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CONTEMPORARY REVIEW

Women's Reproductive Milestones and Cardiovascular Disease Risk: A Review of Reports and Opportunities From the CARDIA Study

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ABSTRACT: In 1985 to 1986, the CARDIA (Coronary Artery Risk Development in Young Adults) study enrolled 5115 Black or White participants, including 2788 women, aged 18 to 30 years. Over the following 35 years, the CARDIA study amassed extensive longitudinal data on women's reproductive milestones, spanning menarche to menopause. Although not initially conceived as a study of women's health, >75 CARDIA study publications address relationships between reproductive factors and events with cardiovascular and metabolic risk factors, subclinical and clinical cardiovascular disease, and social determinants of health. The CARDIA study was one of the earliest population-based reports to note Black-White differences in age at menarche and associations with cardiovascular risk factors. Adverse pregnancy outcomes, particularly gestational diabetes and preterm birth, have been assessed along with postpartum behaviors, such as lactation. Existing studies have examined risk factors for adverse pregnancy outcomes and lactation, as well as their relationship to future cardiovascular and metabolic risk factors, diagnoses, and subclinical atherosclerosis. Ancillary studies examining components of polycystic ovary syndrome and ovarian biomarkers, such as anti-Müllerian hormone, have facilitated examination of reproductive health in a population-based cohort of young adult women. As the cohort transitioned through menopause, examination of the importance of premenopausal cardiovascular risk factors along with menopause has improved our understanding of shared mechanisms. The cohort is now aged in the 50s to mid-60s, and women will begin to experience a greater number of cardiovascular events as well as other conditions, such as cognitive impairment. Thus, in the next decade, the CARDIA study will provide a unique resource for understanding how the women's reproductive life course epidemiology informs cardiovascular risk, as well as reproductive and chronological aging.

Key Words: fertility ■ lactation ■ menarche ■ menopause ■ polycystic ovary syndrome ■ pregnancy

Examination of the impact of women's reproductive health on cardiovascular disease (CVD) risk began in the 1950s. One of the earliest reports was in *Circulation* in 1953.[1] In that issue, John H. Wuest Jr and colleagues reported that women who had undergone bilateral oophorectomy had significantly greater coronary atherosclerosis than control women, although less than control men.[1] In 1958, Warren Winkelstein Jr and colleagues noted that the male/female ratio in death rates changed at approximately the age of 45 years and could potentially be attributable to shifts in androgens and estrogens.[2] The authors stated that "We thought that a first approximation to such endocrine differences could be obtained by a study of menstrual and pregnancy patterns of patients with coronary artery disease. The preliminary results appeared sufficiently interesting to warrant reporting."[2] The subsequent text comments on the significant

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Nonstandard Abbreviations and Acronyms

APO	adverse pregnancy outcome
ARIC	Atherosclerosis Risk in Communities Study
CARDIA	Coronary Artery Risk Development in Young Adults
CWS	CARDIA Women's Study
GDM	gestational diabetes
HDP	hypertensive disorder of pregnancy
MESA	Multi-Ethnic Study of Atherosclerosis
NAFLD	nonalcoholic fatty liver disease
OCP	oral contraceptive pill
PCOS	polycystic ovary syndrome
VMS	vasomotor symptoms
WISE	Women's Ischemia Syndrome Evaluation

associations between surgical menopause and miscarriages with myocardial infarction. It was not until the 1980s that the more extensive epidemiologic reports from the NHS (Nurses' Health Study) were published. These reports were notable for their longitudinal examination of associations between contraception, parity, and menopause with future CVD.[3,4] Epidemiologic studies, including the CARDIA (Coronary Artery Risk Development in Young Adults) study, were initiated to observe factors associated with CVD risk beginning in early adulthood.

The CARDIA study began enrolling participants aged 18 to 30 years in 1985 to 1986,[5,6] approximately the time that these epidemiologic studies were published. Original aims of the CARDIA study were to examine the distribution and determinants of CVD risk factors in Black and White young men and women and to identify associated risk factors, particularly lifestyle habits and behaviors, and eventually psychosocial factors and social determinants of health. Participants were recruited from 4 centers, located in Birmingham, AL, Chicago, IL, Minneapolis, MN, and Oakland, CA, to achieve a representative sample of Black and White individuals in the United States. At each field center, participants were recruited to achieve balance by sex, self-reported race (Black and White), socioeconomic status (ie, more than high school education compared with high school or less), and age (<25 versus >25 years).

At baseline, Black women and White women had different mean levels of education (13.1 versus 14.5 years, respectively), marital status (21% versus 29%, respectively), full-time employment (46% versus 62%, respectively), residence in impoverished neighborhoods (13% versus 10%, respectively), and difficulty paying for basics (39% versus 32%, respectively).[7] Follow-up examinations occurred every 2 to 3 years during the first decade of the study and approximately every 5 years thereafter, with telephone contact with participants occurring every 6 months. As of September 2022, death rates per 1000 since 1985 were 109.0 in Black women versus 68.2 in White women. Retention of the survivors has been high, with >71% of surviving participants attending the year 30 examination.[5,6] Mortality in Black women exceeded that in White men and White women. At the year 30 examination, Black women (n=957) and White women (n=957) had different mean levels of education (14.5 versus 16.0 years, respectively); 29% of Black women and 14% of White women had less than a high school education.

Along with standard anthropometric measures, blood pressure assessments, and laboratory measures, the CARDIA study has collected medical and reproductive history, extensive nutritional information, physical fitness assessments, body composition imaging, ectopic fat imaging, medications, and CVD events. Participants have also undergone repeated imaging for assessment of vascular calcification, carotid intima-media thickness, echocardiography, and brain structure and function. Ancillary studies have collected additional information on nontraditional risk factors, including oxidative stress and inflammation, and characterization of the genome, epigenome, transcriptome, proteome, and metabolome.

The recruitment of women in their reproductive years has provided a unique opportunity to assess longitudinally common exposures and characteristics in Black and White women with a range of social determinants of health using the core and ancillary measures of cardiovascular risk and a biorepository of stored samples. The repeated measures provided an opportunity to examine trajectories in risk factors from before conception and after pregnancy and lactation. Beginning in year 2, the CARDIA study has repeatedly assessed estrogen use through detailed inquiries about oral contraceptive pill (OCP) use and other hormonal and nonhormonal reproductive measures. The CARDIA study has also collected detailed survey information about fertility and pregnancy characteristics and outcomes, particularly adverse pregnancy outcomes (APOs), such as preterm delivery[8] and gestational diabetes (GDM),[9] as well as lactation duration for sequential pregnancies. One ancillary study focused on polycystic ovary syndrome (PCOS), including symptoms, biochemical measures of androgens,[10] and radiographic imaging of the ovaries and uterus.[11] Another ancillary study of parous women measured adipokines and inflammatory and endothelial function markers in stored blood from multiple examinations beginning with the year 2 examination.[12] As the cohort transitioned through menopause, the CARDIA study assessed menstrual history and vasomotor

symptoms (VMS),[13] CVD risk factor changes around the final menstrual period,[14] and relationships with subclinical measures of disease.[14]

