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WOMEN'S HEALTH

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Alcohol-Related Liver Disease May be More Deadly Among Women, Study Results Suggest



Maternal Cannabis Exposure Is Linked to Placental Dysfunction—Related Adverse Pregnancy Outcomes

By **Grace Halsey**, Senior Editor

Maternal cannabis use was associated with adverse pregnancy outcomes related to dysfunction of the placenta, including small for gestational age (SGA), preterm birth, stillbirth, and hypertensive disorders of pregnancy, according to findings of a National Institutes of Health–funded study published online in *JAMA*.

Compared to women who tested negative for cannabis use during pregnancy, those who tested positive had a 27% increased risk of any of the complications. Moreover, the risk for an adverse outcome was higher among study participants whose cannabis use continued beyond the first trimester, Torri Metz, MD, MS, associate professor of obstetrics and gynecology, maternal-fetal medicine subspecialist, and vice chair of research of obstetrics and gynecology at the University of Utah Health, and colleagues wrote. In fact, the study findings revealed that two-thirds of participants had ongoing cannabis exposure beyond the first 3 months of gestation.

The authors point out that data from past studies suggest use of cannabis by pregnant individuals is underreported, noting that responses to questionnaires on its use in pregnancy may underestimate actual use by as much as 2- to 3-fold when those results are compared with results of hospital urine screens and tissue samples obtained at admission.

The investigators set out to learn more about the association between maternal cannabis use and adverse pregnancy outcomes specifically related to placental dysfunction. They conducted an ancillary analysis of data from participants in the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be, a multicenter cohort study of 10 038 women who were treated at 8 US medical centers from 2010 to 2013. Participants for the analysis were selected based on availability of stored urine samples and abstracted pregnancy outcome data.

To identify cannabis exposure, Metz and colleagues performed urine immunoassay on frozen stored samples obtained at 3 study visits, during gestational age windows of 6 weeks and 0 days to 13 weeks and 6 days (visit 1); 16 weeks and 0 days to 21 weeks and 6 days (visit 2); and 22 weeks and 0 days to 29 weeks and 6 days (visit 3). Results positive for Δ^9 -tetrahydrocannabinol (THC) were confirmed with liquid chromatography tandem mass spectrometry. Researchers defined timing of cannabis exposure as only during the first trimester or ongoing beyond the first trimester.

The primary composite outcome included SGA birth, preterm birth, stillbirth, or hypertensive disorders of pregnancy.

Findings

Investigators included 9275 eligible participants for their analysis from the original population. Of the 6.6% of women who had

cannabis use during pregnancy, 32.4% used cannabis only during the first trimester; twice that proportion, 67.6%, were found to have had ongoing exposure beyond the first trimester.

In propensity score-weighted analyses adjusted for sociodemographics, body mass index, medical comorbidities, and active nicotine use, Metz et al found that cannabis exposure during any time in pregnancy was associated with at least one of the primary composite outcome complications for 25.9% of participants vs 17.4% of those with no exposure (adjusted relative risk [aRR], 1.27; 95% CI, 1.07-1.49). In a 3-part exposure model (no cannabis exposure, exposure during the first trimester only, or ongoing exposure), researchers observed no association between cannabis use during the first trimester only and the primary composite outcome. Ongoing cannabis use, however, was associated with the primary composite outcome (aRR, 1.32; 95% CI, 1.09-1.6).

“Further evaluation in humans of modes of cannabis consumption that do not require inhalation and frequent co-use or contamination with nicotine products may help provide further insight into the relationship between cannabis, nicotine, and fetal growth,” the researchers wrote. ■

SOURCE: Metz TD, Allshouse AA, McMillin GA, et al. Cannabis exposure and adverse pregnancy outcomes related to placental function. *JAMA*. 2023;330(22):2191-2199. doi:10.1001/jama.2023.21146w



New Scientific Statement from American Heart Association Raises Awareness of CVD Risks for Women

By **Sydney Jennings**, *Editor*

A new scientific statement from the American Heart Association (AHA) shows that women with adverse pregnancy outcomes (APOs)—including gestational diabetes, hypertension (HTN), and preterm birth—experience a significantly higher risk of cardiovascular disease

(CVD) and stroke later in life.¹

The findings are featured in a special Go Red for Women Spotlight issue of *Circulation* and were published online February 12, 2024.

