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The co-occurrence and cumulative prevalence of hypertension, rheumatoid arthritis, and hypothyroidism in preterm-born women in the Women's Health Initiative

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Original Article

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Abstract

Emerging evidence suggests that preterm-born individuals (<37 weeks gestation) are at increased risk of developing chronic health conditions in adulthood. This study compared the prevalence, co-occurrence, and cumulative prevalence of three female predominant chronic health conditions – hypertension, rheumatoid arthritis [RA], and hypothyroidism – alone and concurrently. Of 82,514 U.S. women aged 50–79 years enrolled in the Women's Health Initiative, 2,303 self-reported being born preterm. Logistic regression was used to analyze the prevalence of each condition at enrollment with birth status (preterm, full term). Multinomial logistic regression models analyzed the association between birth status and each condition alone and concurrently. 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 coexisting conditions [aOR 1.69, 95% CI (1.14, 2.51)], followed by hypertension and RA [aOR 1.48, 95% CI (1.20, 1.82)]. The aOR for all three conditions was 1.69 (1.22, 2.35). Perinatal history is pertinent across the life course. Preventive measures and early identification of risk factors and disease in preterm-born individuals are essential to mitigating adverse health outcomes in adulthood.

Introduction

Preterm birth (<37 weeks gestation) affects 10% of U.S. births and up to 18% of all births worldwide.[1,2] Increasing preterm birth survival rates has introduced a new population of survivors reaching adulthood, making it critically important to understand the long-term health consequences of preterm birth.[3] Growing evidence associates preterm birth with increased risk for the development of hypertension and other chronic conditions including diabetes, metabolic syndrome, and asthma.[4-11] To date, most preterm-adult disease prevalence studies terminate at early adulthood and are conducted in Nordic European nations with universal health care and less racial diversity, perhaps revealing better outcomes than in the U.S.[12-14] Consequently, it is not known whether chronic health conditions persist, change, occur in higher frequency, and with multiple conditions in preterm-born mid-late U.S. adults. Since preterm birth history is widely known by individuals and their families, early risk is known and can be monitored from infancy to adulthood.

Hypertension, the strongest cardiovascular disease (CVD) risk factor acquired during life, is the most prominent health condition found in preterm-born adults.[5,6,9,15,16] Women, representing 51% of the hypertensive population, experience a steeper increase in blood pressure beginning in the 3rd decade of life, are predisposed to increased CVD risk at lower blood pressure levels, and develop adverse pathophysiologic cardiovascular consequences compared to men.[17-19] Hypertension is highly prevalent among individuals with rheumatoid arthritis

(RA); a comorbidity three times more common in women than men.[20-22] Furthermore, individuals with hypothyroidism are predisposed to the development of hypertension.[23,24] Hypothyroidism affects approximately 30 million people aged ≥18 years in the U.S. and is 5–10 times more likely to occur in women compared to men.[25,26] Studies on the prevalence of concurrent hypertension, RA, and hypothyroidism are limited. Huang et al.[27] found the incidence of hypothyroidism to be 1.74-fold higher in the RA sufferers, hypertension to be the greatest comorbid CVD risk factor in RA individuals, and the risk of hypothyroidism to be increased further in individuals with hypertension. These findings are based on the general adult population. The increased risk of chronic disease multimorbidity in adults born preterm, and preterm-born women has been minimally studied.[10,11]

The underpinnings of the Developmental Origins of Health and Disease (DOHaD) theory substantiate the greater likelihood of multimorbidity in preterm-born adult women.[28] Disrupted organ development associated with preterm birth, together with early-life factors and environmental exposures that precipitate epigenetic modifications, is the basis for this investigation of hypertension and two prominent related conditions in women, RA and hypothyroidism.[21,22,25,27-29] The strong associative evidence of hypertension with RA and hypothyroidism occurring simultaneously supports the rationale of a higher prevalence of the same three conditions in adult women born preterm, an already susceptible population.[10,11] 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 co-occurrence and cumulative prevalence of these three conditions are examined.

The three study aims comparing term-born to preterm-born adult women were to (1) evaluate the prevalence of each condition alone; (2) estimate the co-occurrence of two and three conditions; and (3) determine the cumulative prevalence of each condition alone and concurrently. To answer these aims, 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 women.[30,31]

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 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.[30,31] Briefly, 161,608 women were enrolled in three overlapping clinical trials (WHI-CT, $n = 67,932$) or the longitudinal Observational Study (WHI-OS, $n = 93,676$).[30,31]

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 (Fig. 1).

