). An important consideration in this study was that preterm birth was defined as a birth < 38 weeks gestation (Sparks et al., 2016). The study of low birth weight and hypothyroidism have resulted in inconsistent findings (Brix et al., 2006; Brix et al., 2000; Crump et al., 2011a; Phillips et al., 2002). Small sample populations have limited the ability to evaluate the association between prematurity and underactive thyroid development (Crump et al., 2011a). Crump et al.’s (2011) sufficiently powered evaluation of 27,935 individuals born preterm and later-life hypothyroidism, found young adults born preterm (23-32 weeks), independent of fetal growth, had an increased risk (aOR 1.59, 95% CI [1.18-2.14]) of pharmacologically treated hypothyroidism (Crump et al., 2011a). The principles expressed for altered immunity and HPA axis dysfunction are similar for thyroid
dysfunction except that the neuroendocrine HPA pathway is replaced with the HPT pathway.

Details regarding the events of birth, early-life exposures, and living environments of the women born preterm in the WHI-OS are not available. The women in the WHI-OS who were born preterm did not benefit from current neonatal intensive care or current preventive strategies for CVD risk with contemporary technology or research evidence. Expanding Barker’s empirical work of the DOHaD theory to encompass a long-term, life course approach has resulted in the Lifecourse Health Development Framework by Halfon (Halfon et al., 2014).60 The life course approach provides a perspective that further supports the higher prevalence of disease beyond the perinatal period (Halfon et al., 2014).60 The cumulative effect of stress or bodily “wear and tear” and the adaptive mechanisms of a compromised system over a lifetime may predispose the adult born preterm to greater disease occurrence (Msall et al., 2018).61 The life course framework and the underpinnings of the DOHaD support the findings of this study. The mechanistic pathways and temporal relationships linking the diseases in the preterm-born population have not been established (Mahagna et al., 2018).62

**Strengths and Limitations**

Strengths of this study include its large, national U.S. sample with extensive data collection. The prospective design of the WHI-OS provided the evaluation of 8 years of cumulative disease prevalence. Numerous potential confounders, such as education, income, and lifestyle factors, like BMI, alcohol intake, and physical activity, that may modify underlying associations between birth status and the three diseases of study, were
available for analysis. Notably, studies of multimorbidity in aging preterm-born individuals are limited.

Self-reported exposure and outcome data limited the study. Birth certificates and birth registries are the most reliable birth data collection methods, while medical records are for diagnoses of diseases. Other limitations include cautious interpretation of the data when the sample size was small, an incorrect self-reported condition as other conditions may resemble RA, and the inability to adjust for all covariates (Deane et al., 2017).50

Conclusion

Preterm birth (birth 4 or more weeks early) was significantly associated with higher risks for hypertension, RA, and hypothyroidism, alone and concomitantly. To our knowledge, this is the first known study evaluating the association between birth status and these three conditions concurrently in adults 50 years of age and older. This research provides additional evidence regarding the role of early developmental phenotypes in the development of later-life conditions, further illustrating the importance of targeted interventions across the lifespan to reduce the burden of these CVD-associated conditions. As each condition is an independent risk for CVD, it is plausible to suggest CVD risks would be significantly amplified when all three conditions co-exist. Inquiring about birth status during clinical encounters can heighten awareness to stimulate preemptive screening, earlier identification and treatment, and to help avert adverse cardiovascular outcomes for preterm-born adults.
Acknowledgements. We thank the WHI-OS study participants for their long-term dedication to research and for making this study possible, as well as the WHI principal investigators.

Financial support. The WHI is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268001100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C.

Conflicts of Interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the Helsinki declaration of 1975, as revised in 2008. The WHI Publications and Presentations Committee and the University of Rhode Island Institutional Review Board approved this study. Patient consent was not required for this secondary data analysis as women provided written consent at the time of enrollment and ethics approval was granted by each enrolling center’s institutional review board.

Figure 1. Unadjusted Rates of Cumulative Prevalent Disease at Study’s End (2005)

Figure 2. Fully Adjusted Odd Ratio and 95% Confidence Intervals for Preterm-Born Women
References


Table 10

Manuscript III, Table 1

Table 1. Characteristics of WHI-OS participants by birth status at enrollment and at the end of core study (1993-2005)

<table>
<thead>
<tr>
<th>CUMULATIVE PREVALENCE BY 2005</th>
<th>Birth Status</th>
<th>Full term (n=80,365)</th>
<th>Preterm (n=2,149)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=82,514</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic and lifestyle factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y) (mean, sd)</td>
<td>63.5 (7.4)</td>
<td>62.0 (7.3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age cohort (n, %)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;50-59</td>
<td>25906 (32.2)</td>
<td>882 (41.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>35352 (44.0)</td>
<td>886 (41.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79+</td>
<td>19107 (23.8)</td>
<td>381 (17.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (n, %)</td>
<td></td>
<td></td>
<td></td>
<td>0.220</td>
</tr>
<tr>
<td>American Indian/Alaska</td>
<td>264 (0.3)</td>
<td>9 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2113 (2.6)</td>
<td>44 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian/Other PI</td>
<td>54 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>6189 (7.7)</td>
<td>163 (7.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>69174 (86.1)</td>
<td>1879 (87.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than one</td>
<td>823 (1.0)</td>
<td>17 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown/Not reported</td>
<td>1748 (2.2)</td>
<td>37 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity (n, %)</td>
<td>3396 (4.2)</td>
<td>81 (3.8)</td>
<td>0.393</td>
<td></td>
</tr>
<tr>
<td>Education level (n, %)</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>&lt; high school graduate</td>
<td>3897 (4.9)</td>
<td>77 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school graduate</td>
<td>12775 (15.9)</td>
<td>291 (13.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>28916 (36.0)</td>
<td>783 (36.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>College graduate</td>
<td>34148 (42.5)</td>
<td>979 (45.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>629 (0.8)</td>
<td>19 (0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income level (n, %)</td>
<td></td>
<td></td>
<td></td>
<td>0.447</td>
</tr>
<tr>
<td>$50,000 or greater</td>
<td>30794 (38.3)</td>
<td>851 (39.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$20,000 - $50,000</td>
<td>32270 (40.2)</td>
<td>858 (39.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; $20,000 per year</td>
<td>11549 (14.4)</td>
<td>302 (14.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing/Don’t Know</td>
<td>5752 (7.2)</td>
<td>138 (6.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partnered (n, %)</td>
<td>49997 (62.5)</td>
<td>1372 (64.1)</td>
<td>0.122</td>
<td></td>
</tr>
<tr>
<td>Region of birth (n, %)</td>
<td></td>
<td></td>
<td></td>
<td>0.925</td>
</tr>
<tr>
<td>Not born in US</td>
<td>5670 (7.1)</td>
<td>151 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>22237 (27.9)</td>
<td>579 (27.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>23575 (29.6)</td>
<td>635 (29.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>17439 (21.9)</td>
<td>472 (22.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>10770 (13.5)</td>
<td>299 (14.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status (n, %)</td>
<td></td>
<td></td>
<td></td>
<td>0.056</td>
</tr>
<tr>
<td>Never</td>
<td>40334 (50.9)</td>
<td>1106 (52.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past Smoker</td>
<td>34063 (43.0)</td>
<td>858 (40.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>4904 (6.2)</td>
<td>148 (7.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity (mean, sd)</td>
<td>13.5 (14.5)</td>
<td>13.4 (15.4)</td>
<td>0.878</td>
<td></td>
</tr>
<tr>
<td>Physical activity level (n, %)</td>
<td></td>
<td></td>
<td></td>
<td>0.208</td>
</tr>
<tr>
<td>Inactive: 0-1.7 MET hrs/wk</td>
<td>16872 (21.1)</td>
<td>483 (22.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low: 1.8-8.3 MET hrs/wk</td>
<td>20946 (26.2)</td>
<td>578 (27.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mod: 8.4-20 MET hrs/wk</td>
<td>22751 (28.5)</td>
<td>584 (27.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Medical History

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body mass index (mean, sd)</strong></td>
<td>28 (6.8)</td>
<td>28 (6.7)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Height (cm) (mean, sd)</strong></td>
<td>161.7 (6.8)</td>
<td>161.3 (6.6)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Short stature (HT&lt; 5 ft) (n, %)</strong></td>
<td>5695 (7.1)</td>
<td>168 (7.9)</td>
<td>0.196</td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg) (mean, sd)</strong></td>
<td>127 (17.9)</td>
<td>126 (17.9)</td>
<td>0.508</td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg) (mean, sd)</strong></td>
<td>75 (9.3)</td>
<td>75 (9.3)</td>
<td>0.099</td>
</tr>
<tr>
<td><strong>Diabetes (n, %)</strong></td>
<td>3185 (4.0)</td>
<td>122 (5.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hypertension (n, %)</strong></td>
<td>26308 (32.7)</td>
<td>789 (36.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hyperlipidemia (n, %)</strong></td>
<td>11939 (14.9)</td>
<td>324 (15.1)</td>
<td>0.776</td>
</tr>
<tr>
<td><strong>Angina (n, %)</strong></td>
<td>4488 (5.6)</td>
<td>138 (6.5)</td>
<td>0.087</td>
</tr>
<tr>
<td><strong>Atrial fibrillation (n, %)</strong></td>
<td>3645 (4.6)</td>
<td>102 (4.8)</td>
<td>0.648</td>
</tr>
<tr>
<td><strong>TIA (n, %)</strong></td>
<td>1837 (2.3)</td>
<td>53 (2.5)</td>
<td>0.586</td>
</tr>
<tr>
<td><strong>Heart failure (n, %)</strong></td>
<td>1098 (1.4)</td>
<td>36 (1.7)</td>
<td>0.225</td>
</tr>
<tr>
<td><strong>Breastfed as infant (n, %)</strong></td>
<td>48091 (59.9)</td>
<td>941 (43.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>HTN age onset (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HTN</td>
<td>53959 (67.5)</td>
<td>1355 (63.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Less than 20</td>
<td>230 (0.3)</td>
<td>16 (0.8)</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>739 (0.9)</td>
<td>25 (1.2)</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>2282 (2.9)</td>
<td>71 (3.3)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>5978 (7.5)</td>
<td>197 (9.2)</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>9303 (11.6)</td>
<td>286 (13.4)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>5935 (7.4)</td>
<td>153 (7.2)</td>
<td></td>
</tr>
<tr>
<td>70 or older</td>
<td>1502 (1.9)</td>
<td>30 (1.4)</td>
<td></td>
</tr>
</tbody>
</table>
Table 11

Manuscript III, Table 2

Table 2. Logistic Regression Model Summary for Individual Diagnoses by Birth Status

<table>
<thead>
<tr>
<th></th>
<th>Age Adjusted</th>
<th>Socio-demographics (i)</th>
<th>Lifestyle (2)</th>
<th>Risk Factors (3)</th>
<th>Fully Adjusted (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any RA diagnosis*</td>
<td>1.23</td>
<td>1.27</td>
<td>1.25</td>
<td>1.24</td>
<td>1.28</td>
</tr>
<tr>
<td></td>
<td>(1.07, 1.40)</td>
<td>(1.11, 1.45)</td>
<td>(1.09,1.43)</td>
<td>(1.08,1.42)</td>
<td>(1.12,1.47)</td>
</tr>
<tr>
<td>Any Hypothyroidism diagnosis**</td>
<td>1.18</td>
<td>1.15</td>
<td>1.16</td>
<td>1.17</td>
<td>1.12</td>
</tr>
<tr>
<td></td>
<td>(1.07, 1.31)</td>
<td>(1.04, 1.27)</td>
<td>(1.05, 1.28)</td>
<td>(1.06, 1.29)</td>
<td>(1.01, 1.24)</td>
</tr>
<tr>
<td>Any HTN diagnosis***</td>
<td>1.17</td>
<td>1.20</td>
<td>1.15</td>
<td>1.15</td>
<td>1.14</td>
</tr>
<tr>
<td></td>
<td>(1.07, 1.28)</td>
<td>(1.09, 1.31)</td>
<td>(1.05, 1.26)</td>
<td>(1.05, 1.26)</td>
<td>(1.04, 1.26)</td>
</tr>
</tbody>
</table>

HTN = hypertension; RA = rheumatoid arthritis; reference group = women born full term.

(1) - model covariates include age, race/ethnicity, education, income, marital status, and region of birth.
(2) - model covariates include age, smoking status, physical activity, alcohol intake, and BMI.
(3) - model covariates include age, short stature, diabetes, hyperlipidemia, and breastfed as infant.
(4) - model covariates include those from (1) without marital status, (2), and (3).

*RA models also include indicator variables for hypothyroid disease and hypertension as covariates;
**Hypothyroidism models also include indicator variables for RA and hypertension as covariates; ***HTN models also include indicator variables for hypothyroid disease and RA as covariates.

Table 12

Manuscript III, Table 3

Table 3. Multinomial Logistic Regression Model Summary for the Cumulative Diagnosis Count for Preterm-Born Women

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Age Adjusted</th>
<th>Socio-demographic (i)</th>
<th>Lifestyle (2)</th>
<th>Risk Factors (3)</th>
<th>Fully Adjust (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No disease</td>
<td>28,418</td>
<td>(ref)</td>
<td>(ref)</td>
<td>(ref)</td>
<td>(ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>One disease</td>
<td>39,829</td>
<td>1.22</td>
<td>(1.11, 1.35)</td>
<td>1.23</td>
<td>1.20</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.11, 1.35)</td>
<td>(1.12, 1.36)</td>
<td>(1.08, 1.33)</td>
<td>(1.09, 1.33)</td>
<td>(1.07, 1.31)</td>
</tr>
<tr>
<td>Two diseases</td>
<td>13,138</td>
<td>1.38</td>
<td>(1.22, 1.57)</td>
<td>1.40</td>
<td>1.34</td>
<td>1.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.22, 1.57)</td>
<td>(1.23, 1.60)</td>
<td>(1.17, 1.53)</td>
<td>(1.19, 1.55)</td>
<td>(1.15, 1.51)</td>
</tr>
<tr>
<td>Three diseases</td>
<td>1,129</td>
<td>1.75</td>
<td>(1.27, 2.42)</td>
<td>1.73</td>
<td>1.75</td>
<td>1.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.27, 2.42)</td>
<td>(1.25, 2.39)</td>
<td>(1.27, 2.42)</td>
<td>(1.24, 2.36)</td>
<td>(1.22, 2.35)</td>
</tr>
</tbody>
</table>

Reference group (ref) = women born full term.