Four decades after the CARDIA study began enrolling participants, interest in women's reproductive health and impact on CVD health has grown. In 2021, >500 studies examining reproductive exposures in women and subsequent CVD risk were cited in PubMed. Although initial studies focused on changes in traditional CVD risk factors, more recent reports examine the possible shared mechanisms between reproductive factors and CVD risk. These investigations have been enabled by the measurement of CVD risk factors at multiple time points before and after reproductive events. In this review article, we describe CARDIA studies for each reproductive milestone. We include all of the CARDIA studies that addressed reproductive milestones (ie, menarche, contraception, PCOS, pregnancy, GDM, preterm delivery, hypertensive disorders of pregnancy, preeclampsia, gestational hypertension, lactation, breastfeeding, menopause, reproductive aging, anti-Müllerian hormone, infertility, hot flashes, and VMS). A total of 77 reports are listed in Tables 1 through 5. A brief summary of relevant literature accompanies each description. We also identify content that could be explored further on the relationships between these reproductive milestones and CVD risk, which is particularly relevant as the cohort is transitioning through middle age. Investigations could be conducted through collaborations with CARDIA study investigators as well as through public use data sets.

Table 1. CARDIA Studies Examining Menarche, Contraception, and Cardiovascular Risk Factors

Year	Menarche	References
1992	Black women have earlier menarche than White women	Burke[15]
2015	Each 1-y earlier age at menarche associated with higher BMI	Dreyfus[18]
	Each 1-y earlier age at menarche associated with higher glucose, triglycerides, incident impaired fasting glucose, and metabolic syndrome, with associations stronger in White than Black women	
2015	Each 1-y earlier age at menarche associated with higher prevalence of NAFLD	Mueller[19]
	Each 1-y earlier at menarche associated with greater visceral adiposity	
	Contraception	
1992	OCP use associated with higher white blood cell count	Friedman[46]
1993	OCP use associated with higher fibrinogen	Folsom[47]
1996	OCP use differed between Black and White women	Bild[45]
2002	OCP use associated with lower glucose levels and lower odds of diabetes	Kim[43]

BMI indicates body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; NAFLD, nonalcoholic fatty liver disease; and OCP, oral contraceptive pill.

MENARCHE

At the time of baseline data collection in the CARDIA study, women were aged 18 to 30 years and had already experienced menarche about 5 to 13 years earlier. Thus, misclassification of age at menarche is possible. However, in the CARDIA study, recall of the age at menarche had adequate precision to note a racial discrepancy in menarche, 12.45 years in Black women and 12.73 years in White women[15] (Table 1). Subsequently, the racial discrepancy in age at menarche between Black and White women was reported in other cohorts.[16,17] In the CARDIA study, each earlier year of menarche was associated with greater body mass index (BMI)[18] as well as visceral adiposity.[19] After adjustment for BMI, earlier menarche predicted adverse glucose and lipid levels[18] as well as nonalcoholic fatty liver disease (NAFLD),[19] with associations stronger in White than Black women.

The CARDIA study findings for the association between earlier age at menarche and poorer CVD risk factor profiles are generally congruent with previous studies, but unique in examinations by Black compared with White women. Similar findings were reported in the Fels Longitudinal Study,[20] a cohort of White adolescents. Other reports noted that women who were older at baseline and who recalled early age menarche (<12 years) had increased risk of CVD events and mortality.[21–24] These cohorts consisted of primarily White or East Asian women.[21–24] Two reports noted that menarche after the age of 17 years was also associated with slightly increased risk.[22,23] However, examination of interactions by race or ethnicity have not been reported for those studies.

The associations between menarche and puberty with CVD risk factors have been attributed to several mechanisms (Figure 1). Childhood socioeconomic status and household structure have long been recognized to predict both early menarche[25] as well as later life CVD events,[26,27] although the extent to which these operate through or apart from subsequent lifestyle behaviors and traditional CVD risk factors is not completely understood. These pathways may include greater childhood BMI,[28] catch-up growth during infancy,[29] and associated adipokine dysregulation,[30] which confer risk of early menarche and long-term adiposity, as well as the other exposures indicated in Figure 1. The prolonged exposure to estrogen, which

Table 2. CARDIA Studies Examining PCOS and Its Components

Year	PCOS components	References
2008	Changes in BMI and androgenicity are concurrent	Sternfeld[67]
2010	Androgens predict CAC	Calderon-Margalit[10]
2011	PCOS predicts diabetes and dyslipidemia	Wang[69]
2012	PCOS predicts greater left ventricular mass	Wang[70]
2014	PCOS predicts CAC	Calderon-Margalit[66]
2019	PCOS associated with depression	Greenwood[71]
2016	Cortisol and testosterone predict atherosclerosis better than testosterone alone	Lee[68]
2017	Testosterone predicts NAFLD	Sarkar[10]

BMI indicates body mass index; CAC, coronary artery calcification; CARDIA, Coronary Artery Risk Development in Young Adults; NAFLD, nonalcoholic fatty liver disease; and PCOS, polycystic ovary syndrome.

accompanies early age at menarche, was not associated with higher CVD risk in the WISE (Women's Ischemia Syndrome Evaluation) study.[22]

Two hypotheses comment on the impact of the in utero nutritional environment on offspring CVD risk profiles and have been supported by epidemiologic studies. The Barker or "thrifty-phenotype" hypothesis proposes that fetal deprivation in combination with an enriched nutritional environment in later childhood is associated with CVD risk.[31,32] The Pederson hypothesis notes that fetal overnutrition (maternal overweight or hyperglycemia) can modify fetal metabolism,[33] and maternal overweight and obesity have since been noted to be associated with risk of offspring metabolic syndrome[34] and of CVD events as well.[35–38] Interestingly, both fetal undernutrition[39] as well as overnutrition[40] have also been associated with earlier onset of puberty, suggesting that in utero exposures may modify sexual development as well as offspring cardiovascular risk. Epigenetic modifications in utero or after birth may be a shared mechanism through which early sexual maturation[41] and CVD risk[42] occur, although the precise methylation sites and their role in fetal and infant metabolism and development are still not completely understood. As the CARDIA study cohort ages, such shared mechanisms examining menarche (as well as other reproductive milestones) and CVD risk factors, subclinical atherosclerosis, CVD events, and differences by race should be explored further.

CONTRACEPTION

The CARDIA study has collected data on OCPs and other hormonal contraception at each examination until the cohort transitioned through menopause. Questions have included length of use and no use since the last examination. At the year 10 examination, when women were on average aged 34 (range, 28–40) years, the CARDIA study surveyed women's lifetime history of specific hormonal contraceptive formulations.[43] Subsequent examinations also collected information on contraceptive formulations. Thus, it is possible to link women's CVD risk factor profile with OCP use by age at the time of use, duration, and formulation.[44]

Contraceptive studies in the CARDIA study have focused on OCPs (Table 1). OCP use increased between baseline and the year 7 examination (between 1985 and 1992) in White women, but not in Black women.[45] OCP use at the time of examination was correlated with higher levels of inflammatory markers, including white blood cell count[46] and fibrinogen.[47] However, subsequent CARDIA study reports did not observe that OCP use was cross-sectionally associated with metabolic dysfunction (ie, elevations in insulin, glucose, blood pressure, or lipids) as a pathway to CVD (Table 1). In fact, OCP use was associated with lower levels of glucose, possibly attributable to changes in OCP formulations over the past 30 years.[43] These associations persisted after adjustment for confounders, including age, education, weight, and race, and could represent residual confounding or a true protective effect.