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*, 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) were not collected after 2005 due to the removal of RA from subsequential 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 from enrollment were categorized as sociodemographic, lifestyle, and risk factors. Selected sociodemographic covariates included race/ethnicity, education level (four categories ranging from < high school graduate to college graduate), income level (three 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, and current), physical activity (inactive, low, moderate, and 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 (Table 1).[31]

Ethical considerations

Participants provided written consent at the time of enrollment, and ethics approval was granted by each enrolling center's Institutional Review Board.[30,31]

Statistical analyses

Analyses were performed by birth status (preterm, 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. For continuous variables we looked at the difference in birth status using one-way ANOVA. For categorical variables, we examined the difference in birth status using chi-square analysis. Covariates selected for inclusion in modeling were known risk factors for hypertension, RA, and hypothyroidism. Demographic

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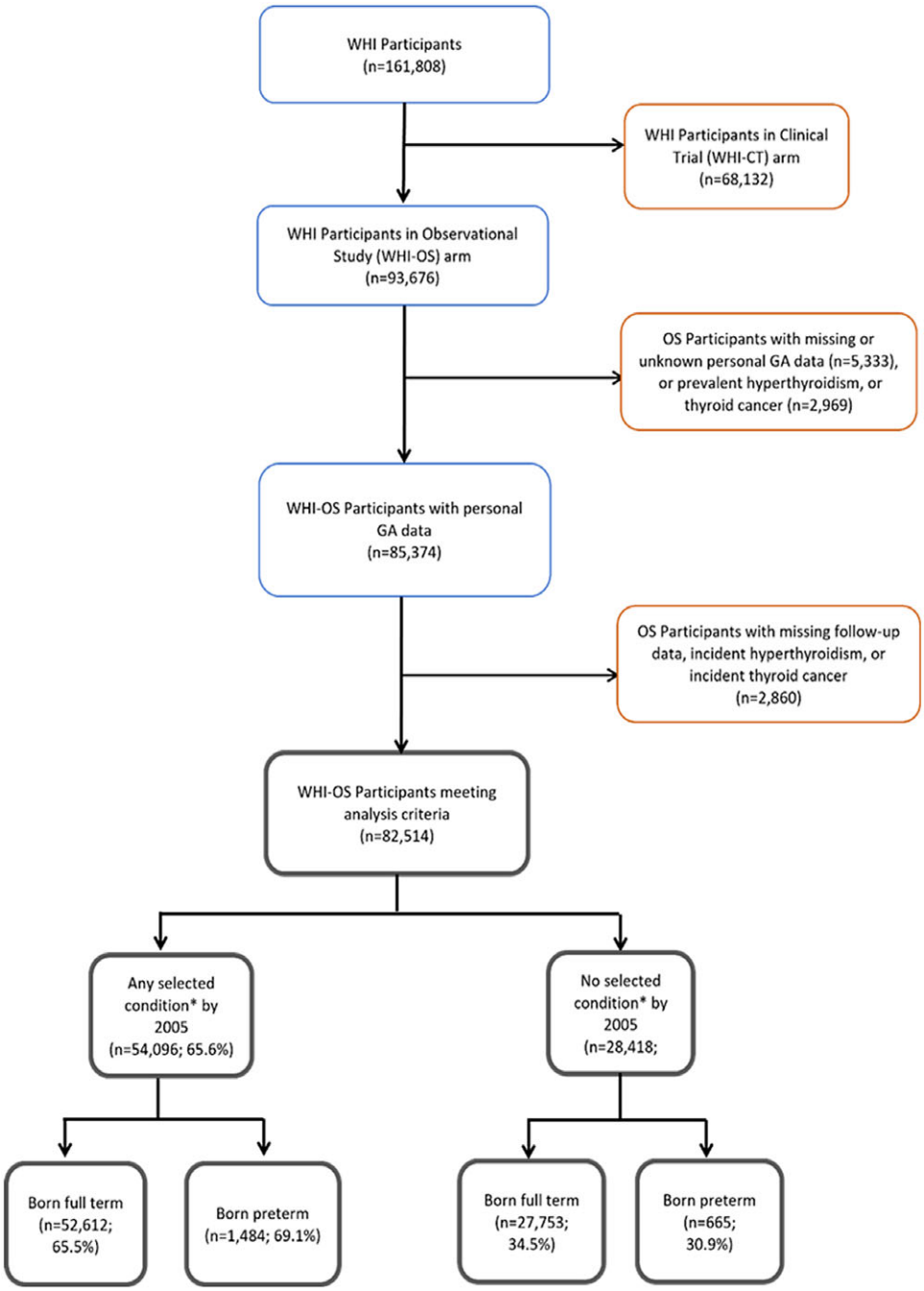