(1) - model covariates include age, race/ethnicity, education, income, marital status, and region of birth.
(2) - model covariates include age, smoking status, physical activity, alcohol intake, and BMI.
(3) - model covariates include age, short stature, diabetes, hyperlipidemia, and breastfed as infant.
(4) - model covariates include those from (1) without marital status, (2), and (3).
Table 13

*Manuscript III, Table 4*

**Table 4. Multinomial Logistic Regression Model Summary for Disease Combinations for Preterm-Born Women**

<table>
<thead>
<tr>
<th>Number of Disease(s)</th>
<th>Total</th>
<th>Age Adjusted</th>
<th>Socio-demographics (1)</th>
<th>Lifestyle (2)</th>
<th>Risk Factors (3)</th>
<th>Fully Adjusted (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No disease</td>
<td>28,418</td>
<td>(ref)</td>
<td>(ref)</td>
<td>(ref)</td>
<td>(ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>One</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA Only</td>
<td>2,457</td>
<td>1.24 (0.96, 1.59)</td>
<td>1.24 (0.96, 1.60)</td>
<td>1.26 (0.98, 1.63)</td>
<td>1.24 (0.96, 1.59)</td>
<td>1.24 (0.95, 1.60)</td>
</tr>
<tr>
<td>Hypothyroid Only</td>
<td>7,715</td>
<td>1.24 (1.06, 1.45)</td>
<td>1.22 (1.05, 1.43)</td>
<td>1.21 (1.03, 1.42)</td>
<td>1.22 (1.04, 1.43)</td>
<td>1.19 (1.02, 1.40)</td>
</tr>
<tr>
<td>HTN Only</td>
<td>29,657</td>
<td>1.21 (1.09, 1.35)</td>
<td>1.24 (1.11, 1.38)</td>
<td>1.19 (1.07, 1.33)</td>
<td>1.19 (1.07, 1.33)</td>
<td>1.18 (1.06, 1.32)</td>
</tr>
<tr>
<td>Two</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroid &amp; RA</td>
<td>740</td>
<td>1.74 (1.18, 2.55)</td>
<td>1.74 (1.18, 2.55)</td>
<td>1.70 (1.15, 2.52)</td>
<td>1.72 (1.17, 2.54)</td>
<td>1.69 (1.14, 2.51)</td>
</tr>
<tr>
<td>HTN &amp; RA</td>
<td>3,835</td>
<td>1.40 (1.15, 1.72)</td>
<td>1.54 (1.25, 1.89)</td>
<td>1.38 (1.12, 1.70)</td>
<td>1.40 (1.14, 1.72)</td>
<td>1.48 (1.20, 1.82)</td>
</tr>
<tr>
<td>HTN &amp; Hypothyroid</td>
<td>8,563</td>
<td>1.34 (1.15, 1.56)</td>
<td>1.33 (1.14, 1.54)</td>
<td>1.28 (1.10, 1.50)</td>
<td>1.30 (1.12, 1.52)</td>
<td>1.22 (1.04, 1.43)</td>
</tr>
<tr>
<td>Three</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>RA, Hypothyroid &amp; HTN</td>
<td>1,129</td>
<td>1.75 (1.27, 2.42)</td>
<td>1.73 (1.25, 2.39)</td>
<td>1.75 (1.26, 2.41)</td>
<td>1.71 (1.24, 2.36)</td>
<td>1.69 (1.22, 2.35)</td>
</tr>
</tbody>
</table>

HTN = hypertension; RA = rheumatoid arthritis; hypothyroid disease = hypothyroidism; reference group (ref) = women born full term.

(1) - model covariates include age, race/ethnicity, education, income, marital status, and region of birth.
(2) - model covariates include age, smoking status, physical activity, alcohol intake, and BMI.
(3) - model covariates include age, short stature, diabetes, hyperlipidemia, and breastfed as infant.
(4) - model covariates include those from (1) without marital status, (2), and (3).
Figure 17

Manuscript III, Figure 1

Figure 1. Unadjusted Rates of Cumulative Prevalent Disease at Study’s End (2005)
**Figure 18**

*Manuscript III, Figure 2*

**Figure 2. Fully Adjusted Odd Ratio and 95% Confidence Intervals for Preterm-Born Women**

HTN = hypertension; RA = rheumatoid arthritis; hypothyroid disease = hypothyroidism; reference group = women born full term. Fully adjusted model covariates include age, race/ethnicity, education, income, region of birth, smoking status, physical activity, alcohol intake, BMI, short stature, diabetes, hyperlipidemia, and breastfed as infant.
Chapter 7: Discussion and Implications

Emerging research findings provide evidence of an association between preterm birth and increased CVD risks that include elevated blood pressure, early-onset heart failure, premature CHD, and cardiovascular-related mortality in adulthood (Andraweera et al., 2021; Aye et al., 2017; Bertagnolli et al., 2016; Burchert & Lewandowski, 2019; Carr et al., 2017; Crump et al., 2021; Crump, Howell, et al., 2019; Crump et al., 2011b; Kajantie et al., 2015; Leeson & Lewandowski, 2017; Lewandowski, 2022; Sipola-Leppanen, Karvonen, et al., 2015; Ueda et al., 2014; Yoshida-Montezuma et al., 2022). In addition to elevated blood pressure, individuals who were born preterm have increased cardiometabolic risk factors, including higher percentage of body fat, lower lean body mass, and impaired glucose regulation (Kajantie & Hovi, 2014; Sipola-Leppanen, Vaarasmaki, et al., 2015; Yoshida-Montezuma et al., 2022). Knowledge about preterm-birth comorbidities and risks in adulthood continues to emerge, though most evidence is from studies on adults aged 20–40 years (Crump, 2020a; Crump et al., 2011b; Flahault et al., 2020; Haikerwal et al., 2020; Hovi et al., 2016; Lewandowski & Leeson, 2014; Paquette et al., 2018; Sipola-Leppanen, Karvonen, et al., 2015; Skudder-Hill et al., 2019; Steen et al., 2015). Data analyzed in this dissertation are from an older, national sample of preterm-born postmenopausal women (≥ 50 years of age).

Evidence about increased CVD risk for adults born prematurely was synthesized into a state-of-the-science report in Manuscript I. Clinical and experimental evidence suggests that disrupted organogenesis due to preterm birth results in alterations in key organs and systems, predisposing those born prematurely to adverse health sequelae later in life. The objective of Manuscript I was to provide awareness and a greater
understanding of the potential for adverse later-life health outcomes for individuals born preterm. A preventive life course approach with early intervention is needed to mitigate increased CVD risk for those born prematurely.

Manuscript II aimed to extend the research evidence that preterm-born adults develop hypertension and CVD at a higher rate than their full-term born peers. This manuscript investigated the associations between preterm birth, hypertension, and incident CVD among postmenopausal adult women participating in the WHI-OS. Preterm birth status had a nonsignificant association with CVD risk, but when stratified by prevalent hypertension, women born preterm without prevalent hypertension showed elevated CVD risk compared to women born full term without prevalent hypertension. The conclusion of Manuscript II was that women who were born preterm have an increased risk of hypertension, CHD, and CVD in mid to late adulthood.

Lastly, Manuscript III used the WHI-OS cohort to investigate the associations between preterm birth and the development of three female-predominant chronic cardiovascular risk-related conditions - hypertension, RA, and hypothyroidism. The results revealed that postmenopausal adult women born preterm had higher prevalence and cumulative prevalence of hypertension, RA, and hypothyroidism alone and concomitantly. The preterm born women also had an increased co-occurrence risk for having all three CVD comorbidities. The findings of Manuscript III support the consideration of preterm birth as an independent risk for CVD as it is plausible that cardiovascular risks are amplified when all three conditions co-exist.

The results presented in these manuscripts significantly contribute to the understanding that the large and growing population of adults born preterm have an
increased risk for developing CVD and comorbidities later in life. With limited adult health research on prematurity outcomes, this research extended the focus of cardiovascular health beyond early adulthood to adults aged 50 years and older. More research is required to discern the long-term outcomes and health needs related to gestational age categories, the underlying mechanisms of organogenesis, the role of epigenetics and social health determinants, and the effectiveness of current treatments in mitigating cardiovascular health consequences. There is an urgent need to increase the awareness for clinicians, preterm-born individuals, and their families about the health risks related to prematurity. These findings will ideally prompt further research to advance scientific knowledge about CVD risk and later-life outcomes, along with clinical practice changes, in this population of individuals born prematurely.

**Findings**

**Participant Characteristics**

Analyses of later-life disease prevalence and incidence among U.S. preterm birth participants in the WHI-OS were conducted to address gaps in the literature (Anderson et al., 2003; Langer et al., 2003; Women's Health Initiative, 2021). WHI-OS participants were recruited from the general population of postmenopausal adult women, primarily by mass mailings. Recruitment efforts focused on women living near one of the 40 WHI clinical centers across the U.S., including underserved areas. At enrollment, data were collected by self-report questionnaires. This included demographic data, personal and family medical history, reproductive history, medication and supplement usage, and lifestyle habits. Clinical measures included fasting blood samples, resting blood pressure, heart rate, weight, height, waist, and hip circumferences. Self-report answers to annual
health questionnaires captured long-term disease outcomes in this sample population (Anderson et al., 2003; Langer et al., 2003, Women’s Health Initiative, 2021).

Analysis of baseline demographics in WHI-OS participants were presented in Manuscripts II and III (Chapters 5 and 6). Preterm-born women were younger at enrollment (62 years vs. 63.5 years, \( p < 0.001 \)), identified as White (87.5%), were more likely to have higher education (some college education and college graduates; 45.2%, \( p = 0.001 \)), partnered (64.4% vs. 62.4%, \( p = 0.047 \)), born in southern U.S. states (30.1%), non-smokers (52.1%), moderately active (27.4%), and higher BMI (28.0 vs. 27.5, \( p = 0.001 \)) compared to their peers who were born full term. Analysis of self-reports at enrollment revealed statistically different disease prevalence for women born preterm compared to their full-term born peers: diabetes (5.8% vs. 4%, \( p < 0.001 \)), hypertension (37.0 vs. 33.1%, \( p < 0.001 \)), and angina (7.0 vs. 5.8%, \( p = 0.019 \)).

**Manuscripts**

The main conclusions for each manuscript in this dissertation are summarized. In Manuscript I, relevant research findings that provide evidence of anatomical and physiological cardiovascular alterations in individuals born preterm are highlighted. The correlation between cardiovascular modifications and higher risk of CVD morbidity and mortality in preterm-born individuals is conveyed. The importance of educating experienced and student clinicians, parents of individuals born preterm, and preterm-born individuals themselves about the long-term health risks of prematurity is stressed. Health education should emphasize that prematurity is associated with a lifelong risk for CVD and CVD events. Clinicians must inquire about birth history, evaluate individuals who were born preterm for early onset of CVD and CVD-related conditions, and provide early
treatment interventions to prevent and/or mitigate risks of adverse cardiovascular outcomes in this population of individuals.

Hypertension is the strongest CVD risk factor and the most extensively studied condition in individuals born preterm. In Manuscript II, findings demonstrated a significant association between preterm birth status and prevalent hypertension [37% vs. 33.1%, aOR 1.26 (95% CI 1.15, 1.28) \( p = .0001 \)], early-onset hypertension (<50 years) [14.7% vs. 11.7%, aOR 1.31 (95% CI 1.15, 1.48) \( p = .0001 \)], and incident hypertension [53.2% vs. 51%; aHR 1.10 (95% CI 1.03, 1.19) \( p = .008 \)] compared to full-term birth status. Preterm-born women reported taking more antihypertensive medications (2.9% vs. 2.6%, \( p = .04 \)). Women who were born preterm showed a nonsignificant association with CVD risk, but when stratified by prevalent hypertension, women born preterm without prevalent hypertension had an elevated CHD and CVD risk [aHR 1.28 (95% CI 1.02, 1.60) \( p = .03 \) and aHR 1.21 (95% CI 1.00, 1.47) \( p = .04 \)] compared to women born full term and without prevalent hypertension.

It was hypothesized that women born preterm with prevalent hypertension would be at a greater risk for CVD. However, similar magnitudes of elevation in CVD risk between birth status (preterm vs. full term) were found using multivariable logistic regression models. Furthermore, the assessment of effect modification by prevalent hypertension did not show a statistically significant effect by birth status on incident CVD, but there was an interaction between birth status and prevalent hypertension on incident CHD (\( p = .011 \)). Given that hypertension is such a strong CVD risk factor in women, it was concluded that hypertension attenuated the risks that may have been associated with preterm birth.
In Manuscript II, another important analysis found a higher but not statistically significant difference in difficult-to-control hypertension between preterm-born women with prevalent hypertension and full-term born women with prevalent hypertension [aOR 1.38 (95% CI 0.98, 1.96), \( p = 0.06 \)]. Although of clinical interest, the small sample size \((n = 37)\) was a limitation. However, given the trend and borderline \( p \) value, it was concluded that women born preterm with prevalent hypertension were more likely to have difficult-to-control hypertension requiring more medication for blood pressure control, warranting further study.

Three CVD-associated conditions were investigated in Manuscript III based on the increased risk but inconclusive evidence of chronic disease multimorbidity (Heikkila et al., 2021; Luu et al., 2016). The findings revealed that women born preterm were significantly more likely to have hypertension, RA, or hypothyroidism, alone or in combination. The adjusted odds ratios (aOR) were 1.14 (95% CI, [1.04, 1.26]) for hypertension, 1.28 (95% CI, [1.12, 1.47]) for RA, and 1.12 (95% CI, [1.01, 1.24]) for hypothyroidism. Hypothyroidism and RA were the strongest correlated conditions (aOR 1.69, 95% CI [1.14, 2.51]), and the aOR for all three conditions was 1.69 (95% CI, [1.22, 2.35]). These findings illustrated the importance of targeted interventions to reduce the burden of CVD-associated conditions across the lifespan of those born prematurely. Since each condition independently increases CVD risk, it is plausible that CVD risks would be significantly amplified in this population when all three conditions co-exist.

In summary, the findings in this dissertation align and extend previous studies’ findings that preterm-born individuals have a higher risk of CVD (Bonamy et al., 2012; Crump et al., 2011b; Darlow et al., 2015; Haikerwal et al., 2020; Hovi et al., 2016; Jones
et al., 2019; Juonala et al., 2015; Keijzer-Veen et al., 2005; Sipola-Leppanen, Karvonen, et al., 2015; Skudder-Hill et al., 2019). However, this study investigated a later-aged sample of women (≥ 50 years), which expands the knowledge of higher risk of adverse cardiovascular health compared to full-term born peers. It would be prudent to use the lens of prematurity to re-examine current prevention approaches and tailor cardioprotective strategies for evaluating and managing CVD risk in preterm-born individuals. A prematurity-specific perspective may lead to the development of more effective interventions, which in turn, could decrease adverse cardiovascular outcomes in individuals born preterm.

Heart disease is already the leading cause of death for U.S. women. Increasing survival rates of individuals born preterm with the potentially underlying risk of heart disease in adulthood could further increase the national rate of heart-related mortalities. Thus, exploring the mechanisms that promote heart disease in adult women born preterm is urgently needed (Center for Disease Control and Prevention, 2022c; Virani et al., 2021). Comparative studies of middle- and older-aged men born preterm have not been undertaken. The only comparable gender-specific study included young Swedish men (average age 18.2 years) who were born preterm and were conscripted for military service, which reported a higher prevalence of hypertension in the preterm-born young men (Johansson et al., 2005). The long-term health outcomes associated with preterm birth are unknown for men in later life and must be explored.