Epidemiologic studies in other cohorts have focused on short-term, rather than long-term, risk of thromboembolic events[48] and ischemic heart disease.[48,49] Beginning in the 1960s, the earliest forms of estrogen-progestin pills contained 150 μg of mestranol or ethinyl estradiol, but the dosage of ethinyl estradiol was decreased because of common adverse effects, including nausea and vomiting, and adverse effects, including thromboembolism.[50] The vast majority of OCPs prescribed today have <35 μg of ethinyl estradiol, including OCPs with <20 μg of ethinyl estradiol. In studies of French[51] and Danish[52] women, 20 μg OCPs were associated with significantly lower risk for pulmonary embolism, ischemic stroke, and myocardial infarction than formulations with 30 to 40 μg of ethinyl estradiol. Pills containing third-generation progestins desogestrel and gestodene were associated with higher risk of pulmonary events than pills with levonorgestrel (the second-generation progestin that also is included in hormonal intrauterine devices and implantable rods).[51] This research is congruent with older studies noting that lower doses of estrogen are linked with lower risk.[53] Therefore, OCPs are not recommended for women at increased risk for thromboembolic disease, including women who smoke and are aged >35 years or women with uncontrolled hypertension, thrombophilia, or history of thromboembolic disease.[54]

Whether OCPs and other hormonal contraception affect atherosclerosis and longer-term CVD risk is

Table 3. CARDIA Studies Examining Pregnancy and Cardiovascular Risk Factors

Year	Pregnancy and parity	References
1992	Black women have earlier age at first childbirth than White women, which may contribute to greater lifetime risk of obesity in Black women.	Burke[15]
1994	Pregnancy associated with 2–3 kg of persistent weight gain	Smith[85]
	First pregnancy associated with changes in waist/hip ratio	
	Black women have greater gains than White mothers	
1994	Parity associated with changes in skinfold distribution in Blacks	Lewis[86]
	Parity not associated with BMI in younger mothers	
1996	Pregnancy associated with decreases in HDL-C	Lewis[91]
2004	HDL-C decrements associated with a first birth pregnancy persist over time	Gunderson[92]
2004	Parity associated with cumulative increases in waist circumference	Gunderson[88]
2004	Smoking during pregnancy reduces weight gain during pregnancy	Gunderson[84]
2005	HDL-C decrements associated with pregnancy vary by apoE phenotype	Gunderson[93]
2008	First birth associated with decreased long-term BP	Gunderson[83]
2008	Pregnancy is associated with increased visceral fat independent of overall adiposity	Gunderson[87]
2017	Pregnancy not associated with maternal telomere length	Lane-Cordova[137]
2022	Prepregnancy weight gain predicts gestational weight gain	Catov[116]
	Preterm birth	
2004	Black women reporting racial discrimination have higher risk of preterm birth and low birth weight deliveries	Mustillo[98]
2009	Prepregnancy depressive mood is a risk factor for preterm birth and contributes to increased risk of preterm birth in Black women.	Gavin[99]
2010	Adverse lipids predict preterm birth	Catov[8]
2013	Preterm delivery predicts higher maternal BP	Catov[107]
2016	Preterm delivery predicts incident metabolic syndrome	Catov[106]
2018	Endothelial dysfunction does not predict preterm birth	Lane-Cordova[100]
2018	Cardiorespiratory fitness does not predict preterm birth	Lane-Cordova[102]
2018	Women with preterm birth have adverse BP patterns and higher risk of CAC	Catov[108]
2019	Prepregnancy kidney function not associated with preterm birth	Harville[103]
2020	Oxidative stress does not predict preterm birth	Harville[101]
2020	Preterm and small for gestational age birth associated with higher maternal ASCVD risk in White women	Lane-Cordova[189]
2020	Preterm birth associated with increases in diastolic BP and greater increases in weight after childbearing period	Sun[105]
	GDM, metabolic syndrome, and diabetes	
1995	Greater waist/hip ratio increases risk of incident GDM	Zhang[114]
2007	Higher parity does not increase risk of diabetes, except among women with a history of GDM	Gunderson[9]
2009	Childbearing associated with increased risk of metabolic syndrome, with greater impact on women with GDM	Gunderson[94]
2010	Adverse cardiometabolic risk factor profiles before pregnancy predict GDM	Gunderson[113]
2013	Women with and without GDM have unhealthy behaviors postpartum	Bennett[90]
2018	Fitness predicts incident GDM	Whitaker[117]
2019	White women with GDM have lower diabetes risk than Black women with GDM	Shen[120]
2020	Women with GDM gain weight faster before pregnancy than women without GDM	Catov[115]
	GDM and CVD risk	
2014	GDM increases risk of early atherosclerosis based on carotid intima-media thickness	Gunderson[121]
2016	GDM associated with increasing left ventricular mass and risk of impaired systolic function	Appiah[122]
2016	GDM associated with increased risk of nonalcoholic fatty liver disease	Ajmera[124]

(*Continued*)

Table 3. Continued

	GDM and CVD risk	
2018	GDM predicts incident chronic kidney disease in Black women	Dehmer[125]
2021	GDM history is associated with 2-fold higher risk of CAC, even if glucose levels normalize, prediabetes, or type 2 diabetes	Gunderson[123]
2021	History of GDM increases risk of ectopic fat deposition	Appiah[139]

ApoE indicates apolipoprotein E; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcification; CARDIA, Coronary Artery Risk Development in Young Adults; GDM, gestational diabetes; and HDL-C, high-density lipoprotein cholesterol.

less clear. There was substantial variation in OCP use within CARDIA study women during follow-up. The repeated measures, however, provide an opportunity to conduct time-varying exposure analyses. The adverse associations with blood pressure[55] and the favorable associations with concurrent glucose levels and diabetes in the CARDIA study are similar in their reports of neutral[56] or beneficial associations[57,58] in other studies. Therefore, prospective studies examining cumulative impact on longer-term risk factor profiles, atherosclerosis markers, and events need to be conducted. Examination of transdermal forms, including the vaginal ring and levonorgestrel formulations, should also be undertaken. Such studies will eventually be possible in the CARDIA study. This is particularly relevant for women who use long-term hormonal contraception for its favorable effects on bleeding, hirsutism, and acne, such as women with PCOS.[59]

POLYCYSTIC OVARY SYNDROME

PCOS is believed to be the most common endocrinopathy among reproductive-aged women, with an estimated prevalence of 5% to 10%.[60] Because it is diagnosed on the basis of hyperandrogenism, oligomenorrhea, and polycystic ovaries, PCOS is typically first identified in the reproductive years. In 2021, a National Heart, Lung, and Blood Institute workshop concluded that women with PCOS commonly were affected by obesity, type 2 diabetes, dyslipidemia, hypertension, NAFLD, and sleep-disordered breathing, but evidence for independent associations between PCOS and CVD was not conclusive.[60] In part, this uncertainty stems from the fact that diagnostic criteria for PCOS and recommendations for screening have evolved over the past several decades.[61–63] Figure 2 shows classification schemes based on symptoms and biochemical measures,[62,64] as well as more recent categories based on unsupervised machine-learning algorithms and genome-wide association studies.[65]