Fig. 1. Prevalence of selected condition by 2005.
WHI, women's health initiative; OS, observational study; GA, gestational age; *, selected condition consist of any of the following: hypertension, hypothyroidism, and/or rheumatoid arthritis.

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 conditions were analyzed using logistic regression models and included the other conditions as covariates.

Modeling of the combined diagnosis outcome was configured in two ways. The first outcome configuration summed the presence of the three diagnoses (conditions) under examination per participant and ranged from 0 to 3 (no diagnosis to all three diagnoses). The second outcome configuration examined the actual diagnoses 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 no diagnosis (no condition) as the reference. Odds ratio (OR) and their associated 95% confidence intervals estimated the association of diagnosis 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

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

CUMULATIVE PREVALENCE BY 2005			
	Birth Status		
	Full term (*n* = 80,365)	**Preterm (*n* = 2,149)**	*P value*
	***n* = 82,514**		
Demographic and lifestyle factors			
Age (y) (mean, SD)	63.5 (7.4)	62.0 (7.3)	<0.001
Age cohort (n, %)			<0.001
<50–59	25,906 (32.2)	882 (41.0)	
60–69	35,352 (44.0)	886 (41.2)	
70–79+	19,107 (23.8)	381 (17.7)	
Race (n, %)			0.220
American Indian/Alaska	264 (0.3)	9 (0.4)	
Asian	2113 (2.6)	44 (2.1)	
Native Hawaiian/Other PI	54 (0.1)	0 (0.0)	
Black	6189 (7.7)	163 (7.6)	
White	69,174 (86.1)	1879 (87.4)	
More than one	823 (1.0)	17 (0.8)	
Unknown/Not reported	1748 (2.2)	37 (1.7)	
Ethnicity (n, %)	3396 (4.2)	81 (3.8)	0.393
Education level (n, %)			0.001
<high school graduate	3897 (4.9)	77 (3.6)	
High school graduate	12,775 (15.9)	291 (13.5)	
Some college	28,916 (36.0)	783 (36.4)	
College graduate	34,148 (42.5)	979 (45.6)	
Missing	629 (0.8)	19 (0.9)	
Income level (n, %)			0.447
$50,000 or greater	30,794 (38.3)	851 (39.6)	
$20,000–<$50,000	32,270 (40.2)	858 (39.9)	
< $20,000 per year	11,549 (14.4)	302 (14.1)	
Missing/Don't Know	5752 (7.2)	138 (6.4)	
Partnered (n, %)	49,997 (62.5)	1372 (64.1)	0.122
Region of birth (n, %)			0.925
Not born in US	5670 (7.1)	151 (7.1)	
Northeast	22,237 (27.9)	579 (27.1)	
South	23,575 (29.6)	635 (29.7)	
Midwest	17,439 (21.9)	472 (22.1)	
West	10,770 (13.5)	299 (14.0)	
Smoking status (n, %)			0.056
Never	40,334 (50.9)	1106 (52.4)	
Past Smoker	34,063 (43.0)	858 (40.6)	
Current	4904 (6.2)	148 (7.0)	
Physical activity (mean, SD)	13.5 (14.5)	13.4 (15.4)	0.878
Physical activity level (n, %)			0.208

(*Continued*)

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Table 1. (*Continued*)