Although APOs are common among pregnant women and women with APOs have a higher incidence of CVD risk factors after delivery, “evidence-based approaches to managing these patients after pregnancy to reduce

cardiovascular disease risk are lacking,” wrote the researchers.¹

In the scientific statement—titled *Opportunities in the Postpartum Period to Reduce Cardiovascular Disease Risk After Adverse Pregnancy Outcomes: A Scientific Statement From the American Heart Association*—investigators reviewed current evidence on interpregnancy and postpartum preventive strategies, blood pressure management, and

lifestyle interventions for optimizing CVD using the AHA's Life's Essential 8 framework.¹

"Adverse pregnancy outcomes can be a wake-up call to a young person that they may be at risk for heart disease and stroke later in life. By identifying these women at a younger age, we will be able to act earlier to prevent and treat risk factors and promote healthy lifestyle changes," said first author and chair of the writing group for the statement, Jennifer Lewey, MD, MPH, in an AHA press release.²

According to the statement, the prevalence of APOs is estimated to be 10% to 20% and varies by race and ethnicity. "These APOs portend higher risk of future long-term complications, including increased lifetime risk of atherosclerotic cardiovascular disease, heart failure, stroke, chronic kidney disease, and vascular dementia," noted Lewey and colleagues in the statement. "This risk appears to be largely mediated by the increased incidence of [CVD] risk factors, including diabetes and [HTN]."¹

For example, according to researchers, persons with gestational diabetes are 8 times more likely to develop subsequent type 2 diabetes compared with those without gestational diabetes. Also, women with hypertensive disorders of pregnancy (HDP), such as gestational HTN and preeclampsia, have a 2- to 4-fold higher risk of developing chronic HTN than those with normotensive pregnancies at 10 to 20 years after delivery.¹

"These CVD risk factors, in turn, place postpartum individuals at a higher risk of developing subsequent CVD and other end-organ effects and thus are important targets for postpartum interventions," wrote the researchers.¹

Lewey and coauthors stated that disparities by race and ethnicity, socioeconomic status, and geography (ie, rural vs urban

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communities) also affect the prevalence of APOs and are important contributors to disparities in prenatal CVD risk factors, access to care, and outcomes for both mother and child.¹

"Compared with non-Hispanic White women, non-Hispanic Black women have an increased risk of developing HDP and severe maternal morbidity in the peripartum period and higher CVD risk across their life span," wrote the investigators. In addition, CVD is a leading cause of pregnancy-related deaths and causes the most deaths in Black women who give birth.¹

Lewey and colleagues stated that the first year after delivery is an important time to examine long-term CVD risk and implement lifestyle changes and treatment in order to improve cardiovascular health in women and reduce the risk of future pregnancy complications. Specifically, the fourth trimester, defined as the 12 weeks after delivery, is "an optimal time to engage postpartum individuals in care to reduce maternal morbidity and improve care transitions," wrote the writing group.¹