Another factor contributing to our incomplete understanding of CVD in PCOS is a lack of prospective and long-term longitudinal studies that include participants with well-characterized PCOS.[60] Accordingly, investigators have sought to use the CARDIA study to gain an understanding of the trajectory of cardiometabolic features in participants with PCOS as they transition to their postreproductive years. In the CWS (CARDIA Women's Study), an ancillary study to the CARDIA study, women participating in the year 15 examination were invited to a year 16 ancillary study visit. The CWS participants consented to measurements of their androgens (testosterone and sex hormone–binding globulin) from the year 2 examination, when they were about 27 years of age, as well as from the year 10 and year 16 examinations.[66] Women were also asked to characterize their menstrual cycles, excess hirsutism, and OCP use between the ages of 20 and 30 years. Initial CWS reports examined relationships between androgens and cardiometabolic risk factors and outcomes, including one report showing that changes in androgens were tightly correlated with changes in BMI[67] (Table 2). In another study, free testosterone levels predicted carotid intima-media thickness.[68] Subsequent studies have further defined PCOS by identifying subjects with both hyperandrogenism (either defined by excess hair growth or biochemical hyperandrogenemia) and

Table 4. CARDIA Studies Examining Lactation and Cardiovascular Risk Factors

Year	Lactation	References
2007	Longer lactation attenuated unfavorable changes in weight, lipids, and insulin associated with pregnancy	Gunderson[141]
2010	Longer duration of lactation is associated with reduced risk of incident metabolic syndrome	Gunderson[12]
2015	Women with less abdominal fat before pregnancy and less gestational weight gain are more likely to lactate	Kierkegard[82]
2015	Longer duration of lactation predicts less carotid intima-media thickness	Gunderson[140]
2018	Longer duration of lactation is associated with reduced risk of incident diabetes in women with GDM and women without GDM	Gunderson[138]
2019	Longer lactation is associated with lower NAFLD prevalence	Ajmera[124]
2021	Longer lactation is associated with less ectopic fat (visceral and pericardial)	Appiah[139]

CARDIA indicates Coronary Artery Risk Development in Young Adults; GDM, gestational diabetes; and NAFLD, nonalcoholic fatty liver disease.

Table 5. CARDIA Studies Examining Reproductive Aging

Year	Reproductive aging	References
2008	Black women more likely to experience infertility than White women	Wellons[160]
2009	Black women are more likely to undergo hysterectomy than White women	Bower[155]
2013	Prediction of future menopause based on menstrual cycles alone is limited	Whitham[13]
2013	AFC predicts menopause	Wellons[11]
2015	AMH predicts menopause	Nair[156]
2015	Hysterectomy does not predict future CVD risk factor levels, once prehysterectomy levels are considered	Appiah[14]
2016	Hypertension associated with CRP during premenopause	Ebong[161]
2017	AMH predicts menopause better than AFC or FSH	Kim[157]
2017	Surgical menopause (oophorectomy) does not predict left ventricular function, once presurgical risk factors are considered	Appiah[166]
2019	Hypertension associated with earlier age at natural menopause, BMI, and waist circumference with older age at menopause	Costanian[162]
2019	Fibroids not associated with CAC	Laughlin-Tommaso[165]
2020	Lower AMH associated with greater oxidative stress	Kim[158]
2021	Menopause is associated with adverse left ventricular indexes, although adjustment for premenopausal risk factors is limited	Ying[163]
2021	Premature menopause is not associated with CAC	Freaney[167]
2022	Age at natural menopause is not associated with left ventricular structure and function once premenopausal factors are considered	Appiah[168]
2022	Postmenopausal women have higher oxidative stress than premenopausal women	Heravi[164]
2022	AMH is not associated with aging markers, including telomeres, mitochondrial DNA copy number, or epigenetic age	Kim[159]

AFC indicates antral follicle count; AMH, anti-Müllerian hormone; BMI, body mass index; CAC, coronary artery calcification; CARDIA, Coronary Artery Risk Development in Young Adults; CRP, C-reactive protein; CVD, cardiovascular disease; and FSH, follicle-stimulating hormone.

oligomenorrhea. Using this approach, investigators found that participants with PCOS had stronger associations with diabetes,[69] dyslipidemia,[69] subclinical atherosclerosis,[10,66] and left ventricular mass compared with those without PCOS. These associations were independent of lifestyle behaviors, such as diet and physical activity, and similar associations were not present when subjects with either isolated hyperandrogenism or oligomenorrhea were considered, suggesting the independence and importance of the full syndrome in predicting cardiometabolic outcomes.[70] However, the relationship between isolated hyperandrogenism and oligomenorrhea with other outcomes, such as APOs and lactation duration, may warrant future investigation.

Other CARDIA studies have reported links between PCOS and factors that may contribute to CVD outcomes. Notably, depression risk,[71] which has predicted adverse cardiovascular health in other CARDIA studies, is also increased in those with PCOS in the CARDIA study, with the highest symptom burden noted in Black women. In non-CARDIA studies, reports using hospitalization data,[72] electronic medical record data,[73] and other cohorts[73] note that PCOS may also be linked with peripartum cardiovascular complications as well as GDM and hypertensive disorders of pregnancy (HDPs), which in and of themselves confer CVD risk (Figure 3). Thus, CARDIA study data could also be used to examine how various life course events, including reproductive events and mood disorders, contribute to the relationships between PCOS and CVD.

Although CARDIA study reports contribute to the growing body of work supporting a link between PCOS and intermediate cardiometabolic outcomes,[74–77] whether PCOS ultimately leads to increased rates of CVD events has not been definitively shown. The ages of participants in most epidemiologic studies that enroll reproductive-aged women, including the CARDIA study, have not been sufficiently advanced to achieve this while the cohort was premenopausal. Furthermore, the magnitude of the associations between PCOS and cardiometabolic outcomes and whether all PCOS subsets are at risk remain unclear. One factor contributing to these uncertainties is the heterogeneity inherent to PCOS and differences in ascertainment of PCOS across various studies.[62,65,78,79] Indeed, studies that rely on physician diagnosis may not identify all patients: In one 2020 study of electronic medical records in the United Kingdom,[80] approximately half of women who met PCOS criteria based on diagnoses of irregular menses, polycystic ovaries, or hyperandrogenism were not diagnosed. Similarly, another study from Australia reported that ≈70% of women meeting PCOS criteria were not diagnosed.[81] Therefore, studies relying on a clinical diagnosis may be subject to