CUMULATIVE PREVALENCE BY 2005			
	Birth Status		
	Full term (*n* = 80,365)	**Preterm (*n* = 2,149)**	*P value*
	***n* = 82,514**		
Inactive: 0–1.7 MET hrs/wk	16,872 (21.1)	483 (22.6)	
Low: 1.8–8.3 MET hrs/wk	20,946 (26.2)	578 (27.0)	
Moderate: 8.4–20 MET hrs/wk	22,751 (28.5)	584 (27.3)	
High: >20 MET hrs/wk	19,392 (24.3)	497 (23.2)	
Alcohol svgs/wk (mean, SD)	2.55 (5.22)	2.61 (5.33)	0.578
Medical History			
Body mass index [BMI] (mean, SD)	27.5 (6.8)	28.0 (6.7)	0.002
Height (cm) (mean, SD)	161.7 (6.8)	161.3 (6.6)	0.003
Short stature (HT <5 ft) (n, %)	5695 (7.1)	168 (7.9)	0.196
Systolic BP (mmHg) (mean, SD)	127 (17.9)	126 (17.9)	0.508
Diastolic BP (mmHg) (mean, SD)	75 (9.3)	75 (9.3)	0.099
Diabetes (n, %)	3185 (4.0)	122 (5.7)	<0.001
Hypertension (n, %)	26,308 (32.7)	789 (36.7)	<0.001
Hyperlipidemia (n, %)	11,939 (14.9)	324 (15.1)	0.776
Angina (n, %)	4488 (5.6)	138 (6.5)	0.087
Atrial fibrillation (n, %)	3645 (4.6)	102 (4.8)	0.648
TIA (n, %)	1837 (2.3)	53 (2.5)	0.586
Heart failure (n, %)	1098 (1.4)	36 (1.7)	0.225
Breastfed as infant (n, %)	48,091 (59.9)	941 (43.9)	<0.001
HTN age onset (n, %)			<0.001
No HTN	53,959 (67.5)	1355 (63.5)	
Less than 20	230 (0.3)	16 (0.8)	
20–29 years	739 (0.9)	25 (1.2)	
30–39 years	2282 (2.9)	71 (3.3)	
40–49 years	5978 (7.5)	197 (9.2)	
50–59 years	9303 (11.6)	286 (13.4)	
60–69 years	5935 (7.4)	153 (7.2)	
70 years or older	1502 (1.9)	30 (1.4)	

WHI-OS = Women's Health Initiative Observational Study; y = year(s); n = number; SD = standard deviation; cm = centimeters; mmHg = millimeters of mercury; PI = Pacific Islander; HT = height; MET = metabolic equivalent for task; hrs/wk=hours per week; TIA = transient ischemic attack; HTN = hypertension. One-way ANOVA was used to determine the difference in birth status for continuous variables and chi-square analysis was used to examine the difference in birth status for categorical variables.

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 of 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 Fig. 2, hypertension was the most prevalent independent condition (52.3%), followed by hypothyroidism (22.0%) and RA (9.9%) in the full cohort of WHI-OS participants ($n = 82,514$). Hypertension and hypothyroidism were the most common comorbidities (11.8%), followed by hypertension and RA (6.0%). The co-occurrence of all three conditions was 1.4% for the WHI-OS participants.

For study aim 1, 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

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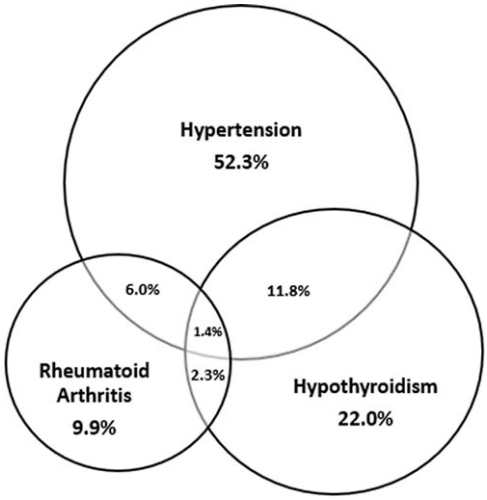

Fig. 2. Unadjusted rates of cumulative prevalent condition at study's end (2005).

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 diagnosis, corrected for the other conditions as covariates by birth status, is shown in Table 2.