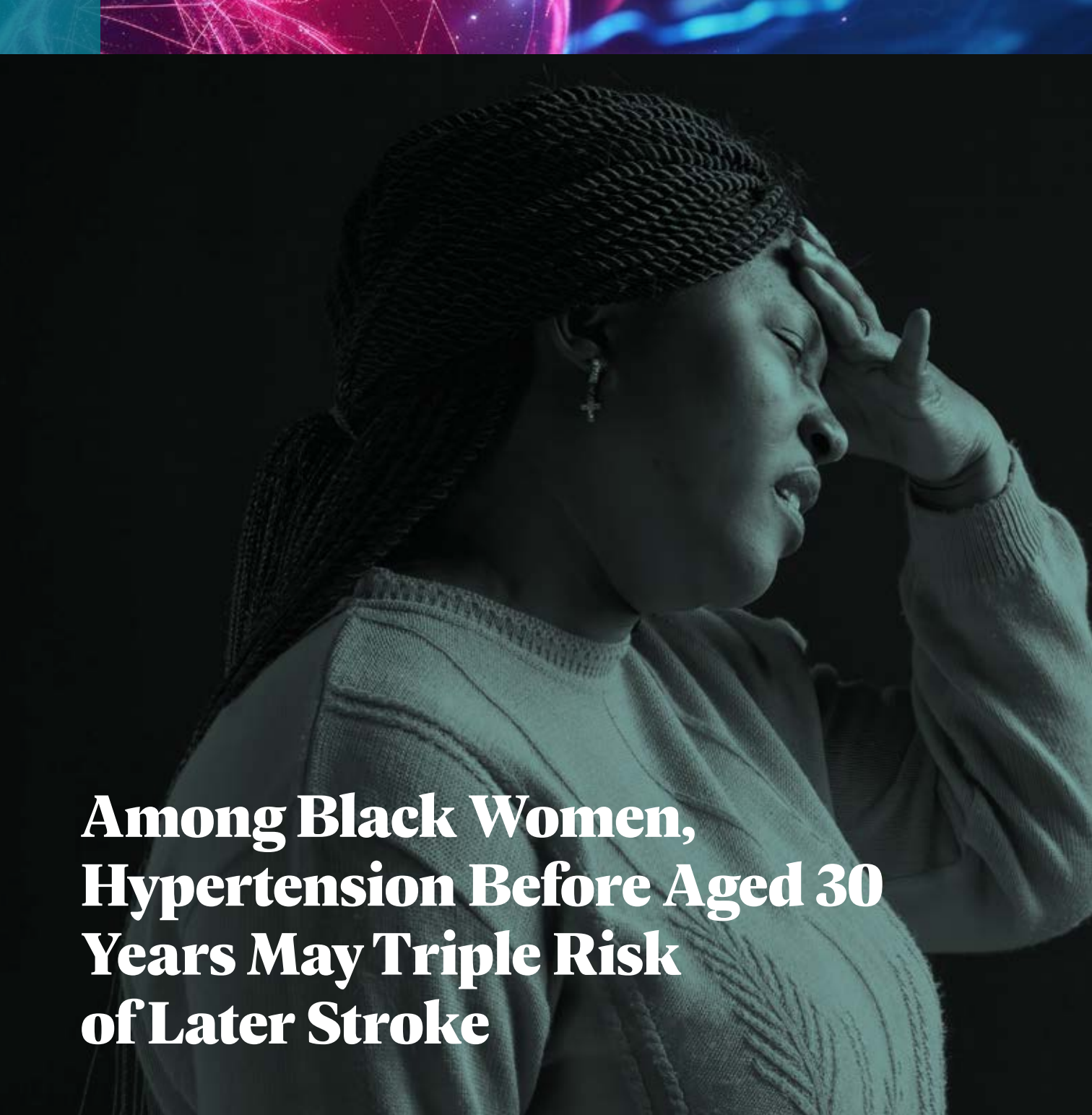
In addition, strategies that promote cardiovascular health in women who are not pregnant may be successfully adapted in the postpartum period and improve

cardiovascular health across their lifetime. Strategies include regular cardiovascular risk factor screening and treatment; ensuring transitions of care among obstetricians, primary care professionals, and the health system; and community-based interventions.¹

"Further studies on long-term reduction of CVD risk and implementation of policy-level changes that mitigate the adverse impact of social determinants of health with innovative health care delivery models and value-based care are essential, especially in resource-limited areas," concluded Lewey et al.¹ ■

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Among Black Women, Hypertension Before Aged 30 Years May Triple Risk of Later Stroke

By **Grace Halsey**, *Senior Editor*

Among Black women who develop elevated blood pressure before age 35 years, the odds of stroke may triple, according to striking findings presented at the American Stroke Association's International Stroke Conference 2024, February 7-9, 2024, in Phoenix, Arizona. Further, developing hypertension before age 45 years could double the risk of having a subsequent stroke.¹

The results are even more concerning given they are

based on analyses controlled for multiple potential confounding variables including smoking, weight, diabetes status, and geographic region—primarily residence in the country's so-called Stroke Belt.¹

The data come from the Black Women's Health Study (BWHS) which includes 59 000 participants from across the US who have been followed since 1995.¹ The rate of hypertension in Black adults in the US is among the highest in the world—approximately 58% of Black women are affected compared with 43% of White women, 38% of Asian women, and 35% of Hispanic women, according

to the most recent American Heart Association statistics.²

“This research was motivated by the glaring disparity I have seen in my own practice. Strokes are occurring at younger ages among my patients who identify as Black and among women,” lead study investigator Hugo J. Aparicio, MD, MPH, an associate professor of neurology at Boston University Chobanian & Avedisian School of Medicine, in Boston, Massachusetts, said in an American Heart Association statement.² “Early onset stroke, particularly at midlife, is even more tragic because these patients often have families or are caretakers for sick family members.”