Strengths

This dissertation analyzed data collected from a large cohort of U.S. women born between 1920–1940s, of which 2.4% of the cohort were born prematurely. The national
sample was geographically distributed and included data on disease prevalence and incidence with longitudinal follow-up, medical record adjudication of CVD outcomes, and important measured covariates. Within the sample, a wide range of lifestyle variables and clinical measurements allowed statistical adjustment of several key confounding and mediating factors in both birth status (preterm vs. full term) cohorts that could not be modeled with smaller samples. Harmonized data collection procedures and safeguarding of data in a secure, central coordinating center strengthened the accuracy of the data. Manuscripts II and III are the first known published studies from this population of postmenopausal adult women born prematurely.

Preterm-born women in the WHI-OS were born before the era of modern neonatal intensive care. One conclusion to draw is that the preterm-born women in the WHI-OS were likely of higher birth weights and hardy infants who survived. In the late twentieth century, survival rates of preterm-born infants significantly improved due to the introduction of new medical treatments for neonates, including mechanical ventilators in the 1960s and surfactant in the 1990s (Henderson-Smart et al., 2002; Jain & Raju, 2013; Philip, 2005; Polin et al., 2014; Raju, Pemberton, et al., 2017). The smallest and most fragile preterm-born infants have benefited the most from successes in modern medical technology (Philip, 2005; Raju, Pemberton, et al., 2017; Taylor, 2017). Today, approximately 95% of all preterm-born infants survive (Crump, 2020a). Even the most premature infants (< 28 weeks gestation) survive into adulthood due to improved neonatal care. However, they may have long-term comorbidities associated with their degree of prematurity and continue to be at risk for developing chronic disease throughout the course of their lives (Crump, 2020). Even with the advancements in
medical technologies, 85% or more of preterm-born infants today are of moderate–late preterm categories (32 to <37 weeks gestation), likely the same gestational age as the WHI-OS survivors from the 1920s–1940s (Martin et al., 2021). Importantly, this is an all-female cohort. Infant mortality rates are higher for preterm-born males born at similar gestational age as preterm-born females (Peacock et al., 2012; Taylor, 2017; Zisk et al., 2011). In conclusion, these findings can be generalized to the current population of adult women born preterm.

Limitations

Limitations of this study can be organized into four areas. These limitations have been identified in each manuscript and are summarized here. The most common limitations include bias, generalizability, sample size, and censoring and confounding.

Bias

Data in the WHI-OS are susceptible to recall, collider, and response bias; all bias that exist when information is self-reported. Most of the data obtained in the WHI-OS was self-reported data. The problem with self-reported data is that it threatens the reliability and validity of the data. Birth status, disease occurrence and onset, medication use, and even age at enrollment were self-reported. Self-reported data introduces the potential for misclassification or inaccurate reporting, which is a concern since the validity of the studies’ findings rely on an exposure and outcomes that were self-reported. However, since participants did not know the exposure-outcome relationship being researched, misclassification is likely non-differential, meaning it probably occurred similarly for both birth cohorts.
It is well established that birth records and national registry databases are the most accurate birth history sources, and medical records are the most reliable sources for disease confirmation (Brumberg et al., 2012). Although self-reported data have been considered reliable proxies for medical history, a margin of error exists (Jackson et al., 2014). Self-reported data of large national cohorts such as the WHI-OS are efficient and provide unique insight into the disease risk of women born preterm, data that would be otherwise unavailable. To counterbalance bias and assure quality data, the clinical coordinating center, with numerous advisory committees and the WHI Program Office, reported routinely to the NHLBI Project Office about the verification process of their data collection methods (Women's Health Initiative, 2021).

Self-reports about medication use, disease onset, or medical event recall captured on the annual WHI-OS questionnaires may result in inaccurate findings. The timing of the questionnaires may have led to important information being misremembered or forgotten, which means it could have been exaggerated, underreported, or omitted.

Lastly, collider bias, a bias that occurs when the exposure and outcome is influenced by a common third variable and that variable is controlled for by the study design, may have occurred with the analyses of incident disease (Holmberg & Andersen, 2022). Collider bias is different from confounding. Confounding occurs when an exposure and outcome have a shared cause that is not controlled for (Holmberg & Andersen, 2022). Collider bias was introduced when women who were most susceptible to the long-term consequences of preterm birth were excluded from the evaluation of incident disease. For example, a subgroup of women who succumbed to the outcome of hypertension, CHD, or CVD prior to data collection, were not included in the analyses of
incident disease. Essentially, these women were systematically different from the population they represented at study enrollment due to collider bias (Holmberg & Andersen, 2022).

**Generalizability**

The results of these two studies may not extrapolate to other preterm populations, including younger preterm-born women, as perinatal treatments have advanced dramatically over the decades. In recent years, some of the most effective new treatments that insured survival of preterm infants may result in unfavorable long-term consequences. The preterm-born women who were enrolled in the WHI-OS did not receive these same advanced treatments when they were infants, and therefore did not run the risk of the same treatment-related health consequences (Doyle et al., 2017; Raju, Pemberton, et al., 2017; Saugstad, 2001; Schreuder et al., 2011).

Lastly, WHI-OS participants may not reflect the diversity of young and middle-aged adults today. Nonetheless, results from the WHI studies have significantly advanced the understanding of women’s cardiovascular health over their lifetimes (LaMonte et al., 2022). The findings from this dissertation research are consistent with findings from international studies of preterm-born women and men; therefore, these findings should not be dismissed (Bonamy et al., 2012; Crump et al., 2011b; Darlow et al., 2015; Haikerwal et al., 2020; Hovi et al., 2016; Jones et al., 2019; Juonala et al., 2015; Keijzer-Veen et al., 2005; Sipola-Leppanen, Karvonen, et al., 2015; Skudder-Hill et al., 2019).

**Sample Size**

The sample size was large, ensuring robust power for analyses. However, in rare instances, one or two small sample cell sizes were noted in a preterm group analysis and
encouraged to be cautiously interpreted. One primary example was in the analysis of 37 preterm-born women who had difficult-to-control hypertension in adulthood; the adjusted odds ratio (aOR) was 1.38 (95% CI [0.98, 1.96], \( p = 0.06 \)). Although this finding is clinically interesting and trending in the direction of significance, their condition was not statistically different compared to their peers born full term. In other analysis with a larger sample population, difficult-to-control blood pressure may be more prevalent in preterm-born women.

**Confounding and Censoring**

The WHI-OS data collection began over 20 years ago. Although the coordinating center carefully monitored and recorded study protocols and methods, a chance of misinterpretation during data collection may have confounded the results. *Confounding* is a distortion that modifies the association between the exposure and the outcome because the variable is independently associated with the exposure and the outcome (Holmberg & Andersen, 2022). Despite careful planning and consideration, an inherent challenge with retrospective studies is the existence of unknown confounding variables (Euser et al., 2009). In addition, prenatal, maternal, and paternal background variables, and early life conditions that affected the long-term health of those born preterm may contribute to residual confounding factors. The understanding that all confounding variables can never be fully accounted for or controlled, which could, in turn, confound the results, also calls for a cautious interpretation of the findings (Euser et al., 2009).

Bias due to censored observations must be considered in longitudinal research. Censoring occurs when information on time to outcome event is not available for all study participants (Lesko et al., 2017). There are various types of censoring: left-sided,
right-sided, interval, random, and more (Lesko et al., 2017). In this study, left-sided censored data may have occurred when analyzing disease incidence. For instance, if an event (e.g., CVD event) or onset of a disease of interest (e.g., hypertension) was detected before enrollment in the study, then incidence findings were attenuated. The nonstatistical difference in incident CHD and CVD in women born preterm compared to full-term born women must be interpreted in this context (Cain et al., 2011; Hernández-Herrera et al., 2022).

Implications

Implications for Research

As emphasized in Manuscript I, there is an urgent need for long-term, prospective follow-up research on preterm-born individuals to delineate their health patterns, including factors that influence their risks for disease and their disease trajectories. A better understanding of the cumulative impact of preterm birth is needed to optimize the health of the 10% of the U.S. population born prematurely. Significant gaps exist in understanding what underlying anatomical or pathophysiological pathways in prematurity lead to adverse health in later life. Such research could help assign a precise prognostic value for preterm birth as a risk factor for CVD, triggering anticipatory screening and preventive practices for adults born preterm. A call for collaborative research among disciplines influencing the lives of individuals born preterm is necessary to bridge the gap between research and practice.

To date, most research has focused on the health outcomes of children, adolescents, and young adults born preterm. Although the trajectories and long-term consequences of subclinical diseases like hypertension have been identified in young
adults, these health patterns are unknown in later-aged adults born preterm. Thus, prospective approaches are needed for temporal sequencing of hypertension and other chronic conditions like RA and hypothyroidism.

Currently, the impact of traditional lifestyle modifications in adults born preterm is undetermined. Research to investigate the effectiveness of dietary and lifestyle interventions for preventing or mitigating disease occurrence in the preterm-born population as they age into middle- and late adulthood is warranted. Future research to evaluate the effectiveness of early identification of and treatments for CVD may provide valuable insights into the long-term health consequences for this susceptible population and improve their cardiovascular outcomes.

Nurse researchers have contributed significantly to the care of preterm-born infants over the past three decades. Research findings have helped pregnant women recognize the symptoms of preterm labor and cope with the preterm labor experience. Findings have also led to medical interventions that improve the care and health of premature infants (Freda, 2003). Environmental neonatology by perinatal research nurses has encouraged nurses to test and implement innovative interventions targeted at reducing stress in the NICU, supporting improved neurodevelopmental outcomes in the preterm infant (Critical Care Management Archives, 2022; Nist et al., 2019; Peters et al., 2009).

In the only known prospective, longitudinal study of premature infants in the U.S., diurnal hypothalamic-pituitary-adrenal (HPA) axis patterns were analyzed (Sullivan et al., 2017). Disrupted organogenesis, neonatal illness, and stress are potential contributors to alterations in HPA axis activity that may have adverse health
consequences, such as increased fat accumulation, insulin resistance, and elevated blood pressure in adulthood (Sullivan et al., 2017; Sullivan et al., 2019; Winchester et al., 2016). A multidisciplinary team evaluated dietary patterns and behaviors of preterm-born young adults compared to age-matched full-term born peers. Findings identified that dietary quality, preference, and lack of restraint contributed to higher blood pressure and serum lipids in the preterm group (Sharafi et al., 2016). These results contributed to a higher cumulative risk for CVD among the preterm population. Clinicians can recommend long-term, outcome-based research that will inform clinical practice (Kelly et al., 2021). Specifically, studies to identify dietary interventions that effectively decrease the CVD risk in adults born preterm will contribute evidence-based knowledge to the field of prematurity.

Most importantly, findings from nursing research must inform the practice of nursing and other healthcare clinicians. Evidence from current research must inform public health policy to provide the necessary financial and structural support for preterm-born individuals. Research findings generated by those interested in preterm birth outcomes must be disseminated to all disciplines that influence the health and wellness of preterm-born individuals. Transdisciplinary nurse scientists can recommend the essential components to develop or lead a patient-centered, multidisciplinary research team. The boundaries of research on prematurity across the lifespan must be expanded to integrate findings to all disciplines (Hickey, 2018).

**Implications for Clinical Practice**

Nurses are uniquely positioned to provide patient care across the lifespan, including acute, primary, and community care. Prematurity often calls for
multidisciplinary care that extends beyond the neonatal years. Nurses of all education levels and in various settings can collaborate with other disciplines, such as occupational therapists, social workers, and developmental specialists, to improve the functional health outcomes of those born preterm. An integrated team approach would support nursing practice standards. An interdisciplinary team can also lead to each discipline incorporating routine clinical practices to promote the health of this population, such as screening for birth status, education about healthy lifestyles, recognition of adverse health risks, and early treatment of disease.

Clinicians must recognize the long-term CVD risk conferred by preterm birth and employ appropriate screening and ongoing education, which is essential to reducing CVD in this population. Clinicians must also acknowledge the multi-organ system sequelae of prematurity that may necessitate earlier intervention for those at higher risk of later-life disease. Reducing the CVD risk for preterm-born individuals requires collaborative and interdisciplinary care across the lifespan, from obstetricians and neonatologists to pediatricians to adult care providers. Advanced nurse practitioners (APNs) possess the extensive education and clinical experience necessary to work with a multidisciplinary team to provide comprehensive, holistic care for preterm-born individuals across their lifespans.

Employing technological applications for predicting and identifying those most at risk for CVD has proven efficient and effective in clinical practice (Karunathilake & Ganegoda, 2018). Primary and secondary CVD prevention strategies have been implemented using data mining, associative classification and genetic algorithms, and regression trees (Karunathilake & Ganegoda, 2018). Nurses and health providers of all
educational levels can utilize the information obtained through these predictive models to encourage nonmedical interventions such as weight control and dietary adherence to reduce CVD risk in the preterm population. Clinician-developed structured assessments and data collection can assure the completeness of pertinent long-term outcome domains (Beck et al., 2020; Kajantie et al., 2021). Furthermore, these preventive measures can improve the quality of life and reduce the financial burdens associated with CVD. Early primary prevention measures have proven to be the most beneficial (Karunathilake & Ganegoda, 2018). As advanced educators, APNs can utilize their vast knowledge about heart health to aid in developing predictive technology and, based on findings, provide appropriate clinical interventions to improve overall cardiovascular health for all individuals.

Preterm survival rates have increased, yet the causes of preterm birth and later health risks for individuals who were born prematurely are largely unknown (Ferrero et al., 2016). Nurses and nurse midwives provide prenatal, antenatal, and neonatal care that may alter the negative long-term consequences of preterm birth. For example, Boivin et al. (2015) found that women who were born before 32 weeks of gestation had a 1.63-fold (95% CI, [1.22, 2.19]) increased risk of delivering prematurely. Women born between 32–36 weeks of gestation had a 1.41-fold (95% CI, [1.27, 1.57]) increased risk of delivering their infants prematurely compared to women born full term. Nurses in neonatal care can advocate for (1) nephroprotective strategies that enhance neonatal nephrogenesis, (2) reduced NICU environmental stress, and (3) balanced nutrition vital to premature infants’ short- and long-term development (Wood et al., 2018). It is essential
for nurses to integrate the knowledge gained from DOHaD research and apply the results to daily pre- and postnatal clinical practice.

Pediatric nurses can be instrumental in improving risk screening by monitoring blood pressure and metabolic status and promoting healthy lifestyle behaviors in children, such as eating nutritious foods and exercising. Re-designing practice standards to include birth history may identify those born prematurely and at risk for later-life disease (D'Agata et al., 2022; Kelly et al., 2021). Monitoring growth trajectories and understanding appropriate catch-up growth patterns for preterm-born individuals may improve long-term health outcomes (Han et al., 2021; Han et al., 2022). Prevention and interventions may be less effective if applied too late; therefore, early recognition is critical for those born preterm.