The cumulative prevalence count of the three conditions for birth status, using full term women as the reference is depicted in Table 3. As shown, preterm-born women were at a greater risk for morbidity and multimorbidity. For aim 2, the actual diagnosis combinations are shown in Table 4. Women born preterm were found to be at an increased risk for hypertension, RA, and hypothyroidism, alone, concomitantly, and in any combination compared to women born full term (Table 4 and Fig. 3). 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 diagnosis combinations (aim 3), preterm-born women were 69% more likely to have RA and hypothyroidism [aOR 1.69 (1.14, 2.51)], 48% more likely to have RA and hypertension [aOR 1.48 (1.20, 1.82)], and 22% more likely to have hypertension and hypothyroidism [aOR 1.22 (1.04, 1.43)]. 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 comorbidities in the general population, but not in preterm-born adults to our knowledge. Our findings concur with research of adults born preterm having an increased risk of elevated blood pressure.[4,32-40] We found preterm-born women of the WHI-OS had a 20% higher risk for the development of hypertension. Their hypertension onset was reported at a younger age and required more medication for control (Table 1). International studies have reported SBP 2–8 mmHg higher, greater 24-hour variability in those born preterm starting as young as six years of age, and more antihypertensive agents for blood pressure control compared to hypertensive full-term peers.[4-6,39] However, the lack of comparative studies in older preterm-born adults hinders our understanding of the life trajectory and cardiovascular consequences of early-onset hypertension.

Our examination of RA in preterm-born adult women found preterm birth associated with a 24% greater likelihood of RA. When paired with a comorbidity such as hypertension or hypothyroidism, prematurity resulted in a 40–75% greater likelihood of RA. Few studies have explored this association and those that did found low birth weight and preterm birth associated with a reduced risk of RA.[41-43] In one study, the sample size was small ($n = 15$), and the OR was nonsignificant 1.4 (0.7, 3.0).[43] Another found low birth weight (<3000 g) and preterm birth (gestational age ≤37 weeks) were not statistically associated with the development of RA [OR 0.6 (0.7, 1.0)].[41] Similar results for women [RR 1.1 (0.8, 1.5)] were found by Simard et al.[44] in the Nurses' Health Study, a comparable sized study to the WHI. It is important to note that in these cited investigations, the cut-off points or references defining preterm status differed from the accepted definitions. For instance, in Simard et al.'s[44] study preterm birth was defined as a birth <38 weeks gestation and Carlens et al.'s[41] definition of low birth weight was <3000 g rather than <2500 g as defined by the World Health Organization.[45,46] In short, there are no large-scale, longitudinal studies of preterm-born adults to compare our RA findings.

Research on hypothyroidism and preterm birth have resulted in variable findings.[12,47-49] Small sample populations have limited the ability to discern an association between prematurity and underactive thyroid development.[12] An evaluation of 27,935 young adults born preterm (23–32 weeks) found preterm birth associated with an increased risk (aOR 1.59, 95% CI [1.18–2.14]) of pharmacologically treated hypothyroidism, independent of fetal growth.[12] Our findings align with this literature. The WHI-OS preterm-born adult women were on average 20% more likely to have hypothyroidism, approximately 30% more likely to have hypothyroidism paired with hypertension, and 70% more likely to have hypothyroidism and rheumatoid arthritis.

In summary, our findings add to the literature associating preterm birth with a higher prevalence of chronic disease comorbidity and multimorbidity. The increased awareness of multimorbidity in preterm-born adult women, presently non-existent, is necessary as the large and growing preterm-born population age into mid-late adulthood. Importantly, each condition examined in this study independently increases the risk for CVD, and as high as a fourfold increased risk when any combination of these conditions occur concomitantly.[50] Recognition and treatment of these co-occurring conditions and CVD risk factors may be crucial in reducing CVD in women.

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 conditions of study, were included in the analysis. Notably, studies of multimorbidity in aging preterm-born individuals are limited.

Self-report data, specifically in regard to birth status and the prevalence of each condition limits our findings. Birth certificates

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Table 2. Adjusted odds ratio with 95% confidence intervals from logistic regression model for individual diagnoses by birth status

	Birth Status	Total N	Age Adjusted	Socio-demographics (1)	Lifestyle (2)	Risk Factors (3)	Fully Adjusted (4)
Any RA diagnosis*	FT	7,909	(ref)	(ref)	(ref)	(ref)	(ref)
	PT	252	1.23 (1.07, 1.40)	1.27 (1.11, 1.45)	1.25 (1.09,1.43)	1.24 (1.08,1.42)	1.28 (1.12,1.47)
Any Hypothyroidism diagnosis**	FT	17,620	(ref)	(ref)	(ref)	(ref)	(ref)
	PT	527	1.18 (1.07, 1.31)	1.15 (1.04, 127)	1.16 (1.05, 1.28)	1.17 (1.06, 1.29)	1.12 (1.01, 1.24)
Any Hypertension diagnosis***	FT	42,014	(ref)	(ref)	(ref)	(ref)	(ref)
	PT	1,170	1.17 (1.07, 1.28)	1.20 (1.09, 1.31)	1.15 (1.05, 1.26)	1.15 (1.05, 1.26)	1.14 (1.04, 1.26)