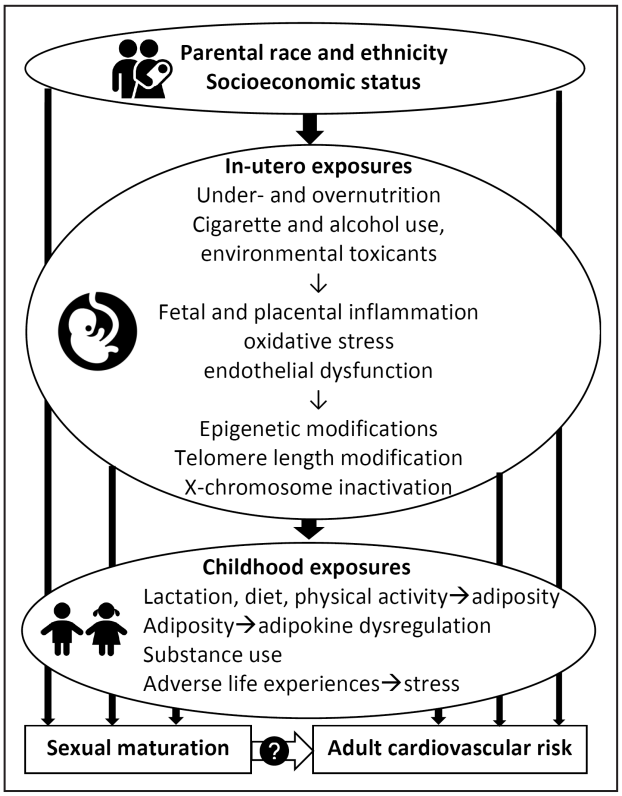

Figure 1. Potential shared mechanisms between sexual maturation and cardiovascular risk.

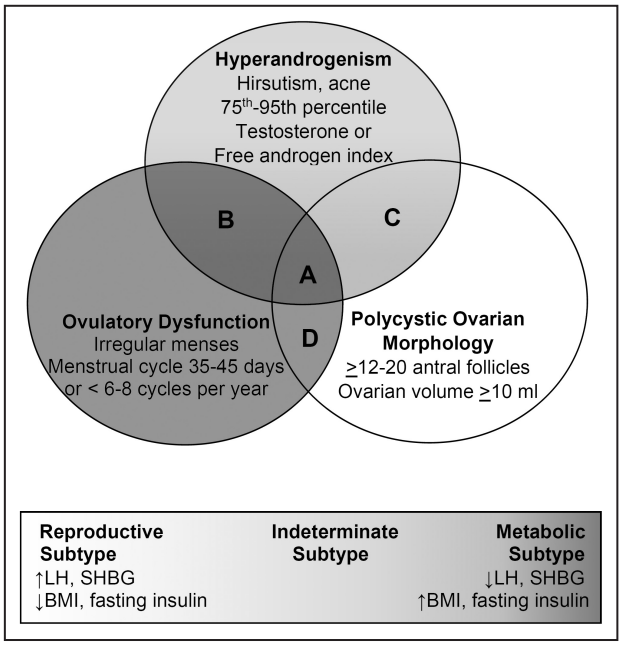

Figure 2. Polycystic ovary syndrome (PCOS) classification schemes.
Top panel: Phenotype "A" consists of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Phenotype "B" consists of hyperandrogenism and ovulatory dysfunction. Phenotype "C" consists of hyperandrogenism and polycystic ovarian morphology. Phenotype "D" consists of ovulatory dysfunction and polycystic ovarian morphology. Bottom panel: PCOS subtypes include a reproductive subtype, a metabolic subtype, and an indeterminate subtype distinguished by levels of luteinizing hormone (LH), sex hormone–binding globulin (SHBG), body mass index (BMI), and fasting insulin. (Levels of testosterone were elevated compared with controls but did not distinguish between PCOS subtypes.)

various forms of selection bias, including overrepresentation of subjects with more adverse features, and/or improved health care access. Improved strategies to identify PCOS in epidemiologic studies are needed to improve our understanding of PCOS and CVD risk across a more diverse sample. Toward this end, recent genome-wide association studies suggest that -omics data could potentially serve as an adjunct to clinical criteria in identifying subtypes of women with PCOS at high risk for chronic diseases,[65] including CVD and malignancy.

ADVERSE PREGNANCY OUTCOMES

The CARDIA study has examined the relationships between several adverse pregnancy outcomes with CVD risk factors (Table 3). Pregnancy features were reported at every examination, and the CARDIA validation studies have demonstrated excellent maternal recall of infant birth weight, preterm birth, gestational weight gain, and GDM.[8,9,82] Although women tended to overreport instances of HDPs,[83] the sensitivity of maternal recall of HDP was high, thus providing reliable data for normotensive pregnancies. Because of its periodic assessment of BMI and anthropometrics as well as laboratory measurements, the CARDIA study is one of the few longitudinal cohorts able to examine prepregnancy, postpregnancy, and postlactation cardiometabolic health. This has been particularly useful for examination of racial disparities in relation to APOs and childbearing as they influence CVD risk factors.

The CARDIA study was one of the earliest studies to note that first pregnancy resulted in permanent weight gain of several kilograms, except in smokers,[84] and not in women aged <25 years, and that pregnancy might adversely affect distribution of adiposity as well as total number of kilograms.[15,85–88] Waist circumference and visceral fat increases were cumulative with each child, independent of overall adiposity,[87] which may be partially attributable to less physical activity and increased caloric intake.[89,90] After adjustment for weight gain and lifestyle behavior changes after pregnancy, the CARDIA study has also reported that pregnancy is linked with lower high-density lipoprotein cholesterol following a first birth[91,92] and varies by apolipoprotein E phenotype,[93] and parity is associated with increased risk of incident metabolic