Premature birth has been labeled a “chronic condition” and carries a lifelong risk (Raju, Buist, et al., 2017). Nurses are well-trained to care for chronic health conditions, yet most are unaware of the long-term health effects of prematurity in their daily practices. Many nurses in clinical practice, including APNs, care for adult individuals who were born preterm without knowing it. There are endless opportunities for nurses caring for adults born preterm to impact their health positively. APNs in adult practice can provide and ensure quality care for women of reproductive age and develop data systems to understand and inform preventive efforts. Nurses can contribute to the development of much-needed national birth registries by advising on pertinent prenatal and postnatal data, neonatal treatments, and infant outcomes and aid in identifying health trends and associations.
Nursing education, at both the undergraduate and advanced practice levels, is another area that must keep pace with the latest research on prematurity. Curricula must be updated to disseminate findings from DOHaD research and expand academic training related to the outcomes of preterm infants that can positively influence their future health risks (Kelly & Michalek, 2019). Like most health fields, nursing has areas of specialties that concentrate on age-based populations. Nursing curricula should emphasize the importance of adopting a life course approach in all age-based populations, which may reduce the disease risk or severity of disease of preterm-born individuals across their lifespan. Considering that preterm birth is common and may have long-term health sequelae, nurses of all levels and all clinical settings should make birth history part of an individual’s medical history. Questions to start with include Were you born prematurely? If they answer yes, a follow-up question could be Do you know why? Additional questions should elicit information about birth weight, gestational age, length of hospitalization, use of mechanical ventilation, perinatal complications, and any other factors that could have been a perinatal, antenatal, or postnatal stressor.

**Implications for Health Policy**

Nurses can advocate for public programs to provide interventions for at-risk populations such as those born prematurely. All clinicians must seek a birth history, including gestational age and neonatal illness, and recognize this health history data as an integral part of clinical evaluations (Crump, 2020a; Kelly et al., 2021; Miller et al., 2009; Raju, Buist, et al., 2017). Birth history is often omitted from health information once the preterm-born child has reached school age; integrating birth status into permanent records is an important, necessary change in clinical practice (Kelly et al., 2021). If birth history
questions are asked, and the relevance of the information is explained, parents and, eventually, preterm-born individuals themselves will understand its importance. Nurses are in the ideal position to advocate how care is accessed and delivered to this vulnerable population.

Sources of health policy can be divided into three categories – public, organizational, and professional (Taft & Nanna, 2008). Nurses can influence the healthcare for patients through participation at any one of the three levels. Involvement in professional nursing organizations like the American Nurses Association and the American Heart Association, other special interest groups, pharmaceutical industry, and other suppliers, or lobbying with associations like the American Medical Association or the American Hospital Association can positively impact health policy change. For example, with professional membership in an organization like the American Academy of Nursing (AAN), which serves both the nursing profession and the public, nurses can advocate for changing or advancing health policy by generating, synthesizing, and disseminating nursing knowledge about lifetime health risks of being born prematurely (American Academy of Nursing, 2021). Serving as a member of a health benefits committee in membership organizations like religious groups, provider organizations, insurers, or research organizations to influence their internal health policies can positively impact outcomes for other members. Multiple advocacy roles exist with involvement in a non-profit organization like the March of Dimes, which can influence public policy (March of Dimes, 2022). A position on a policy workgroup committee in an advocacy organization like the March of Dimes can help champion education and the development of best practices in maternal and neonatal care to improve health equality and preterm
birth outcomes (March of Dimes, 2022). Lastly, disseminating research findings across multiple platforms, including public social media sites, can promote and increase awareness among providers, healthcare organizations and groups, insurance companies, and philanthropies, and individuals who were preterm themselves, as well as their loved ones (Taft & Nanna, 2008).

Despite the steady increase in preterm births, which have been consistently associated with adverse health consequences in later life, there is a lack of nationally standardized screening and tracking guidelines for those born prematurely. Specifically, standardized CVD risk screening and routine CVD risk follow-up may enable early identification and treatment of preterm-born individuals at risk. As new evidence emerges on the prevalence of early CVD risks, new or revised preventive treatment strategies may be necessary to combat CVD.

Morphologic changes in the hearts of preterm-born young adults was first detected by Lewandowski (Lewandowski, Augustine, et al., 2013; Lewandowski, Bradlow, et al., 2013). Additional research has detected similar results, associating the degree of alteration with the degree of prematurity (Aye et al., 2017; Goss et al., 2017; Vrselja et al., 2021). These pathophysiological alterations call for recommendations for early cardiac screening to define the evolution of cardiac modifications (Arjaans et al., 2021). Such measures may facilitate a better understanding of the cardiac remodeling process and influence the development of preventive and therapeutic measures (Arjaans et al., 2021). Currently, there are no cardiovascular guidelines that include preterm birth as a CVD risk factor nor address how to manage the long-term risk for the development of CVD. APNs are well-positioned to hold positions on national committees to review
and disseminate research findings and create national, evidence-based recommendations and screening guidelines.

Neonatal screening with echocardiography may detect anatomical and physiological cardiac modifications, promoting early risk stratification and possibly averting later life CVD (Abushaban et al., 2020; Arjaans et al., 2021). Establishing universally accepted echocardiogram values for preterm infants’ hearts, especially left ventricular (LV) mass measurements, may prove beneficial in facilitating early detection and treatment of CVD comorbidities and altering the long-term cardiovascular outcomes for preterm-born individuals (Abushaban et al., 2020). Neonatal and pediatric APNs can advocate for health policy change that requires the life-saving clinical practice of measuring LV mass (Arjaans et al., 2021).

The Adults Born Preterm International Collaboration (APIC), a professional medical organization advocating for the preterm-born population, recently published recommendations on “common core assessments” to be used consistently in follow-up assessments of adults born preterm (Kajantie et al., 2021). Supporting, implementing, and translating these recommendations into clinical practice may result in the development of targeted interventions that benefit the long-term health of individuals born prematurely. The suggested measurement values are proposed to aid clinicians and researchers in collecting outcome variables so that comparisons can be made across cohorts and countries (Kajantie et al., 2021).

**Implications for DOHaD Theory**

The DOHaD theory has influenced numerous research areas and has become well-accepted among medical and biological science researchers (Suzuki, 2018). It was
criticized when it was a new theory because the empirical research was weak, due to retrospective research designs, methodological flaws, and epidemiological approaches (Skogen & Overland, 2012; Sullivan et al., 2008). These initial flaws and criticisms have been substantially lessened as more rigorous clinical research and reliable experimental evidence has emerged to support the underlying mechanisms for anatomical and pathophysiological cardiac changes in those born preterm (Suzuki, 2018).

Research on developmental origins has been fundamental to highlighting the benefits of a life course approach to health development for those who survive preterm birth (Msall et al., 2018). Numerous prenatal and neonatal medical advances have emerged because of DOHaD research (Kajantie et al., 2021; Msall et al., 2018). A paradigm shift in research priorities— from strict focus on perinatal and early neonatal management to an inclusion of survivors' later-life health—can facilitate a greater understanding of potential genetic, epigenetic, and social determinants for those born prematurely, improving health outcomes across their lifetimes. Evidence suggests that the socioeconomic environment during childhood profoundly affects adult health more than any other life point (Gluckman et al., 2007; Power et al., 2013).

As noted throughout this dissertation, the knowledge of longer-term health outcomes of preterm birth mainly exists from international cohorts (Crump, 2020b; Raju, 2017; Risnes et al., 2021). Despite the high preterm birth rates in non-Hispanic Black and Hispanic women in the U.S., the few U.S.-based studies that have been conducted on prematurity used cohorts with limited racial or ethnic diversity (Hack et al., 2004; Miller et al., 2009; Msall et al., 2018; Osterman et al., 2021; Sullivan et al., 2017). Research has shown that gestational age and birth weight are not the only factors influencing adult
health outcomes; racial and ethnic disparities are important influences too (Wolke, 2018).

*Social determinants of health* (SDH), or the conditions and the environment in which individuals are born, grow, live, and work, significantly contribute to health outcomes throughout their lives (Beck et al., 2020). In conceptualizing a life course perspective, SDH, such as socioeconomic status, social and environmental exposures, family support, and access to health care, can positively or negatively influence later-life health outcomes in individuals born preterm (Raju, Buist, et al., 2017). In Figure 19, *A Life Course Perspective and Conceptual Framework*, the pink box labeled “Environmental/ SES” lists SDH poverty, education, and air pollution as stressors that negatively impact health outcomes throughout life. The effects of SDH on the health of adults born preterm in the U.S. are unknown, mainly due to the lack of birth history in adults (Kelly et al., 2021).

**Figure 19**

*A Life Course Perspective and Conceptual Framework*

Note. This figure depicts a life course perspective and conceptual framework that may influence health outcomes later in life for individuals born preterm. From “Adults born
Beck et al. (2020) proposed three causal pathways of racial inequality: (1) increased risk, (2) lower quality care, and (3) socioeconomic disadvantages. Beginning in infancy and persisting throughout life, structural racism adversely affects health outcomes in individuals born preterm. Structural racism refers to large-scale situations or conditions, like residential segregation and institutional policies, that limit healthcare opportunities and resources based on race/ethnicity, gender, or socioeconomic status (U.S. Department of Health and Human Services, 2022).

Assessing societal factors that influence health is a way to improve health equity (Institute for Healthcare Improvements, 2022). Healthcare providers can assess and aid in removing obstacles to healthcare access; educate community partners, the families of infants born prematurely, and the preterm-born individual on potential health outcomes; and communicate the need for screening and assessing SDH in clinical and community settings (Beck et al., 2020). Newer advances in science and technology, such as geospatial mapping, could identify regional areas with high preterm birth rates so that modifications in healthcare systems and negative influences can be assessed (Beck et al., 2020).

Socioeconomic and demographic factors were collected in the WHI studies. Factors such as race, ethnicity, region of birth, education, and income were self-reported by participants and were used for modeling in Manuscripts II and III. Although the more
precise measurements from geospatial coding had not been invented when the WHI study began, socioeconomic measures have been validated specifically in the WHI-OS and are known to be valid measures in longitudinal studies. However, analyses of preterm-born women enrolled in the WHI-OS revealed that the influence of demographics and socioeconomic status on their health outcomes in later-life health was not statistically significant.

The research of this dissertation was primarily guided by the DOHaD framework, specifically the anatomical and physiological impact of preterm birth. Research results in Manuscripts II and III are supported by the concept of pathophysiological adaptations and alterations in function of cardiac tissue in those born prematurely; concepts that are depicted by figures in Chapter 2. Preterm birth can permanently impede cardiomyocyte growth and development, resulting in altered myocardial tissue structure. Altered myocardial structure has been reported in the hearts of preterm-born young adults as increased left and right ventricular mass and changed morphology. Physiological differences, such as a lower ejection fraction, strain rate, and stroke volume, may result from these structural alterations and/or the impaired growth and development of the cardiomyocyte unit. Such structural and functional modifications may have predisposed the preterm-born women of the WHI-OS to a higher prevalence and incidence of hypertension and CVD later in adulthood (Gluckman et al., 2016). Immature, impaired, and dysfunctional anatomical and physiological systems, as well as environmental exposures, are hypothesized to be the reason for the higher prevalence of RA and hypothyroidism in preterm-born women.
Moreover, a broader perspective encompassing social and economic elements is clinically important. Merging chronic disease epidemiology with DOHaD research, including SDH, over the life course of preterm-born individuals may accelerate the development of new or more effective health promotion strategies starting in their early childhood and throughout the remainder of their lives. In the U.S., preterm birth rates remain steady at around 10%. Therefore, embracing a life course approach to health based on the foundational principles of the DOHaD theory may not only improve the health outcomes of this unique population but may inform changes in healthcare practices at the individual, provider, and system levels (Kelly et al., 2021; Msall et al., 2018; Osterman et al., 2021; Sullivan et al., 2022). Indeed, emerging research on the lifelong health effects of prematurity, including the predisposition to various chronic diseases, warrants a full review and possible revamping of current strategies for health screening and education, as well as evaluation and treatment approaches, to be more inclusive of this vulnerable population.

Although macro theories present challenges for empirical testing, life course theory can have significant implications for nursing and other health professionals. Broadening the theory can encourage an interdisciplinary approach to health promotion strategies and collaboration among various healthcare team members, like parents, teachers, civic leaders, and other interested parties necessary for health promotion (Barnes et al., 2016). Research opportunities within the realms of DOHaD are continuously growing, such as predictive epigenetic testing and profiling (Lynch et al., 2022). Long-term generational research that evaluates health promotion strategies and
risk reduction interventions is needed and falls within the scope of DOHaD theory (Barnes et al., 2016).

In summation, the DOHaD theory is a valuable and appropriate framework for exploring chronic disease risks in adults born preterm. A greater understanding of interactions between intrinsic mechanisms of development and growth and extrinsic factors such as lifestyle, social, and ecological determinants of health may have enhanced these WHI study findings. In congruence with the DOHaD theory, a shift from focusing on early developmental factors that may predispose individuals to disease to measures that promote lifelong health and resilience should be explored.

**Significance and Future Perspectives**

Advances in healthcare technologies and improvements in neonatal care have resulted in increased survival of preterm-born individuals. Emerging research has shifted from a sole focus on neonatal survival to a focus on longitudinal health trajectories and long-term health. Research has shown that preterm birth is associated with increased health risks later in life, although the underlying causal mechanisms are not fully understood (Lewandowski et al., 2020).

The two data-based studies in this dissertation reveal that postmenopausal adult women born preterm may be at a greater risk of developing CVD. In Manuscript II, preterm birth was associated with a higher risk of prevalent hypertension (26%), early-onset hypertension (31%), and incident hypertension (10%). Furthermore, effect modification by prevalent hypertension indicated that risks for incident CHD and CVD were significantly increased for women born preterm without hypertension (29% and 23%, respectively). Manuscript III investigated co-occurring conditions known to
increase CVD and found that postmenopausal adult women born preterm were 20% more likely to develop hypertension, RA, and hypothyroidism. Women born preterm had up to a 69% increased likelihood of comorbidity and were 69% more likely to have all three conditions than women born full term. These findings support the hypothesis that women born preterm are predisposed to a greater risk of developing CVD. Nurse clinicians and other healthcare providers are encouraged to stay informed of emerging research findings on preterm birth and embrace a life course approach to CVD prevention, as described in Manuscript I. Based on the collective evidence presented in this dissertation, there is an urgent need to recognize preterm birth as a significant risk factor for CVD. For clinicians, a simple inquiry about birth history, documentation of preterm birth status, and recognition of its relevance to cardiovascular health is a place to start.
Appendix A: Women’s Health Initiative Manuscript Proposal Application Form

(Manuscript II)

WHI MANUSCRIPT PROPOSAL APPLICATION FORM

DUE DATE:  See WHI website for upcoming submission deadlines.
SUBMIT TO:  P&P@WHI.org
REFER TO:  Write a Paper Resources on whi.org.
GUIDELINES:
- Cancer mortality and survival analyses generated from WHI data
- Post-intervention analyses of the original WHI trials
- Combined CT and OS data in observational analyses
- Body Composition Analysis
- Diet Dataset Documentation for guidelines and information about Dietary Quality Indices, FFQ Analysis of Folate, Biomarker Calibration Information, FFQ Diet-Disease Analysis, and FFQ Nutrient Database Estimations.