N = number; reference group (ref) = women born full term; FT = full-term born women; PT = preterm-born women; RA = rheumatoid arthritis.
(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 hypothyroidism and hypertension as covariates; **Hypothyroidism models also include indicator variables for RA and hypertension as covariates; ***Hypertension models also include indicator variables for RA and hypothyroidism as covariates.

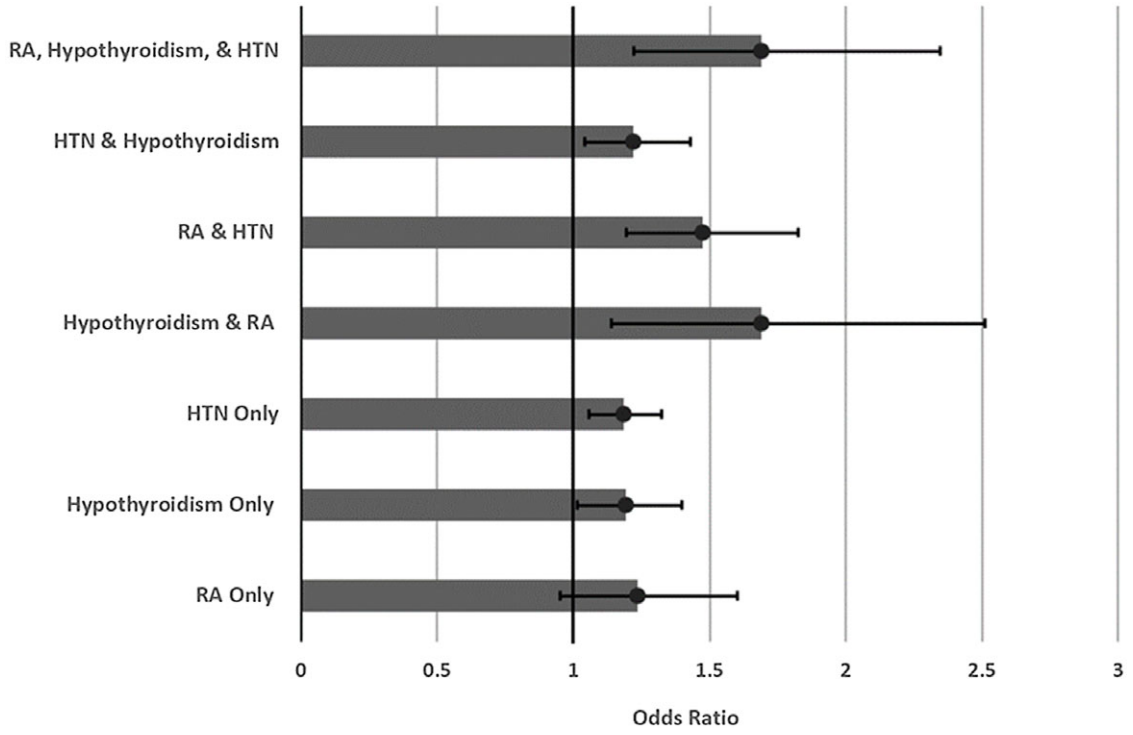

Fig. 3. Fully adjusted odds ratio and 95% confidence intervals for preterm-born women.
HTN, hypertension; RA, rheumatoid arthritis; reference group = women born full term. Fully adjusted model covariates include age, race/ethnicity, education, income, region of birth, smoking status, physical activity, alcohol intake, BMI, short stature, diabetes, hyperlipidemia, and breastfed as infant.

and birth registries are the most reliable birth data collection methods, while medical records are for diagnosis of disease or condition. Without documented birth records, the self-report of a woman's own gestational age is a weakness. However, the correlation between maternal recall and the accuracy of childbirth has been found to be as high as 89%, particularly when they occurred at earlier gestational ages.[51-53] Other limitations include cautious interpretation of the data when the subsample size was small, an incorrect self-reported condition as other conditions may resemble RA, and the inability to adjust for all covariates.[54]