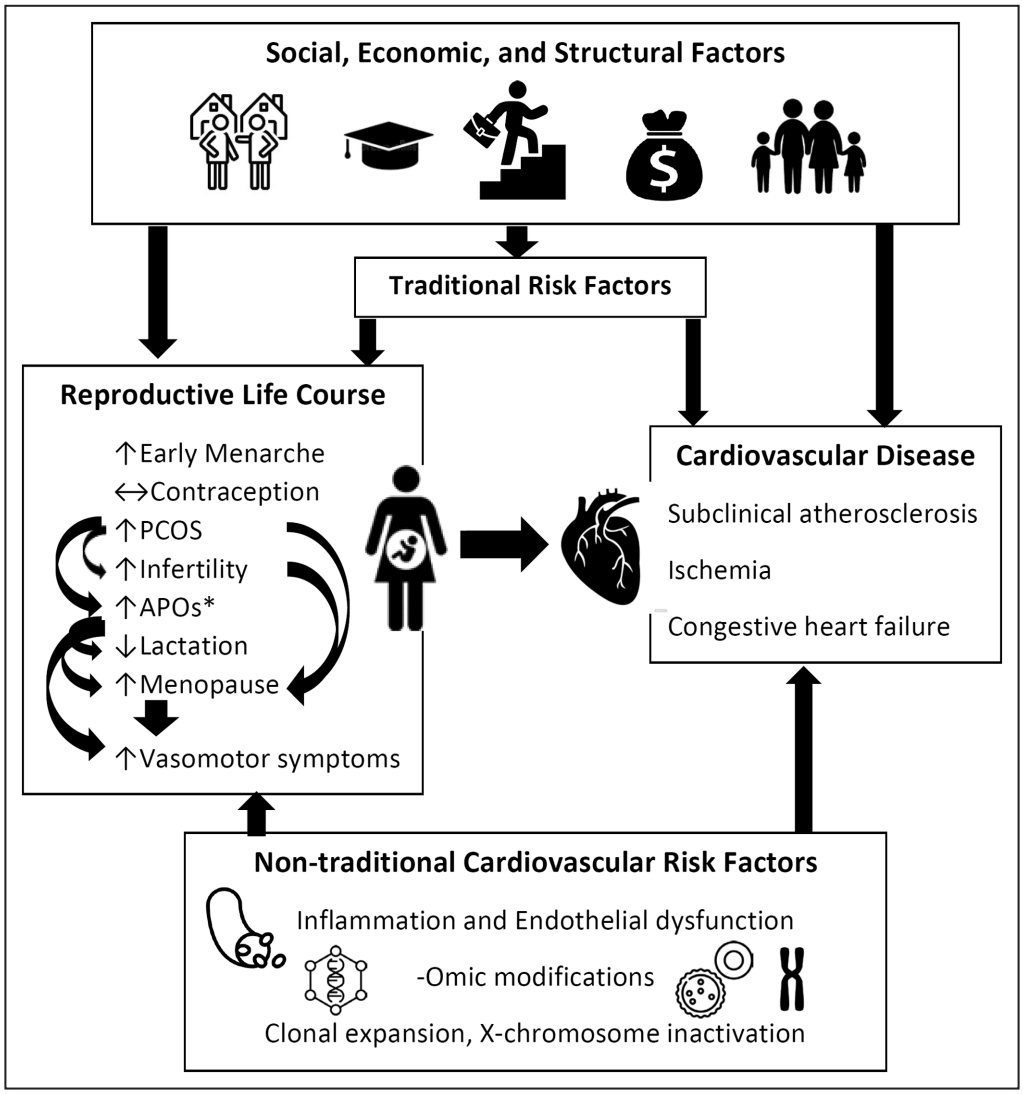

Figure 3. Reproductive life course events may be associated with each other and share precursors with cardiovascular disease (CVD) and jointly contribute to CVD.
Upward arrows indicate higher associated CVD risk, and downward arrows indicate lower associated CVD risk. *Adverse pregnancy outcomes (APOs) include gestational diabetes, hypertensive disorders of pregnancy, and preterm birth. PCOS indicates polycystic ovary syndrome.

syndrome.[94] In contrast, increasing parity was not associated with future risk of developing overt diabetes, unless women had a history of GDM.[9] Having at least one birth was also associated with lower long-term blood pressure in the CARDIA study, but only among women who did not develop HDPs.[83] Biologic plausibility of a beneficial relationship of pregnancy with blood pressure has been supported by smaller studies that demonstrated that the characteristic decreases in peripheral resistance during pregnancy persist postpartum.[95,96]

Preterm births, pregnancies characterized by delivery before 37 weeks of gestation, are a key contributor to Black-White disparities in infant mortality in the United States.[97] The CARDIA study was one of the earliest studies to report that racial discrimination contributes to preterm birth risk and low birth weight risks and to note the Black-White disparity in preterm birth rates, even after accounting for known risk factors, such as tobacco and substance use, as well as gestational weight gain.[98] Prepregnancy depressed mood also likely contributed to racial differences in preterm birth.[99] In the CARDIA study, adverse risk profiles predicted poorer pregnancy outcomes, including preterm birth.[8] Interestingly, hypothesized predictors, such as endothelial dysfunction,[100] oxidative stress,[101] and cardiorespiratory fitness[102] or chronic kidney disease,[103] did not predict preterm birth. Apolipoprotein E2 allele was also associated with greater risk of miscarriage.[104]

The CARDIA studies have also noted that preterm birth was independently associated with future adverse CVD risk profiles[105] and metabolic syndrome[106] as well as inflammatory markers and subclinical atherosclerotic markers, including carotid intima-media thickness.[107,108] These studies are congruent with studies from Norwegian cohorts on the associations between preterm delivery and risk of future adverse CVD risk factor levels[109] and CVD events.[110] In these Norwegian women, 10-year CVD risk scores were higher in women with histories of APOs than in women without APOs.[111] Taken together, these studies suggest that preterm birth itself may modify CVD risk. Alternatively, preterm birth and CVD could potentially share precursors, such as CVD risk factors, but risk is incremental,[112] and novel modifiable targets are not currently known.

The CARDIA study has also examined the relationship of prepregnancy CVD risk factors with the risk of future GDM. In the CARDIA study, cardiometabolic risk factors independently associated with several fold higher risk of future GDM included elevated fasting glucose (ie, prediabetes), fasting insulin, and lower high-density lipoprotein cholesterol levels independent of prepregnancy BMI and waist circumference.[113] These findings were the first to show that dysmetabolism strongly predicted GDM better than overall adiposity. Others showed that women with greater waist/hip ratio[114] and greater speed of weight gain before pregnancy[115] had greater risk of gestational weight gain[116] and incident GDM, even after adjustment for BMI. Along similar lines, the CARDIA study women with poorer CVD risk factor profiles[113] and lower study-assessed fitness levels[117] were more likely to develop GDM. Others later reported findings that were similar in large cohorts of women, particularly for blood pressure and weight.[118,119]

In the CARDIA study, GDM was associated with a higher risk of developing metabolic syndrome, and a 4-fold higher risk of incident diabetes after pregnancy,[94] particularly in Black women.[120] In the CARDIA study, GDM history has also been associated with higher carotid artery intima-media thickness in midlife among women who did not develop the metabolic syndrome, prediabetes, or overt diabetes.[121] Even after consideration of BMI and traditional CVD risk factors, a history of GDM may still be associated with higher risk of impaired systolic ejection fraction.[122] A history of GDM was associated with a 2-fold higher relative risk of coronary artery calcification for all levels of glucose tolerance (euglycemia, prediabetes, and overt diabetes) in midlife, suggesting that other established CVD risk factors may contribute substantially to atherosclerotic CVD risk.[121] Risk was elevated even when normoglycemia persisted many years after delivery.[123] In the CARDIA study, GDM history was also associated with adverse outcomes, such as the metabolic syndrome,[94] NAFLD,[124] and chronic kidney disease.[125] These studies are congruent with studies from other cohorts demonstrating associations between GDM and adverse outcomes, particularly diseases related to greater adiposity, including the metabolic syndrome, type 2 diabetes, CVD, NAFLD, and breast cancer.[126,127] At least part of this risk is attributable to preconception BMI as well as higher postpartum weights among women with GDM, which tend to be higher compared with women without GDM.[128]

Maternal recall of HDP in the CARDIA study, as in other epidemiologic studies enrolling women in perimenopause or postmenopause, is not adequate to distinguish between subtypes of HDPs (prepregnancy chronic hypertension, gestational hypertension, preeclampsia/eclampsia, and preeclampsia superimposed on chronic hypertension) or accurately ascertain a history of HDPs. These subtypes of HDPs likely have different pathophysiology and different CVD sequelae.[129] Thus, examination of such studies has been limited in the CARDIA study. Studies from other cohorts have demonstrated that women with gestational hypertension have greater risk of CVD events compared with women who are normotensive during pregnancy,[130–132] and the link with future CVD is particularly marked for women who have preeclampsia.