Section 1: GENERAL QUESTIONS (Required)

Today’s Date: 3/12/2021  
Is this a resubmission to P&P?  ☒ No
☐ Yes → Submit both:
1. Revised application form AND
2. Two copies of proposal (1 clean and 1 track changes).

1. Proposal title: Cardiovascular Health of Preterm-Born Adult Women: A Double Disadvantage?

2. Lead author
   Name: Pamela Brewer
   Institution: University of Rhode Island
   Phone: 401-327-5789
   Email: pamela_brewer@uri.edu

3. Are you any of the following? (mark all that apply)
   ☒ Pre-doc
   ☐ Post-doc
   ☐ Early Stage Investigator as defined by NIH?

4. Is this your first WHI Manuscript Proposal?
   ☐ No  ☒ Yes

5. Are you currently leading any manuscript proposals that were approved by P&P >3 years ago?
   ☒ No  ☐ Yes → Please explain.

6. Are you leading any draft manuscripts that were approved by P&P >1 year ago and have not yet been submitted to a journal for publication?
7. What is your affiliation to WHI?

☐ WHI Principal Investigator
☐ WHI Co-Investigator
☐ WHI Associate Member

☒ None of the above

↓

WHI Sponsoring PI: Dr. Charles Eaton

☒ Check here to confirm that the Sponsoring PI has reviewed and approved this proposal.

Note: If the lead author is not a WHI Principal Investigator, Co-Investigator, or Associate Member, a Sponsoring PI is required. The Sponsoring PI must review and approve all materials before submission to P&P.

8. Co-authors

Co-author 1 name: Amy D’Agata
Co-author 1 email: amydagata@uri.edu

Co-author 2 name: Mary Roberts
Co-author 2 email: mary_roberts@brown.edu

Co-author 3 name: Mary Sullivan
Co-author 3 email: mcsullivan@uri.edu

Co-author 4 name: Charles Eaton
Co-author 4 email: cbeaton51@gmail.com

Note: The proposal may not have more than five total authors, including the lead author and the Sponsoring PI, or it will be returned for immediate revision. The P&P Committee Policies note exceptions to this rule. The lead author may add more co-authors after the proposal is approved.

Names of additional co-authors (if exceptions apply): MS2012 led by Kelli K Ryckman proposed to look at birthweight and preterm gestational age and incident hypertension. She published on birthweight but not preterm status. We discussed this with her, and she has agreed to be a co-author and have Pamela be the lead author.

Section 2: DATA QUESTIONS (Required)

9. What WHI data are you using? (mark all that apply)

☒ Observed Study
☐ Clinical Trial (Hormone Therapy, Dietary Modification, Calcium/Vitamin D)

10. What is your primary outcome? Hypertension

11. What data source are you using to identify this outcome? (mark all that apply)

☒ Adjudicated outcomes
☒ Self-report
☐ Medicare/CMS data
☐ Other: Describe and justify this selection.

12. Are you using any of the following data sources for this proposal? (mark all that apply)

☐ National Death Index
☐ Supplemental Questionnaire (Form 156, Form 157, Form 158)
☐ WHI Ancillary Study (AS), Core Study (W), and/or BAA Study (if checked, please answer the next three questions)
i. Please list the study numbers: Enter all applicable study numbers.

ii. Was the source of funding for the study a commercial entity?
   ☐ No  ☐ Yes

iii. Has all AS data, Core Study data, and/or BAA Study data been submitted to the CCC?
    ☐ No  ☐ Yes

Note: If you are using WHI AS data, it is strongly recommended that you include the study PI or a representative from the study on your writing group.

13. Will this proposal use data from studies other than WHI?
   ☒ No  ☐ Yes → List all cohorts: Enter all cohorts.

A consortium/pooling project is a research project that is developed by an organized group of scientific investigators representing various study cohorts and usually with an independent governance structure.

Answer the three questions below. If you answer yes to any of these questions, complete the WHI Consortium/Pooling Project Application Form.

i. Will the consortium/pooling project have an independent governance structure?
   ☐ No  ☐ Yes

ii. Will the consortium/pooling project have a Publications and Presentations Committee?
    ☐ No  ☐ Yes

iii. Will the consortium/pooling project have an External Advisory Board?
    ☐ No  ☐ Yes

Section 3: OTHER/MISCELLANEOUS (Required)

14. Use the Excel spreadsheet with a listing of all papers/proposals to identify potential overlap. Specify what unique data will be added with this proposal.

Potential overlap with MS2012, see above, Dr. Kelli K Ryckman agreed to have Pamela be the lead author with the additional analyses proposed and Kelli agree to be a co-author.

Note: Failure to identify overlap could lead to cancellation of your paper, even if overlap is identified after your proposal is approved.

15. Please list at least 5 keywords: Preterm-born adults, hypertension, cardiovascular health, cardiovascular outcomes, blood pressure trajectory

16. You are required to include power calculations in the proposal to demonstrate adequate power to conduct the analyses for each aim. Check to confirm this step is complete.

   ☒ Yes, power calculations are included.

17. Did this proposal stem from a discussion within a WHI Scientific Interest Group (SIG)?

   ☒ No  ☐ Yes (mark all that apply)

   □ Aging: Cognition & Functional Status  □ Nutrition/Energy Balance
   □ Bone/Fracture & Body Composition  □ Obesity & Diabetes
   □ Cancer  □ Physical Activity/Body Composition
   □ CVD (includes AF & HF sub-SIGs)  □ Physical & Built Environment
Section 4: FINAL ITEMS (Required)

19. Additional comments or information you would like the P&P to consider with your application.
Enter comments.

20. Application Checklist
   ☑ Completed application form with current date.
   Proposal:
   • Not to exceed six pages, not including references or tables.
   • If this is a resubmission, submit two copies of the proposal (1 clean and 1 track changes).
   • A sample proposal is available for reference.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death for men and women in the United States.\(^1\) It is estimated that 1 out of every 3 American women die from ASCVD, while 1 out of every 25 die from breast cancer.\(^2, 12\) Consistent evidence highlights gender disparities in treatment and adverse outcomes, primarily due to grossly underestimated and unrecognized ASCVD risks in women that stem from underrepresentation in cardiovascular research.\(^3, 4\) Treatment plans for women tend to be less aggressive and often women are less likely to receive evidence-based therapies, invasive interventions, and referrals for rehabilitation.\(^4, 14\) A major milestone in cardiology has been the appreciation that ASCVD affects women differently than men.\(^4\)

Gender differences in the pathophysiology of ASCVD exist with a greater prevalence of microvascular coronary dysfunction, hypertension and hypertensive heart disease, and endothelial and vasodilatory parasympathetic dysfunction in women.\(^5-8\) Furthermore, in general, women have smaller hearts, smaller and stiffer arteries, faster pulse rates, sharper increases in systolic blood pressure, more diffuse atherosclerotic plaque patterns, and greater hormonal influences compared to men.\(^5-7\) Some of the “traditional” risk factors, specifically...
hypertension (odds ratio [OR] 1.5), diabetes (OR 1.6), smoking (OR 1.3) and obesity, which are more common and more potent in women than men, play a role in greater ASCVD risk.\textsuperscript{3,18,23} Additionally, non-traditional risk factors unique to women, namely preterm delivery, hypertensive disorders of pregnancy, depression, autoimmune conditions, and polycystic ovarian disease postulate an increased ASCVD risk.\textsuperscript{3,4,18}

Sex-based disparities in outcomes are apparent with women exhibiting greater ASCVD morbidity and mortality.\textsuperscript{16} Woodward (2019) reported women who survive a cardiovascular event are 7.2% more likely to experience a recurrent event within 1 year (compared to 6.8% in men) while 26% will die within the year (compared to 15% in men).\textsuperscript{17} Mehta’s (2016) expansion to 5 years determined more women than men will die (47% of women and 36% of men), develop heart failure or suffer a stroke.\textsuperscript{18} Hypertension, a well-established, major risk factor for ASCVD poses a greater mortality risk in women compared to men, with less than 30% of hypertensive women appropriately controlled (compared to 50% of men).\textsuperscript{7,13,21} Numerous studies have analyzed the blood pressures of women from within the Women’s Health Initiative. The findings are consistent; 53-60% of WHI participants display hypertensive readings, despite treatment.\textsuperscript{19,20}

High blood pressure dominates current evidence associating preterm birth and poor ASCVD outcomes.\textsuperscript{15} Research in the preterm-born adult population, although greatly limited and almost non-existent in the United States, supports not only higher blood pressures, but lower lean body mass, impaired glucose regulation and insulin sensitivity, and more atherogenic lipid profiles.\textsuperscript{9-11} Distinct myocardial structure and function anomalies compared to full term counterparts are noted as well.\textsuperscript{9,10} Altered autonomic regulatory function, increased biventricular mass, smaller right ventricles, lower right ventricular ejection fractions, and increased left ventricular mass index with steep pressure volumes have been detected in hearts of preterm-born adults.\textsuperscript{10,11} These physiologic preterm-born cardiovascular differences increase cardiovascular risk and are predictors for cardiovascular morbidity and mortality in preterm-born adults.\textsuperscript{10,11}

Twenty-three hundred observational cohort (OS) women of the Women’s Health Initiative (WHI) self-identified as being born preterm or less than 37 weeks gestational age. As a participant in the OS arm of the WHI, new medical conditions were assessed annually for almost 10 years in some participants. Cardiovascular and cerebrovascular outcomes were adjudicated as reported.\textsuperscript{22} The vulnerabilities of the preterm heart, higher prevalence of hypertension, and a greater risk factor predisposition portends poorer ASCVD outcomes for the preterm-born adult female. The proposed investigation will analyze the cardiovascular health of preterm women by longitudinally sequencing risk factors, linking comorbidities, and narrowing the gap in cardiovascular outcomes. The findings of this study may necessitate gender-specific screening and guideline development, along with a heighten awareness of ASCVD markers in the preterm population. The greatest contribution of studying the cardiovascular health of preterm-born adult women is an enhanced understanding of the preterm cardiovascular system, the facilitation of early cardiovascular screening and identification of risk factors, and the development of preventative strategies for the younger preterm population.

OBJECTIVES

1. To examine whether the prevalence, age of onset, and incidence of hypertension is higher and earlier in preterm-born women compared to term born women.
2. To determine whether hypertensive preterm-born women require more antihypertensive agents for control and/or are more difficult to manage/achieve blood pressure goal (<140/90 mmHg) compared to hypertensive term born women.

3. To examine the combined effect of birth status and prevalent hypertension on the incidence of CHD and CVD events.

ANALYSIS PLAN

Study Population
Baseline data from the Women’s Health Initiative Observational Study will be used to examine the relationship between duration of gestation (preterm versus term) and the incidence and age of hypertension onset and cardiovascular outcomes. The Women’s Health Initiative Observation Study (OS) enrolled 93,676 participants, 93% self-reported duration of gestation at birth (n=88,343). Of these women, 97% (n=86,040) reported birth at full-term, while 2.4% (n=2,303) reported being born preterm (defined as 4 weeks or more premature; form 42, question #2). Table 1 shows the distributions of responses.

For gestational age, the variable will be defined as full term (i.e., 9-month pregnancy) and preterm (born 4 or more weeks premature). This will allow for assessment of both early birth and full-term birth as a risk for hypertension and ASCVD (cardiovascular and cerebral vascular) outcomes.

Study Outcomes

- **Hypertension prevalence and age onset** will be measured from enrollment self-report of hypertension diagnosis (HYPT) and age onset (HYPTAGE), and the screening visit blood pressure measurements (SYST, DIAS) and medications (extracted from FORM 44).

- **Prevalent Hypertension** will be defined as untreated systolic blood pressure >140 mmHg or untreated diastolic blood pressure >90 mmHg or the physician diagnosis of hypertension and use of antihypertensive medications.

- A sensitivity analysis will evaluate prevalent hypertension defined only by self-report of physician diagnosis with medications like incident treated hypertension.

- **Early onset hypertension will be defined as hypertension prior to age 50.**

- **Hypertension incidence** will be determined from self-report of hypertension diagnosis with medication treatment from updated medical history after enrollment (F33PILLSHYP)

- **Difficult to control**, often labeled resistant hypertension, will be defined as a blood pressure that remains >140/90 mmHg despite 3 antihypertensive agents from different classes or BP that is controlled ≤140/90 mmHg and on 4 antihypertensive agents.
Incident Cardiovascular & cerebrovascular will be determined from adjudicated outcomes: clinical MI (MI), revascularization (CAGB, PCI) and stroke (STRKISCH)

**Variables**

- Exposure/Primary explanatory variable
  - Preterm birth, 4 weeks or more preterm (FULLTERM)

- Primary comorbidities at enrollment (FORM 2, FORM 30)
  - Angina (ANGINA)
  - Heart Failure (CHF_F2, CHF_F30)
  - TIA (TIA)
  - Treated hyperlipidemia (HICHOLRP)
  - Arrhythmia/Atrial fibrillation (ATRIALFB)

**Confounders**

- Age (AGE)
- Birth cohort (AGER)
- Race/ethnicity (RACE)
- US region of birth (BRTHREGN)

**Covariates**

- Marital status (MARITAL)
- Education (EDUC)
- Income level (INCOME)
- Physical activity (TEXPWK)
- Smoking (SMOKING)
- Alcohol consumption (ALCSWK)
- Comorbidities at enrollment (ANGINA, CHF, TIA, HICHOLRP, ATRIALFB)

**Potential mediators**

- Diabetes (DIABTRT)
- BMI (BMI)
- Breastfed as infant (BRSTFED)

**Statistical Analysis**

Analyses will be performed by preterm status using baseline data. Descriptive statistics by preterm status will be used (mean and standard deviation for continuous variables, and count and percentage for categorical variables) to summarize socio-demographic characteristics including risk factors for ASCVD. Potential confounders will be determined based on DAG (figure 1) and results of univariate analyses with a p-value < 0.10. Person-years of follow-up for each
participant will be based on time from enrollment to either outcome of interest, loss to follow-up, or death.

For objective 1, logistic regressions will be used to examine the association of and birth status (term vs preterm with prevalent hypertension at the baseline) after adjusting for potential confounders such as age, birth cohort, race/ethnicity, geographic region. Additionally, multinominal logistic regression will be used to examine the association of birth status with hypertension defined in 3 levels (no HTN, early onset hypertension [age<50 years], and later onset hypertension [age 50+ years]).

Cox Proportional Hazards models will be used to examine the association birth status with development of incident hypertension in individuals free of prevalent hypertension. Model 1 will adjust for age and race. Further model building will include potential confounders, covariates, and finally potential mediators as defined above.