Conclusion

Preterm birth was significantly associated with higher risks for hypertension, RA, and hypothyroidism, alone and concomitantly in a national U.S. sample of preterm-born postmenopausal women. To our knowledge, this is the first known study of its kind to evaluate the association between birth status and three CVD risk conditions concurrently in preterm-born adults over 50 years of age. This research provides additional evidence regarding the role of early developmental phenotypes in the development of later-life

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Table 3. Adjusted odds ratio with 95% confidence interval from multinomial logistic regression model for the cumulative diagnosis count for preterm-born women

	Total N		Age Adjusted	Socio-demographic[1]	Lifestyle[2]	Risk Factors[3]	Fully Adjust[4]
	FT	PT					
No diagnosis	27,753	665	(ref)	(ref)	(ref)	(ref)	(ref)
One diagnosis	38,769	1,060	1.22 (1.11, 1.35)	1.23 (1.12, 1.36)	1.20 (1.08, 1.33)	1.20 (1.09, 1.33)	1.18 (1.07, 1.31)
Two diagnoses	12,755	383	1.38 (1.22, 1.57)	1.40 (1.23, 1.60)	1.34 (1.17, 1.53)	1.36 (1.19, 1.55)	1.31 (1.15, 1.51)
Three diagnoses	1,088	41	1.75 (1.27, 2.42)	1.73 (1.25, 2.39)	1.75 (1.27, 2.42)	1.71 (1.24, 2.36)	1.70 (1.22, 2.35)

N = number; reference group (ref) = women born full term; FT = full-term born women; PT = preterm-born women.
(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 4. Adjusted odd ratio with 95% confidence interval from multinomial logistic regression model for diagnosis combinations for preterm-born women

Number of Diagnosis(es)		Total N		Age Adjusted	Socio-demographic[1]	Lifestyle[2]	Risk Factors[3]	Fully Adjusted[4]
		FT	PT					
No diagnosis		27,753	665	(ref)	(ref)	(ref)	(ref)	(ref)
One Diagnosis	RA Only	2,388	69	1.24 (0.96, 1.59)	1.24 (0.96, 1.60)	1.26 (0.98, 1.63)	1.24 (0.96, 1.59)	1.24 (0.95, 1.60)
	Hypothyroidism Only	7,498	217	1.24 (1.06, 1.45)	1.22 (1.05, 1.43)	1.21 (1.03, 1.42)	1.22 (1.04, 1.43)	1.19 (1.02, 1.40)
	Hypertension Only	28,883	774	1.21 (1.09, 1.35)	1.24 (1.11, 1.38)	1.19 (1.07, 1.33)	1.19 (1.07, 1.33)	1.18 (1.06, 1.32)
Two Diagnoses	Hypothyroidism & RA	712	28	1.74 (1.18, 2.55)	1.74 (1.18, 2.55)	1.70 (1.15, 2.52)	1.72 (1.17, 2.54)	1.69 (1.14, 2.51)
	Hypertension & RA	3,721	114	1.40 (1.15, 1.72)	1.54 (1.25, 1.89)	1.38 (1.12, 1.70)	1.40 (1.14, 1.72)	1.48 (1.20, 1.82)
	Hypertension & Hypothyroidism	8,322	241	1.34 (1.15, 1.56)	1.33 (1.14, 1.54)	1.28 (1.10, 1.50)	1.30 (1.12, 1.52)	1.22 (1.04, 1.43)
Three Diagnoses	Hypertension, RA, & Hypothyroidism	1,088	41	1.75 (1.27, 2.42)	1.73 (1.25, 2.39)	1.75 (1.26, 2.41)	1.71 (1.24, 2.36)	1.69 (1.22, 2.35)

N = number; reference group (ref) = women born full term; FT = full-term born women; PT = preterm-born women; RA = rheumatoid arthritis.
(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).

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. Directions for future research include large prospective studies of women and men with lifelong follow-up to substantiate findings and expand our understanding of the interplay of organ systems and prematurity. In addition to human studies, mechanistic experimental animal research may identify pathways that contribute to organ alterations which may be translated into human clinical interventions that reduce the CVD risk in preterm-born individuals.

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Ethical standard. 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.

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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.

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