The CARDIA study has previously validated women's self-report of pregnancy metrics compared with medical records and found high correlation for most outcomes, including diabetes and weight.[9,83] In general, although self-report has limited accuracy to distinguish subtypes of HDPs in the CARDIA study and other studies, maternal report of key pregnancy metrics has high correlation with birth certificates[133] and electronic medical records. For example, one report[133] noted that 98% of mothers noted gestational age within 1 week of the date noted on the birth certificate, and sensitivity and specificity of self-report of preterm birth were 99% and for low birth weight were also high. Correlation between women's self-report of GDM,[134] gestational age, and birth weight also had high correlation with medical records, years after diagnosis.[135] Obviously, examination of particular exposures during pregnancy, such as alcohol or tobacco use, may be subject to social desirability biases and might limit the accuracy of such analyses.

In general, the implications of APOs for prevention and treatment of future maternal chronic disease are not entirely elucidated. In the studies of Norwegian women, differences in the proportion of women who would be classified in different risk categories based on APOs was low.[111] In other words, the findings did not support reclassifying women with histories of APOs for different CVD screening procedures, beyond existing recommendations for CVD risk factor screening. However, interventions target preconception, prenatal,

and postpartum periods as potentially sensitive windows in which interventions could be useful.[136] Future potential studies in the CARDIA study could serve as exploratory studies leveraging the multiple ancillary studies in the CARDIA study to determine whether novel risk factors, such as epigenetic factors and telomere length,[137] might differ between women with normotensive pregnancies and women with HDPs. As the cohort ages, examining the relationships of specific types and severity of APOs with measures of later-life functioning, particularly cognitive functioning, will be possible.

LACTATION

The CARDIA study was one of the first epidemiologic studies to examine the beneficial associations of breastfeeding on metabolic outcomes, such as diabetes. Gunderson and colleagues noted that lactation was related to ~50% lower risk of incident metabolic syndrome[12] as well as overt diabetes,[138] independent of preconception cardiometabolic risk profiles, BMI, perinatal outcomes, social factors, and follow-up lifestyle behaviors, as well as strong protective associations among Black women, and among women with histories of GDM. The CARDIA study also noted that breastfeeding behavior may be related to other factors, including fat distribution, apart from BMI.[82] Independent of these factors, longer duration of lactation was associated with reduced odds of pericardial and visceral fat deposition,[139] NAFLD,[124] and carotid intima-media thickness[140] (Table 4). CARDIA's prospective studies across the childbearing years show much stronger protective association for lactation than studies that obtained information on lactation close to or after the end of the reproductive lifespan. These cohorts have also reported longer duration of lactation to be favorable[141] and associated with improved glucose uptake,[142,143] insulin sensitivity,[142,143] and lipid metabolism,[142,144,145] leading to the reversal of some of the adverse metabolic changes brought on by pregnancy,[146] particularly lower risk of future diabetes among women with previous GDM.[147] These studies reported weaker associations of 10% relative risk reduction per year of lactation than observed in CARDIA, perhaps attributable to lack of adjustment for antecedent cardiometabolic risk factors before pregnancy or history of APOs. The positive effects of lactation on maternal metabolic health have been reported to last for >7 to 15 years after the last birth,[148] and are associated with lower risk of CVD,[149] although the extent to which these findings are independent of preconception risk factors and history of APOs is unclear.

The mechanisms through which lactation may improve maternal health are not completely understood. To some extent, the favorable association may also reflect the fact that mothers who are obese before pregnancy face greater challenges to breastfeed their offspring, arising from medical conditions and adverse maternal and infant outcomes. These mothers are less likely to receive education on the benefits of lactation or be offered lactation support compared with normal weight mothers.[150,151] Interestingly, in Sprague-Dawley rats, lactation has favorable effects on oxidative stress markers.[152] Oxidative markers are available at several time points in the CARDIA study, including before and after pregnancy, and could assist in investigations of whether lactation modifies these markers significantly.

Finally, the benefits of lactation in combination with healthy infant feeding practices for childhood obesity have been well documented.[153] Studies from other cohorts have noted that women with GDM may have reduced breastmilk production as well as different quality breastmilk than women without GDM.[154] Whether the quality of breastmilk among infants with GDM has independent adverse effects on infant growth is not yet established.

REPRODUCTIVE AGING AND MENOPAUSE

When the CARDIA study women were on average aged 40 years at the year 16 CWS ancillary study examination, 1163 women underwent transvaginal ultrasonography assessing ovarian volume, cysts, and uterine structure. The presence of uterine fibroids on the imaging also was noted. In the CARDIA study, Black women were more likely to undergo hysterectomy than White women.[155] The CARDIA study has used the ultrasound information along with surveys on menstrual frequency and ovarian markers (anti-Müllerian hormone and follicle-stimulating hormone) to expand prediction of menopause and understanding of nontraditional risk factors (Table 5). In addition to reporting associations between these markers and menopause,[156,157] the CARDIA study reports also noted that anti-Müllerian hormone does correlate with oxidative stress,[158] but does not correlate with other aging markers[159] that have been associated with CVD risk. These data were also used to examine infertility and race-specific explanations. The CARDIA study women were asked whether they had not conceived during the past year despite unprotected intercourse.[160] Black women were more likely to have experienced infertility compared with White women, even after considering fibroids, ovarian volume, and smoking.[160]

Because the CARDIA study was able to collect data on CVD risk factors before premenopause, the CARDIA study reports have been able to examine the relationships between premenopausal risk factors,

menopausal status, and CVD risk.[161–164] One of the most interesting findings from the CARDIA study is that surgical menopause and age at natural menopause after 45 years were not strong predictors of CVD risk factors, subclinical atherosclerosis, or left ventricular indexes once presurgical or premenopausal risk factors were considered.[165–168] The CARDIA study's reproductive aging reports complement those from studies that enrolled perimenopausal women, such as the SWAN (Study of Women Across the Nation), or perimenopausal and postmenopausal women enrolled in cardiovascular cohorts, such as the ARIC (Atherosclerosis Risk in Communities Study) and MESA (Multi-Ethnic Study of Atherosclerosis).[169,170] The CARDIA study and SWAN have both reported that risk factors are generally less favorable in the postmenopausal period than in the premenopausal period. Such changes are largely attributable to linear changes in aging, with the exception of lipids, which may change more rapidly during the perimenopausal transition.[171,172]

An exception to this relationship is menopause occurring before the age of 40 years, which may represent a particularly high-risk population.[169,170] For instance, in other investigations of premature menopause, menopause before the age of 35 years doubles the risk of an incident CVD event.[173] The CARDIA study adds to these studies in noting that premature menopause does not seem to be associated with greater risk of coronary artery calcification, suggesting that the relationship between premature menopause and CVD events occurs through pathways other than atherosclerosis.[167] In addition, other examinations suggest that inclusion of premature menopause as a CVD risk factor does not significantly improve assessment of risk based on traditional CVD risk factors.[174] However, CARDIA study data could be used to reveal causal pathways that enhance accelerated aging, because the CARDIA study measured repeated nontraditional risk factors before and after the last menstrual period. These pathways likely do not involve estrogen per se. Although the menopausal transition ultimately results in declines in endogenous estrogen levels, estrogen supplementation has had only slight beneficial to neutral impact on markers of subclinical atherosclerosis when given in the 5 years after the final menstrual period in KEEPS (Kronos Early Estrogen Prevention Study)[175] and the ELITE (Early Versus Late Intervention Trial With Estradiol).[176] Aging mechanisms contributing both to early menopause as well as CVD risk in postmenopausal populations have included clonal hematopoiesis of indeterminate potential,[177] epigenetic age acceleration,[178] and telomere length,[179] which could potentially be assessed using premenopausal and postmenopausal measures in the CARDIA study.