For objective 2 among those diagnosed with hypertension, numbers and types of hypertension medications will be examined by birth status. We will also examine different combinations of HTN medications (including difficult to control HTN) by birth status. Medication regimes will be examined at enrollment, year 3 and year 4 during extension 1. P-values will be determined from Poisson models for total count variables and chi-square analysis for individual medication use.

For objectives 3, Cox Proportional Hazards models will be used to estimate the hazards ratio (HR) and 95% confidence intervals (CIs) for the joint effect of preterm status and prevalent hypertension on the risk for CHD or CVD events. The first model will adjust for age and race/ethnicity. A second model will also include education, income, marital status, region of birth, and breastfed as infant. Building upon models 1 and 2, the third model will have additional adjustments for potential confounders/mediators including BMI, hyperlipidemia, diabetes mellitus, smoking status, physical activity, and alcohol intake. Potential confounders will be kept in the model based upon the current clinical literature and statistical significance, or if the variable is associated with CHD/CVD (p-value < 0.10), is associated with the birth status and hypertension (p-value < 0.10). Alternatively, a confounder will be included if adding the variable changes the point estimate of the hazard ratio by more than 10%. The proportional hazard assumption will be tested based on the smoothed plots of the scaled Schoenfeld residuals. Models will be weighted by WHI extension 2 status to account for differential outcome follow-up.

Analyses will be conducted using SAS v9.4 (Cary, NC). A significance level of p≤0.05 will be used for all analyses unless otherwise noted.

Power Calculation

WHI analysis cohort has median follow-up time 12.6 years with a maximum of 25.5 years. As of March 2020, the overall number of CVD events in the analysis sample is 8,072. Using preterm status to determine the necessary sample size, a total number of events equal to 7423 with a 0.05 two-sided significance level will have 80% power to detect a constant hazard ratio of 1.21.23

Conclusion
We expect that preterm-born women will have a higher prevalence, earlier age of onset, and a greater incidence of hypertension than term born women. Additionally, more antihypertensive drugs will be required to manage and achieve blood pressure control in hypertensive preterm-born women. Lastly, hypertensive preterm-born women will reveal a higher incidence of CHD and CVD events.

Tables

Table 1: WHI OS Demographics by Birth Status

<table>
<thead>
<tr>
<th>Demographic and lifestyle factors</th>
<th>Birth Status</th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full term (n=86,040)</td>
<td>Preterm (n=2,303)</td>
<td>P value</td>
<td></td>
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<tr>
<td>Age (y) (mean, sd)</td>
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<tr>
<td>Age cohort (n, %)</td>
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<tr>
<td>Race (n, %)</td>
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<tr>
<td>Education level (n, %)</td>
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<tr>
<td>Income level (n, %)</td>
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<tr>
<td>Marital status (n, %)</td>
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<tr>
<td>Region of birth (n, %)</td>
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<tr>
<td>Smoking status (n, %)</td>
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<tr>
<td>Physical activity (mean, sd)</td>
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<td>Alcohol consumption (mean, sd)</td>
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<tr>
<td>Body mass index (mean, sd)</td>
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<tr>
<td>Systolic blood pressure (mmHg) (mean, sd)</td>
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<tr>
<td>Diastolic blood pressure (mmHg) (mean, sd)</td>
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<tr>
<td>Diabetes (n, %)</td>
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<td></td>
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<tr>
<td>Hyperlipidemia (n, %)</td>
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<td></td>
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<tr>
<td>Hypertension (n, %)</td>
<td></td>
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<tr>
<td>Angina (n,%)</td>
<td></td>
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<tr>
<td>Atrial fibrillation (n, %)</td>
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<td></td>
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<tr>
<td>TIA (n, %)</td>
<td></td>
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<td></td>
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<tr>
<td>Heart failure (n, %)</td>
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<tr>
<td>HTN age onset (n, %)</td>
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<tr>
<td>Breastfed as infant (n, %)</td>
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Table 2a-c: WHI OS Demographics by Prevalent Hypertension (Early Onset HTN/Incident HTN)
<table>
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<th>Demographic and lifestyle factors</th>
<th>Prevalent HTN</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No (n=58,033)</td>
<td>Yes (n=28,747)</td>
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<td>Age (y) (mean, sd)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age cohort (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education level (n, %)</td>
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<tr>
<td>Income level (n, %)</td>
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<td></td>
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<tr>
<td>Marital status (n, %)</td>
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<td></td>
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<tr>
<td>Region of birth (n, %)</td>
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<tr>
<td>Smoking status (n, %)</td>
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<tr>
<td>Physical activity (mean, sd)</td>
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<tr>
<td>Alcohol consumption (mean, sd)</td>
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<td></td>
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<tr>
<td>Body mass index (mean, sd)</td>
<td></td>
<td></td>
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<tr>
<td>Systolic blood pressure (mmHg) (mean, sd)</td>
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<tr>
<td>Diastolic blood pressure (mmHg) (mean, sd)</td>
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<tr>
<td>Diabetes (n, %)</td>
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<tr>
<td>Hyperlipidemia (n, %)</td>
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<tr>
<td>Angina (n, %)</td>
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<td></td>
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<tr>
<td>Atrial fibrillation (n, %)</td>
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<td></td>
</tr>
<tr>
<td>TIA (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breastfed as infant (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth status (n, %)</td>
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<td></td>
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</tbody>
</table>

Table 3a. Logistic Models for Prevalent Hypertension by Birth Status

<table>
<thead>
<tr>
<th></th>
<th>Full Term</th>
<th>Preterm</th>
</tr>
</thead>
<tbody>
<tr>
<td># cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence rate (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Odds Ratio for Prevalent HTN Model (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>(ref)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>(ref)</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>(ref)</td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>(ref)</td>
<td></td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, race.
Table 3b. Multinomial Logistic Models for Hypertension Onset by Birth Status

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<thead>
<tr>
<th></th>
<th>Full Term</th>
<th>Preterm</th>
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<tbody>
<tr>
<td><strong>Early Onset HTN (age&lt;50 years)</strong></td>
<td></td>
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</tr>
<tr>
<td># cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence rate (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HTN Onset after age 50+ years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td># cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence rate (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Odds Ratio (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Onset HTN vs No HTN</td>
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<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>(ref)</td>
<td></td>
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<tr>
<td>Model 2</td>
<td>(ref)</td>
<td></td>
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<tr>
<td>Model 3</td>
<td>(ref)</td>
<td></td>
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<tr>
<td>Model 4</td>
<td>(ref)</td>
<td></td>
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<tr>
<td>Onset After age 50 vs No HTN</td>
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<tr>
<td>Model 1</td>
<td>(ref)</td>
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<td>Model 2</td>
<td>(ref)</td>
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<tr>
<td>Model 3</td>
<td>(ref)</td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>(ref)</td>
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</tr>
</tbody>
</table>

Model 1: adjusted for age, race.
Model 2: age, race, income, education, marital status, region of birth.
Model 3: model 2+ smoking status, physical activity, alcohol intake, medical history.
Model 4: model 3+ BMI, diabetes, breastfed as infant.

Table 4. Cox Models for Incident Hypertension by Birth Status

<table>
<thead>
<tr>
<th></th>
<th>Full Term</th>
<th>Preterm</th>
</tr>
</thead>
<tbody>
<tr>
<td># cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total # years follow-up</td>
<td></td>
<td></td>
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<tr>
<td>Age-adjusted incidence rate (95% CI)</td>
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<tr>
<td><strong>Cox Proportional Hazards Model (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>(ref)</td>
<td></td>
</tr>
</tbody>
</table>
Model 1: adjusted for age, race.
Model 2: age, race, income, education, marital status, region of birth.
Model 3: model 2+ smoking status, physical activity, alcohol intake, medical history.
Model 4: model 3+ BMI, diabetes, breastfed as infant.

Table 5: Treatment of HTN in WHI OS by Birth Status

<table>
<thead>
<tr>
<th>Birth Status</th>
<th>HTN Medications</th>
<th>Full term (n=xxx)</th>
<th>Preterm (n=xxx)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>Total # HTN medications (mean, sd)</td>
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<tr>
<td>Beta blocker (n, %)</td>
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<tr>
<td>Ca channel blocker (n, %)</td>
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<tr>
<td>Diuretic (n, %)</td>
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<tr>
<td>ACE (n, %)</td>
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<tr>
<td>ARB (n, %)</td>
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<tr>
<td>Other (n, %)</td>
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<tr>
<td>Medication combinations ...</td>
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<tr>
<td>Difficult to control HTN (n, %)</td>
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<tr>
<td>Year 3</td>
<td>Total # HTN medications (mean, sd)</td>
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</tr>
<tr>
<td>Beta blocker (n, %)</td>
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<tr>
<td>Ca channel blocker (n, %)</td>
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<tr>
<td>Diuretic (n, %)</td>
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<tr>
<td>ACE (n, %)</td>
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<tr>
<td>ARB (n, %)</td>
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<tr>
<td>Other (n, %)</td>
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<tr>
<td>Medication combinations ...</td>
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<tr>
<td>Difficult to control HTN (n, %)</td>
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<tr>
<td>Year 4 Extension 1</td>
<td>Total # HTN medications (mean, sd)</td>
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<td></td>
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<tr>
<td>Beta blocker (n, %)</td>
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<tr>
<td>Ca channel blocker (n, %)</td>
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</tr>
</tbody>
</table>
Diuretic (n, %) |  
ACE (n, %) |  
ARB (n, %) |  
Other (n, %) |  
Medication combinations ... |  
Difficult to control HTN (n, %) |  

Table 6. WHI OS Demographics by Birth Status and Prevalent HTN

<table>
<thead>
<tr>
<th></th>
<th>Full Term No HTN</th>
<th>Preterm No HTN</th>
<th>Full Term HTN</th>
<th>Preterm HTN</th>
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<tr>
<td>Age cohort (n, %)</td>
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<tr>
<td>Race (n, %)</td>
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<tr>
<td>Education level (n, %)</td>
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<td>Income level (n, %)</td>
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<td>Marital status (n, %)</td>
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<tr>
<td>Region of birth (n, %)</td>
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<tr>
<td>Smoking status (n, %)</td>
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<tr>
<td>Physical activity (mean, sd)</td>
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<tr>
<td>Alcohol consumption (mean, sd)</td>
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<tr>
<td>Body mass index (mean, sd)</td>
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<tr>
<td>Systolic blood pressure (mmHg) (mean, sd)</td>
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<tr>
<td>Diastolic blood pressure (mmHg) (mean, sd)</td>
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<td>Diabetes (n, %)</td>
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<td>Hyperlipidemia (n, %)</td>
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<tr>
<td>Angina (n, %)</td>
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<tr>
<td>Atrial fibrillation (n, %)</td>
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<tr>
<td>TIA (n, %)</td>
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<tr>
<td>Heart failure (n, %)</td>
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<tr>
<td>Breastfed as infant (n, %)</td>
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Table 7a-b. Cox Models for CHD (CVD) by Birth Status and Prevalent HTN
<table>
<thead>
<tr>
<th>No HTN</th>
<th>HTN</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Full term</td>
</tr>
<tr>
<td># cases</td>
<td></td>
</tr>
<tr>
<td>Total # years follow-up</td>
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<tr>
<td>Age-adjusted incidence rate (95% CI)</td>
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</table>

### Cox Proportional Hazards Model (95% CI)

<table>
<thead>
<tr>
<th>Model 1</th>
<th>(ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 2</td>
<td>(ref)</td>
</tr>
<tr>
<td>Model 3</td>
<td>(ref)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, race.
Model 2: age, race, income, education, marital status, region of birth, breastfed as infant.
Model 3: model 2+ BMI, hyperlipidemia, diabetes mellitus, smoking status, physical activity, alcohol intake.

**Figure 1. Aim 1 DAG for Hypertension**
REFERENCES


Appendix A.1: Women’s Health Initiative Manuscript Proposal 4447 Approval Letter

(Manuscript II)

MEMORANDUM

Date: March 26, 2021
To: Pamela Brewer
From: Lindsey Bull
P&P Committee Coordinator

Subject: Manuscript Proposal 4447 – Cardiovascular health of preterm-born adult women: A double disadvantage?

Congratulations! The Publications and Presentations (P&P) Committee has approved this proposal with required changes. Please see the reviews at the end of this memo for details. Please note: you are not required to submit a revised proposal for additional review unless you would like to dispute the required changes.

WHI has a number of active Scientific Interest Groups (SIGs) that bring together investigators in scientifically themed areas. The SIGs can be an excellent resource for authors as they develop their manuscripts. P&P urges you to present your analyses to a SIG and solicit their input. If you are interested in working with a SIG, please visit the SIG page on the WHI website and contact the SIG Chair(s) relevant to your topic.

Writing group nominations will be held soon. The CCC will send you a list of nominees to review when the nomination period closes. If you have any questions about the steps involved in the development of your manuscript, please refer to the P&P Policy.

Any BAA PI, AS PI, or lead author on an approved manuscript proposal seeking access to the WHI data must sign a Data Use Agreement (DUA) with a WHI PI. Please fill out and return the WHI DUA to the WHI helpdesk at helpdesk@whi.org. Upon submission of the DUA you will be granted 90 days of access to the data. When you are ready to begin your 90 days of access, you must contact helpdesk@whi.org to request your username and password. Extensions to this 90 day window will not be granted so please plan accordingly.

Lead authors please note: you must circulate all manuscript drafts, abstracts, press releases, etc. to all members of your writing group for input prior to submission. Authors are encouraged to check for existing literature in their area of interest. Failure to identify overlap could lead to cancellation of the paper, even if overlap is identified after proposal approval. When this document is submitted for P&P review as a manuscript, the committee requests that you send a line-numbered version of the paper. In addition, please include complete contact information (U.S. Postal address and e-mail address) for all lead authors on the face page of your manuscript.
Review 1:

Required changes:
Approve with required change that NSES be included as a covariate.

Review 2:

Comments:
This will be an important analysis and the WHI dataset is large enough to allow analysis of the health of preterm born adult women.

Required changes:
SES will be a very important confounder of this analysis, because low SES is associated with more preterm births and more CVD. The authors should use the variable NSES (neighborhood Socioeconomic status) that has been developed in the dataset to be a comprehensive variable to be used in analyses such as the current proposal.
Appendix B: Women’s Health Initiative Manuscript Proposal Application Form

(Manuscript III)

WHI MANUSCRIPT PROPOSAL APPLICATION FORM

DUE DATE: See WHI website for upcoming submission deadlines.
SUBMIT TO: P&P@WHI.org
REFER TO: Write a Paper Resources on whi.org.
GUIDELINES: - Cancer mortality and survival analyses generated from WHI data
- Post-intervention analyses of the original WHI trials
- Combined CT and OS data in observational analyses
- Body Composition Analysis
- Diet Dataset Documentation for guidelines and information about Dietary Quality Indices, FFQ Analysis of Folate, Biomarker Calibration Information, FFQ Diet-Disease Analysis, and FFQ Nutrient Database Estimations.