Early menopause has also predicted greater risk of heart failure in other cohorts.[180–185] As more heart failure cases are observed in the CARDIA study, there will be an opportunity to replicate these findings while taking into account premenopausal measurements of obesity in CARDIA study women. The relationship between menopause and heart failure has been further validated by studies involving NT-proBNP (N-terminal pro-B-type natriuretic peptide), which is a known biomarker for heart failure diagnosis and prognosis.[186–188] In cohorts of primarily perimenopausal and postmenopausal women, associations between age at the final menstrual period and sex hormones with NT-proBNP have been demonstrated.[186–188] The CARDIA study has measurements of sex hormones and will be measuring heart failure biomarkers, and future studies can determine whether such associations exist during the reproductive years.

Finally, the CARDIA study has collected information on VMS, the severity of which were independent predictors of CVD risk.[189] Interestingly, such risk was synergistic with history of preterm birth, suggesting shared pathways spanning the reproductive years. Other studies, including SWAN, as well as meta-analyses note that VMS are associated with increased risk of CVD by as much as 28%, even after adjustment for standard CVD risk factors.[190,191] However, the specificity of VMS, the importance of length of symptoms and onset in relation to the final menstrual period, and the added benefit for reclassification of CVD risk have not been examined.

CONCLUSIONS

The CARDIA study has contributed to our understanding of how premenopausal reproductive events are associated with CVD risk factors and subclinical markers of atherosclerosis. As the CARDIA study cohort finishes its current round of data collection, the current age range of the surviving women is roughly 55 to 65 years. Thus, life course analyses can examine contributions to existing marked racial disparities in women's health. Such analyses can examine associations between reproductive span and pregnancy-lactation outcomes on CVD outcomes in the near future (Table 6).

As an observational cohort, CARDIA study analyses cannot prove causal relationships between reproductive milestones and CVD risk. However, such examinations may serve as the basis through which to question potentially harmful practices, such as the routine performance of bilateral oophorectomy before epidemiologic analyses that such practices might be harmful for CVD health. In addition, the CARDIA study and other cohort studies may help to identify which reproductive factors might benefit from modification by examining dose-response relationships, as with lactation or length of OCP use. Observational studies can also identify specific disorders and populations who

Table 6. Limitations of CARDIA for Reproductive Milestone Analyses and Future Directions

Limitations
Represents Black and White populations in 4 metropolitan areas and may not extend to other areas of the United States
Information on contraception and pregnancy obtained through survey and less accurate for distinguishing between hypertensive disorders of pregnancy
Frequently repeated measurements during reproductive transitions (such as during each pubertal stage, pregnancy trimester, or each menopausal stage) not performed compared with studies designed to assess these transitions
Strengths and future directions
Examinations of interactions between trajectories of social determinants of health and reproductive milestones
Examination of clusters of reproductive milestones and joint relationships with CVD risk
Examination of relationships between reproductive milestones and cognitive and physical outcomes, including brain structure and cognitive performance
Combining data with other observational cohorts to increase representativeness and statistical power for examination of reproductive milestones.

CARDIA indicates Coronary Artery Risk Development in Young Adults; and CVD, cardiovascular disease.

might be useful to target in future randomized trials or through policy, such as provision of mental health services for women with preterm deliveries.

In addition to the suggestions for additional explorations noted under each reproductive milestone, there are general areas for which rich data are available but not fully leveraged. In consortia using data from multiple cohorts, CARDIA study genome-wide association study data have been used to identify single-nucleotide polymorphisms associated with several reproductive characteristics, including fibroids,[192] age at menarche,[193] age at natural menopause,[194] and sex hormones, such as sex hormone–binding globulin.[195] In combination with closer examination of social determinants of health, such data could be used to reduce residual confounding by unmeasured sociocultural, economic, or psychosocial factors when examining racial differences in such outcomes. The CARDIA study has serial assessments of social determinants of health in a cohort stratified by both education and Black versus White race. Trajectory analyses examining structural factors, including wealth, employment status, single parenthood, neighborhood-level determinants, and access to health care, during a time of economic change (1985-present), policies, and social support networks for postdelivery care and relationships with a broad range of CVD outcomes are possible; such analyses have been performed to some extent for Black and White participants overall but not by both race and sex. These issues affect women and men differently, and comparisons by sex could be conducted. The CARDIA study has recently reported that the higher risk of premature CVD in Black versus White adults was statistically explained by clinical and neighborhood factors in women, compared with clinical and socioeconomic factors in men.[7] Such factors include mental health, discrimination, and substance use, which have been collected repeatedly in the CARDIA study and whose relationship with reproductive milestones could provide rich areas for exploration.

Comparisons between Black and White women of trajectories of social determinants of health and how these interact with reproductive milestones should also be examined. Specifically, how disparities in CVD risk factors in Black versus White women are influenced by reproductive disparities could be examined more closely. Although it is a plausible hypothesis that higher-risk reproductive milestones are associated with poorer social determinants of health and CVD risk factors, which, in turn, influence future reproductive outcomes and CVD outcomes, such lifecourse analysis has not been conducted. Such analyses have the potential to influence not only epidemiologic analyses but also health policies. For example, the examination of the impact of single parenthood on cardiovascular health has been limited, because of inadequate data on cardiovascular risk before and after parenthood, whether such parenthood was modified by divorce and social support systems, and potential mediators, such as lifestyle behaviors and access to health care. Exploring these questions in the CARDIA study along with other observational studies would increase representativeness as well as statistical power.

Comprehensive reproductive life course models that take into account the correlations between fertility, adverse pregnancy outcomes, and VMS may have greater impact than models considering only one of these dimensions (Figure 3). In particular, the linkages between adverse pregnancy outcomes, such as preterm birth, early age at menopause, and presence of VMS, may confer a particularly high-risk CVD profile. Another high-risk grouping may be represented by PCOS, GDM, and absence of lactation, which would be of value to examine because of lactation as a potentially modifiable behavior that might ameliorate CVD risk. Combining CARDIA study data with other observational studies would increase statistical power.

The CARDIA study has collected information on COVID-19 infection and vaccination. As the cohort ages, the next wave of data collection involves collection of data relevant to aging. Future studies might examine the relationship between reproductive events on cognition, fitness, and aging metrics. Ancillary studies have already characterized lung function, sleep apnea, cardiometabolic disease, as well as cognitive functioning, bone markers, and physical functioning. Linkages between reproductive exposures with epigenetic, genetic, and metabolomic markers that have already been measured in CARDIA study subsets have

not been fully explored. Thus, the contribution of reproductive milestones to these other aspects of health will be possible as the cohort ages.

ARTICLE INFORMATION

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