Section 1: GENERAL QUESTIONS (Required)

Today’s Date: 5/27/2021 Is this a resubmission to P&P? ☒ No
☐ Yes → Submit both:
3. Revised application form
   AND
4. Two copies of proposal (1 clean and 1 track changes).


22. Lead author
   Name: Pamela Brewer Phone: 401-327-5789
   Institution: University of Rhode Island Email: pamela_brewer@uri.edu

23. Are you any of the following? (mark all that apply)
   ☒ Pre-doc
   ☐ Post-doc
   ☐ Early Stage Investigator as defined by NIH?

24. Is this your first WHI Manuscript Proposal?
   ☒ No ☐ Yes

25. Are you currently leading any manuscript proposals that were approved by P&P >3 years ago?
   ☒ No ☐ Yes → Please explain.

26. Are you leading any draft manuscripts that were approved by P&P >1 year ago and have not yet been submitted to a journal for publication?
   ☒ No ☐ Yes → Please explain.
27. What is your affiliation to WHI?

☐ WHI Principal Investigator
☐ WHI Co-Investigator
☐ WHI Associate Member

☒ None of the above

WHI Sponsoring PI: Dr. Charles Eaton
☒ Check here to confirm that the Sponsoring PI has reviewed and approved this proposal.

Note: If the lead author is not a WHI Principal Investigator, Co-Investigator, or Associate Member, a Sponsoring PI is required. The Sponsoring PI must review and approve all materials before submission to P&P.

28. Co-authors

Co-author 1 name: Amy D’Agata
Co-author 1 email: amydagata@uri.edu

Co-author 2 name: Mary Roberts
Co-author 2 email: mary_roberts@brown.edu

Co-author 3 name: Mary Sullivan
Co-author 3 email: mcsullivan@uri.edu

Co-author 4 name: Charles Eaton
Co-author 4 email: cbeaton51@gmail.com

Note: The proposal may not have more than five total authors, including the lead author and the Sponsoring PI, or it will be returned for immediate revision. The P&P Committee Policies note exceptions to this rule. The lead author may add more co-authors after the proposal is approved.

Names of additional co-authors (if exceptions apply): Enter names of additional co-authors.

Section 2: DATA QUESTIONS (Required)

29. What WHI data are you using? (mark all that apply)

☒ Observational Study
☐ Clinical Trial (Hormone Therapy, Dietary Modification, Calcium/Vitamin D)

30. What is your primary outcome? Hypertension

31. What data source are you using to identify this outcome? (mark all that apply)

☐ Adjudicated outcomes
☒ Self-report
☐ Medicare/CMS data
☐ Other: Describe and justify this selection.

32. Are you using any of the following data sources for this proposal? (mark all that apply)

☐ National Death Index
☐ Supplemental Questionnaire (Form 156, Form 157, Form 158)
☐ WHI Ancillary Study (AS), Core Study (W), and/or BAA Study (if checked, please answer the next three questions)

iv. Please list the study numbers: Enter all applicable study numbers.

v. Was the source of funding for the study a commercial entity?

☐ No ☐ Yes
vi. Has all AS data, Core Study data, and/or BAA Study data been submitted to the CCC?

☐ No  ☐ Yes

**Note:** If you are using WHI AS data, it is strongly recommended that you include the study PI or a representative from the study on your writing group.

33. Will this proposal use data from studies other than WHI?

☒ No  ☐ Yes → List all cohorts: Enter all cohorts.

A **consortium/pooling project** is a research project that is developed by an organized group of scientific investigators representing various study cohorts and usually with an independent governance structure.

Answer the three questions below. If you answer yes to any of these questions, complete the [WHI Consortium/Pooling Project Application Form](#).

iv. Will the consortium/pooling project have an independent governance structure?

☐ No  ☐ Yes

v. Will the consortium/pooling project have a Publications and Presentations Committee?

☐ No  ☐ Yes

vi. Will the consortium/pooling project have an External Advisory Board?

☐ No  ☐ Yes

---

### Section 3: OTHER/MISCELLANEOUS (Required)

34. Use the [Excel spreadsheet with a listing of all papers/proposals](#) to identify potential overlap.

Specify what unique data will be added with this proposal.

Click or tap here to enter text.

**Note:** Failure to identify overlap could lead to cancellation of your paper, even if overlap is identified after your proposal is approved.

35. Please list at least 5 keywords: hypertension, hypothyroidism, rheumatoid arthritis, preterm-born adults, Women’s Health Initiative-OS

36. You are required to include power calculations in the proposal to demonstrate adequate power to conduct the analyses for each aim. Check to confirm this step is complete.

☒ Yes, power calculations are included.

37. Did this proposal stem from a discussion within a WHI Scientific Interest Group (SIG)?

☒ No  ☐ Yes (mark all that apply)

☐ Aging: Cognition & Functional Status  ☐ Nutrition/Energy Balance

☐ Bone/Fracture & Body Composition  ☐ Obesity & Diabetes

☐ Cancer  ☐ Physical Activity/Body Composition

☐ CVD (includes AF & HF sub-SIGs)  ☐ Physical & Built Environment

☐ Genetics, Proteomics & Biomarkers  ☐ Psychosocial & Behavioral Health

☐ Minority & Health Disparities
Note: Investigators are strongly encouraged to consult a SIG (if applicable) prior to submission to P&P. Proposals that benefit from SIG input tend to be stronger, which can result in quicker approval from P&P. Visit the WHI website for a list of SIG Chairs and their contact information.

38. What is your preference for where the analyses will be performed?  
☐ CCC Choose a rank.  ☐ Southeast RC Choose a rank.  
☐ Midwest RC Choose a rank.  ☒ Do your own Choose a rank.  
☐ Northeast RC Choose a rank.

Note: Please rank in order of preference if more than one is marked. Analyses performed at a Regional Center (RC) requires advance discussion with/permission from that RC. If you selected an RC as your preference, write the name of the analyst with whom you are collaborating: Mary Roberts

Section 4: FINAL ITEMS (Required)

39. Additional comments or information you would like the P&P to consider with your application.  
Enter comments.

40. Application Checklist  
☒ Completed application form with current date.  
☒ Proposal:  
• Not to exceed six pages, not including references or tables.  
• If this is a resubmission, submit two copies of the proposal (1 clean and 1 track changes).  
• A sample proposal is available for reference.

INTRODUCTION

Hypertension represents a major global health concern. Hypertension affects 26.4% of the global adult population and is the leading preventable risk factor for premature death and disability worldwide. More than 50% of older adults have three or more chronic co-existing conditions, increasing the complexity of care. Additionally, hypertensive individuals are associated with a greater number of concurrent conditions compared to normotensive individuals. Diabetes, coronary heart disease, and hyperlipidemia are the most common co-existing conditions associated with hypertension, while the literature is scarce in regards to less common conditions associated in hypertensive adults. Endocrine disorders such as hypo- and hyperthyroidism are often overlooked as contributors to the development of hypertension. Saito, Kunihiko, and Saruta (1983) confirmed after evaluating 477 women between the ages of 20 to 69 years with thyroiditis that hypertension (sustained BPs >160/95 mmHg) was significantly associated with hypothyroidism, and a reduction in blood pressure resulted with thyroid hormone replacement therapy. Klein & Ojamaa (2001) identified hyperthyroidism as a precursor to hypertension. Thyroid hormones have a profound effect on the cardiovascular system. Thyroid hormone imbalance, particularly hypothyroidism, directly alters cardiac function, resulting in decreased cardiac output, cardiac contractility, and heart rate. Hypothyroidism also impedes the release of endothelial derived relaxing factor (EDRF), which in turn excites the vascular smooth muscle cells, causing increased peripheral vascular resistance. These systemic hemodynamic and vascular tissue structural changes contribute to increased
peripheral vascular resistance and lipid dysregulation that activates atheromatous changes.\textsuperscript{8} Ryodi et al (2014) studied the association between thyroid dysfunction and cardiovascular disease and determined that individuals with thyroid dysfunction were 50% more likely to develop hypertension, coronary artery disease and heart failure, and experience cardiovascular and cerebrovascular events.\textsuperscript{9}

Another overlooked associated condition with hypertension is rheumatoid arthritis (RA). Up to 73\% of individuals with RA have hypertension, yet the underlying mechanisms are ill-defined.\textsuperscript{10-15} Several mechanisms are purported as causative factors for the pathogenesis of hypertension. The use of anti-inflammatory agents and disease-modifying drugs prescribed for RA treatment are known to increase blood pressure.\textsuperscript{12-15} Chronic inflammation, as in RA, is another. This cytokine mediated inflammation, along with increased oxidative stress, results in endothelial dysfunction, impaired vasodilatation, and increased arterial stiffness. Insulin resistance, also common in RA individuals, alters renal tubular sodium reabsorption, exacerbates endothelial dysfunction, and increases sympathetic activity; all contributing to elevated blood pressure. Manavathongchai et al. (2013) discredited the inflammatory connection, noting elevated homocysteine and leptin levels in individuals with RA. Homocysteine and leptin, known to impair vascular homeostasis, were determined to be the primary precursors to hypertension.\textsuperscript{11} Any one mechanism or combination of, coupled with physical limitations, synergistically contribute to the development of hypertension common to individuals with RA.\textsuperscript{10,11} Regardless of the pathogenesis, a strong correlation between increased cardiovascular morbidity, mortality, and RA exists with unrecognized and poorly managed hypertension at the forefront.\textsuperscript{10-15}

The link between preterm birth and hypertension is well-established, yet there is less data examining this association in females.\textsuperscript{16-19} Large studies have focused exclusively on males, hindering our ability to conclusively establish the association between preterm birth and hypertension among adult women.\textsuperscript{20} This proposed study is unique in that the study population of preterm born adult women are at greater risk for hypertension and hypertension related conditions such as thyroid disease and rheumatoid arthritis. The scope of this analysis is broader than previous studies as multiple correlations will be investigated and authenticated to one common, modifiable atherosclerotic cardiovascular disease (ASCVD) risk factor- hypertension. The method of analysis is exclusive in that it involves a careful examination of over 2,300 preterm born adult women and their health conditions compared to approximately 86,000 full term-born counterparts. Lastly, the gender prevalence of the proposed hypertensive related conditions (hypothyroid disease and rheumatoid arthritis) is more common in women than men.\textsuperscript{7,8,10,11,12} Hypertension portends significant cardiovascular morbidity and mortality. Ladak (2018) identified 86\% of individuals with RA and hypertension were neither treated nor referred for treatment.\textsuperscript{12} The findings of this study may contribute to heightened clinical awareness and close the gap on unrecognized and untreated hypertension in a susceptible population.\textsuperscript{12}

**OBJECTIVES**

The objectives of this study are four-fold.

**AIM 1:** To determine the prevalence and incidence of rheumatoid arthritis and its association with birth status (premature versus full term) in a cohort of post-menopausal women.
AIM 2: To determine the prevalence and incidence of hypothyroidism and its association with birth status (preterm versus full term) in a cohort of post-menopausal women.

AIM 3: To determine the incidence of hypertension and its association with prevalent rheumatoid arthritis (or hypothyroidism) and birth status (premature versus full term) in a cohort of post-menopausal women.

AIM 4: To explore the relationship between treatment for hypothyroid disease in preterm-born and term-born women and hypertension.

ANALYSIS PLAN

Study Population
Baseline data from the Women’s Health Initiative Observational Study will be used to examine the association between duration of gestation (preterm versus term) and the prevalence and incidence of two hypertension associated conditions. The Women’s Health Initiative Observation Study (OS) enrolled 93,676 participants, 93% self-reported duration of gestation at birth (n=88,343). Of these women, 97% (n=86,040) reported birth at full-term, while 2.4% (n=2,303) reported being born preterm (defined as 4 weeks or more premature; form 42, question #2). Table 1 shows the distributions of responses.

For gestational age, the variable will be defined as full term (i.e., 9-month pregnancy) and preterm (born 4 or more weeks premature). This will allow for assessment of both early birth and full-term birth as a risk for hypertension and the association with less common conditions.

Study Outcomes

Primary Outcomes

- **Hypertension**: will be measured as a self-reported history of physician diagnosed hypertension, age of onset, and/or the use of hypertensive medication.

- **Thyroid Dysfunction** will be measured as a self-reported history of hypothyroidism and the use of thyroid medication.

- **Rheumatoid arthritis** will be measured as a self-reported history of rheumatoid arthritis.

Secondary Outcomes

- The use of thyroid medication as captured on the medication form.

Variables

Exposure/Primary explanatory variable
• Preterm birth, 4 weeks or more preterm (FULLTERM)

Primary Outcome variables

• Hypertension: defined according to the Seventh Report of the Joint National Committee recommendation (2003) as >140/90 mmHg or the self-reported use of an antihypertensive medication.
  ▪ Prevalent hypertension: self-reported, physician diagnosed TREATED hypertension from FORM 30 (strict HTN definition)
  ▪ Incident hypertension: self-reported TREATED hypertension from FORM 33.

• Thyroid disease: the prevalence of hypothyroidism was identified at baseline. The incidence of hypothyroidism was captured at Year 3 and annually through Year 8/9. Reconciled thyroid medications were captured at baseline and Year 3.
  ▪ Prevalent hypothyroid disease: self-reported from FORM 30.
  ▪ Incident hypothyroid disease: self-reported from OS follow-up FORMS 143-148.

• Rheumatoid arthritis: the prevalence and incidence of rheumatoid arthritis was obtained through questionnaires asked at baseline and annually through Year 8/9 on the updated medical history questionnaire. Reconciled medications for the treatment of rheumatoid arthritis were captured at baseline and Year 3.
  ▪ Prevalent rheumatoid arthritis: self-reported from FORM 30.
  ▪ Incident rheumatoid arthritis: self-reported from FORM 33.

Secondary Outcome Variables

• Medication use

Confounders

• Age (AGE)
• Birth cohort (AGER)
• Race/ethnicity (RACE)
• US region of birth (BRTHREGN)
• Breastfed as infant (BRSTFED)

Covariates

• Marital status (MARITAL)
• Education (EDUC)
• Income level (INCOME)
• Physical activity (TEXPWK)
• Smoking (SMOKING)
• Alcohol consumption (ALCSWK)
• BMI (BMI)
Statistical Analysis

Analyses will be performed by preterm status using baseline data. Descriptive statistics by preterm status will be used (mean and standard deviation for continuous variables, and count and percentage for categorical variables) to summarize socio-demographic characteristics. Potential confounders will be determined based on the results of univariate analyses with a p-value <0.10. Person-years of follow-up for each participant will be based on time from enrollment to either outcome of interest, loss to follow-up, or death.

For **AIM 1**, logistic regressions will be used to examine the association of and birth status (term vs. preterm) with prevalent rheumatoid arthritis (RA) at baseline after adjusting for potential confounders such as age, birth cohort, race/ethnicity, and geographic region.

Cox Proportional Hazards models will be used to examine the association of birth status (term vs. preterm) with the development of incident rheumatoid arthritis in individuals free of prevalent RA. Model 1 will adjust for age and race. Further model building will include potential confounders and covariates as defined above.

For **AIM 2**, data will be analyzed similarly to AIM 1 except the outcome of interest is hypothyroid disease instead of RA.

In **AIM 3**, Cox Proportional Hazards models will be used to estimate the hazards ratio (HR) and 95% confidence intervals (CIs) for the effect of preterm status on incident hypertension stratified by prevalent RA. The incident HTN models will also be stratified by prevalent hypothyroid disease.

A sensitivity analysis will be performed for **AIM 4** to examine the association between hypothyroid disease treatment and hypertension (HTN) by preterm status. Both prevalent and incident HTN will be examined. Measures of blood pressure, types/counts of HTN treatment, and treated versus untreated HTN will be compared among those with prevalent hypothyroid disease by treatment and preterm status. ANOVA will be used for continuous variables and chi-square analysis for categorical comparisons.

Analyses will be conducted using SAS v9.4 (Cary, NC). A significance level of p ≤0.05 will be used for all analyses unless otherwise noted.

Power Calculation

WHI analysis cohort has median follow-up time 12.6 years with a maximum of 25.5 years. As of March 2020, the overall number of incident rheumatoid arthritis, hypothyroid disease, and hypertension cases in the sample are 4283, 6958, and 34,696, respectively. Using preterm status to determine the necessary sample size, a total number of events equal to 4160 with a 0.05 two-sided significance level will have 80% power to detect a constant hazard ratio (HR) of 1.29.21

Using proportions for prevalence estimates, the minimum detectable risk ratio (RR) for the sample cohort with a 0.05 two-sided significance level and 80% power is 1.11 for rheumatoid arthritis and 1.19 for hypothyroidism.22

Conclusion
We expect to find preterm-born women with a higher prevalence of hypertension and hypertension associated conditions such as hypothyroid disease and rheumatoid arthritis when compared to term born women. We also expect preterm-born women medically treated for thyroid dysfunction or rheumatoid arthritis to have higher blood pressures and earlier onset hypertension.

The results of this study will contribute to the body of knowledge surrounding prematurity across the lifespan. The findings may impact the screening and treatment approach for preterm-born young adults, honing earlier identification and more accurate diagnosis and a heightened awareness of hypertension risk factors, as well as hypertension associated conditions.

**Tables**

**Table 1: Self-Reported Birth Status**

<table>
<thead>
<tr>
<th>Total OS Population</th>
<th>93,676</th>
</tr>
</thead>
<tbody>
<tr>
<td>• OS participants missing or unknown GA data</td>
<td>5,333</td>
</tr>
<tr>
<td>• OS participants with personal GA data</td>
<td>88,343</td>
</tr>
<tr>
<td>• OS participants born Full term</td>
<td>86,040 (97.4%)</td>
</tr>
<tr>
<td>• OS participants born Preterm</td>
<td>2,303 (2.4%)</td>
</tr>
</tbody>
</table>

Gestational Age = GA

**Table 2: Sample characteristics by preterm status**

<table>
<thead>
<tr>
<th>Sociodemographic Variables</th>
<th>Preterm population (N=2303)</th>
<th>Full Term population (N=86040)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
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<tr>
<td>Black</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
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<td></td>
<td></td>
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<tr>
<td>Education level</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt; High school graduate</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>High school graduate</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>College graduate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household income level</td>
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<td></td>
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<td>$50,000 or greater</td>
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<td></td>
</tr>
<tr>
<td>$20,000 - &lt;$50,000</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; $20,000 per year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing/Don't Know</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status/Partnered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S. Region of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sociodemographic Variables</td>
<td>No prevalent RA (N=83676)</td>
<td>Prevalent RA (N=4667)</td>
<td>P value</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------------------</td>
<td>-----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Age</td>
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</tr>
<tr>
<td>Race/ethnicity</td>
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<tr>
<td>White</td>
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<tr>
<td>Black</td>
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<tr>
<td>Hispanic</td>
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<td>Asian</td>
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<td>Other</td>
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<tr>
<td>Education level</td>
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<tr>
<td>&lt; High school graduate</td>
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<tr>
<td>&lt;$20,000 per year</td>
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<tr>
<td>Missing/Don't Know</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Marital status/Partnered</td>
<td></td>
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</tr>
</tbody>
</table>

Table 3a. Sample characteristics by prevalent RA and prevalent hypothyroidism (Aim 1/Aim 2)
<table>
<thead>
<tr>
<th>U.S. Region of birth</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Midwest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>West</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breastfed as infant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Insurance Coverage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full term</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lifestyle Variables**

<table>
<thead>
<tr>
<th>Smoking Status</th>
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</thead>
<tbody>
<tr>
<td>Never Smoked</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Past Smoker</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Current Smoker</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age started smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Smoker/cigs per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Smoker/years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
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<tr>
<td>Drinking status</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
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<tr>
<td>Body Mass Index (BMI)</td>
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<td>25.0-29.9</td>
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<td>35.0+</td>
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</tr>
<tr>
<td>Waist circumference, cm</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Waist/Hip Ratio</td>
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</tbody>
</table>

---

### Table 3b. Sample characteristics by incident RA and incident hypothyroidism (Aim 1/Aim 2)

<table>
<thead>
<tr>
<th></th>
<th>No incident RA (N=79393)</th>
<th>Incident RA (N=4283)</th>
<th>p value</th>
<th>No incident hypothyroidism (N=67761)</th>
<th>Incident hypothyroidism (N=6958)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
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<td>&lt; $20,000 per year</td>
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<td>Breastfed as infant</td>
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<td>Health Insurance Coverage</td>
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<tr>
<td>Preterm Status</td>
<td>Preterm</td>
<td>Full term</td>
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**Lifestyle Variables**

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Never Smoked</th>
<th>Past Smoker</th>
<th>Current Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age started smoking</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Current Smoker/cigs per day</td>
<td></td>
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<tr>
<td>Current Smoker/years</td>
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<tr>
<td>Alcohol consumption</td>
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<tr>
<td>Drinking status</td>
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<tr>
<td>Physical activity</td>
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<tr>
<td>Body Mass Index (BMI)</td>
<td></td>
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<tr>
<td>BMI Category</td>
<td>&lt; 25.0</td>
<td>25.0-29.9</td>
<td>30.0-34.9</td>
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<td>35.0+</td>
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<td>Waist circumference, cm</td>
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<tr>
<td>Waist/Hip Ratio</td>
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</table>

**Table 4. Logistic models by preterm status for prevalent RA and prevalent hypothyroidism (Aim 1/Aim 2)**

<table>
<thead>
<tr>
<th>Rheumatoid Arthritis</th>
<th>Full Term</th>
<th>Preterm</th>
</tr>
</thead>
<tbody>
<tr>
<td># cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence rate (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>(ref)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>(ref)</td>
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<tr>
<td>Model 3</td>
<td>(ref)</td>
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<table>
<thead>
<tr>
<th>Hypothyroidism</th>
<th>Full Term</th>
<th>Preterm</th>
</tr>
</thead>
<tbody>
<tr>
<td># cases</td>
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<tr>
<td>Prevalence rate (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td></td>
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</table>
Table 5: Cox models by preterm status for incident RA and incident hypothyroidism (Aim 1/Aim 2)

<table>
<thead>
<tr>
<th></th>
<th>Full Term</th>
<th>Preterm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td># cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total # years follow-up</td>
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<td></td>
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<tr>
<td>Age -adjusted incidence rate (95% CI)</td>
<td></td>
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<tr>
<td>Cox Proportional Hazards Model (95% CI)</td>
<td></td>
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<tr>
<td>Model 1</td>
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<td>Model 2</td>
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<tr>
<td>Hypothyroidism</td>
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<tr>
<td># cases</td>
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<tr>
<td>Total # years follow-up</td>
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<tr>
<td>Age -adjusted incidence rate (95% CI)</td>
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<tr>
<td>Cox Proportional Hazards Model (95% CI)</td>
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<td>Model 1</td>
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<td>Model 2</td>
<td>(ref)</td>
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<tr>
<td>Model 3</td>
<td>(ref)</td>
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</tbody>
</table>

Model 1: adjusted for age, race.
Model 2: age, race, income, education, marital status, region of birth, breastfed as infant.
Model 3: model 2+ all covariates.

Table 6: Sample characteristics by incident HTN (Aim 3)

<table>
<thead>
<tr>
<th>Sociodemographic Variables</th>
<th>No incident HTN (N=31741)</th>
<th>Incident HTN (N=34696)</th>
<th>P value</th>
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<td>Education level</td>
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<td>&lt; $20,000 per year</td>
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<tr>
<td>Marital status/Partnered</td>
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<td>U.S. Region of birth</td>
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<td>Health Insurance Coverage</td>
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<td><strong>Exposure Variables</strong></td>
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<td>Current Smoker/cigs per day</td>
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<td>Current Smoker/years</td>
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<td>Alcohol consumption</td>
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<td>Waist/Hip Ratio</td>
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Table 7. Effect modification – HR (95% CI) for Incident Hypertension (Aim 3)

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<td>Preterm</td>
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<tr>
<td>Total # years follow-up</td>
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<tr>
<td>Age-adjusted incidence rate (95% CI)</td>
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**Cox Proportional Hazards Ratio (95% CI)**

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</thead>
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<tr>
<td>Age-adjusted incidence rate (95% CI)</td>
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</tbody>
</table>

**Model 2**: age, race, income, education, marital status, region of birth, breastfed as infant.

**Model 3**: model 2+ other covariates.

Table 8: Hypertension characteristics by preterm status and prevalent hypothyroid treatment (Aim 4)

<table>
<thead>
<tr>
<th></th>
<th>Preterm population with untreated hypothyroidism</th>
<th>Preterm population with treated hypothyroidism</th>
<th>Full term populations with untreated hypothyroidism</th>
<th>Full term population with treated hypothyroidism</th>
<th>P value</th>
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</thead>
<tbody>
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<td>No Prevalent HTN n</td>
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<tr>
<td>At Enrollment</td>
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<td></td>
<td></td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
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<td></td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
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<td></td>
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<tr>
<td>At Year 3</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>Diastolic blood pressure (mmHg)</td>
<td>Prevalent HTN</td>
<td>n</td>
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<tr>
<td>At Enrollment Systolic blood pressure (mmHg)</td>
<td>Diastolic blood pressure (mmHg)</td>
<td>Age onset</td>
<td>Treatment/Rx</td>
<td></td>
<td></td>
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<tr>
<td>At Year 3 Systolic blood pressure (mmHg)</td>
<td>Diastolic blood pressure (mmHg)</td>
<td>Age onset</td>
<td>Treatment/Rx</td>
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<td>Incident HTN</td>
<td>n</td>
<td>At Enrollment Systolic blood pressure (mmHg)</td>
<td>Diastolic blood pressure (mmHg)</td>
<td>At Year 3</td>
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<td>Systolic blood pressure (mmHg)</td>
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<td>Diastolic blood pressure (mmHg)</td>
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<td>Age onset</td>
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<tr>
<td>Treatment/Rx</td>
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<tr>
<td>Agent/Class</td>
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</tbody>
</table>
REFERENCES


Appendix B.1: Women's Health Initiative Manuscript Proposal 4495 Approval

Letter

(Manuscript III)

MEMORANDUM

Date: June 11, 2021

To: Pamela Brewer
    Charles Eaton

From: Lindsey Bull
    P&P Committee Coordinator

Subject: Manuscript Proposal 4495 – An exploratory analysis of less common hypertension associated conditions in preterm-born adult women

Congratulations! The Publications and Presentations (P&P) Committee has approved this proposal with required changes. Please see the reviews at the end of this memo for details. Please note: you are not required to submit a revised proposal for additional review unless you would like to dispute the required changes.

WHI has a number of active Scientific Interest Groups (SIGs) that bring together investigators in scientifically themed areas. The SIGs can be an excellent resource for authors as they develop their manuscripts. P&P urges you to present your analyses to a SIG and solicit their input. If you are interested in working with a SIG, please visit the SIG page on the WHI website and contact the SIG Chair(s) relevant to your topic.

Writing group nominations will be held soon. The CCC will send you a list of nominees to review when the nomination period closes. If you have any questions about the steps involved in the development of your manuscript, please refer to the P&P Policy.

Any BAA PI, AS PI, or lead author on an approved manuscript proposal seeking access to the WHI data must sign a Data Use Agreement (DUA) with a WHI PI. Please fill out and return the WHI DUA to the WHI helpdesk at helpdesk@whi.org. Upon submission of the DUA you will be granted 90 days of access to the data. When you are ready to begin your 90 days of access, you must contact helpdesk@whi.org to request your username and password. Extensions to this 90 day window will not be granted so please plan accordingly.

Lead authors please note: you must circulate all manuscript drafts, abstracts, press releases, etc. to all members of your writing group for input prior to submission. Authors are encouraged to check for existing literature in their area of interest. Failure to identify overlap could lead to cancellation of the paper, even if overlap is identified after proposal approval.
When this document is submitted for P&P review as a manuscript, the committee requests that you send a line-numbered version of the paper. In addition, please include complete contact information (U.S. Postal address and e-mail address) for all lead authors on the face page of your manuscript.

Review 1:

Comments:
Please see attached comments in the proposal. Does one expect to see increased rates of hypothyroidism and RA in participants who were preterm? There is no reference given. Are these associations part of what you are trying to prove?

Required changes:
Please address the comments in the attached proposal.

There was some confusion about what is known, are hypothyroidism and RA known to be increased in men or women who were born prematurely? I would think that you want to state that BP should get more attention and screening in those born prematurely if they also have these 2 conditions.

Review 2:

Recommended changes:
1. Be sure to adhere to the recent WHI document on Race and Ethnicity
2. Remove last line in Table 1 and insert it under the table
The first set of questions asks about your birth and when you were a baby.

1. When you were born, about how much did you weigh? (Give your best guess.)

   Less than 6 pounds  6 pounds to 7 pounds, 15 ounces  8 pounds to 9 pounds, 15 ounces  10 or more pounds  Don't know
   □ 1  □ 2  □ 3  □ 4  □ 5

2. When you were born, were you:
   Full term (pregnancy lasted about 9 months)  4 or more weeks premature  Don't know
   □ 1  □ 2  □ 3

3. When you were born, were you a twin or triplet?
   □ 0 No □ 1 Yes

4. When you were a baby, did your mother breast feed you?
   □ 0 No □ 1 Yes □ 2 Don't know
Appendix D: The Race/Ethnicity of the WHI-OS

Race/Ethnicity of Observational Study

- Am Indian/Alaskan: 1324
- Asian/Pacific Islander: 2671
- Non-Hispanic Black/AA: 7635
- Hispanic/Latina: 3609
- Non-Hispanic White: 78016
- Unknown: 421

Note. Forty clinical enrolling centers with recruiting sites in 23 states across the U.S. were involved in the WHI. A 20% minority enrollment rate was set for all components of the studies to accurately represent the proportion of minorities within the study demographic. Ten minority recruitment sites were designated to find ways to overcome racial and ethnic barriers to achieve a representative sample of minority women.
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