Tapping data collected by the BWHS, Aparicio and colleagues investigated how early-life hypertension may influence risk for a “potentially disabling” stroke in later life.²

BWHS participants respond to biennial questionnaires that collect information related to reproductive health, lifestyle, medication use, finances, mental health, demographics, family history, and psychosocial factors. The baseline year for the current analysis was the questionnaire administered in 1999.¹

Investigators identified 46 754 women with no history of stroke and who were younger than 65 years when they completed the 1999 questionnaire. The mean age of the cohort was 42.6 years (range, 26-64 years). Participants were followed from 1999 until whichever occurred first: incident stroke, death, loss to follow-up, or the end-of-study follow-up on December 31, 2019. Mean length of follow-up was 17.1 years.¹

To estimate risk of midlife stroke, Aparicio et al compared participants with and without treatment for hypertension before age 45 years, between age 45 and 64 years, and within 10-year age intervals from 1999 to 2019 using Cox proportional hazard models.¹ They determined a history of hypertension by participant self-report using as a definition



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“physician diagnosed hypertension with use of an antihypertensive medication or diuretic or use of an antihypertensive medication alone.”¹

FINDINGS¹

The researchers documented baseline hypertension in 2980 participants younger than 45 years (10.5%) and among 7147 of those aged 45 to 64 years (38.7%). Over up to 23 years of follow-up, 1485 (3.2%) experienced stroke.

When they compared BWHS participants who experienced a stroke to Black women with no stroke history, the researchers found that women with a history of treatment for hypertension before age 45 years were at 2.2 times greater risk of midlife stroke (HR, 2.23; 95% CI, 1.79-2.78) after multivariable adjustment for age, neighborhood socioeconomic status, residence in Stroke Belt states, smoking, body mass index, and diabetes.

Aparicio and colleagues reported the greatest increase in risk for midlife stroke, at more than 3-fold, was among study participants with youngest age of hypertension onset, those aged 24 to 34 years (HR, 3.15; 95% CI, 1.92-5.16). The risk among women who developed hypertension at midlife (aged 45-64 years) was more than 1.5 times greater (HR, 1.69; 95% CI, 1.47-1.95).

“We expected to see an association between having high blood pressure at a younger age and having a stroke during midlife and later life, however, we were surprised and concerned to see the magnitude of the relationship, especially for women who were taking antihypertension medications before age 35,” Aparicio said.²

He added: “My hope is that health care professionals are persuaded to pay special attention to high blood pressure screening and treatment over the life course for African American women, such as during child-bearing years and both before and at the start of middle age. Health care policy changes are needed so that primary prevention is promoted and funded because by the time a Black woman has a stroke at middle age, it is often too late,” Aparicio concluded.² ■

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Alcohol-Related Liver Disease May be More Deadly Among Women, Study Results Suggest

By **Grace Halsey**, Senior Editor

Women with fatty liver disease related to alcohol consumption may be at up to twice the risk for mortality associated with alcohol-related liver disease (ALD) and metabolic dysfunction-associated and alcohol-related liver disease (MetALD), according to results of new research published in the *Journal of Hepatology*.¹

According to the findings, all forms of steatotic liver disease (SLD) were approximately twice as common among men than women in the study. However, MetALD was associated with an 83% higher hazard of all-cause mortality in women and showed no significant association with mortality among men.¹ The investigators also reported that although the presence of ALD was significantly associated with mortality in both sexes, the risk of mortality was 160% greater among women.¹

Further, when the researchers assessed SLD phenotypes in “putative order of etiologic severity (ie, metabolic dysfunction-associated steatotic liver disease [MASLD], MetALD, ALD),” they found trends across the deteriorating phenotypes were not significant for sex differences in the prevalence of the conditions but were significant for both sexes in the risk for mortality.¹

“Steatotic liver disease is a major and increasingly prevalent condition that is likely an underlying precursor to many conditions,

including those involving the heart,” Susan Cheng, MD, MMSc, MPH, director of the Institute for Research on Healthy Aging in the department of cardiology in the Smidt Heart Institute at Cedars-Sinai and the study’s lead author, said in a news release.² “We are paying even more attention to steatotic liver disease because we are seeing how it tracks closely with established cardiovascular risk factors such as hypertension, high cholesterol, and diabetes.”

prognosis differ by sex, and potentially to understand why.¹

The researchers analyzed representative data from the National Health and Nutrition Examination Survey (NHANES) III, conducted from 1988 to 1994, that included standardized ultrasound measures of hepatic steatosis, assessment of cardiometabolic risk traits, and questionnaire data on alcohol intake for 31 311 participants.¹

After excluding individuals younger than 20 years and without

“Steatotic liver disease is a major and increasingly prevalent condition that is likely an underlying precursor to many conditions, including those involving the heart.”

Recently revised nomenclature for the term nonalcoholic fatty liver disease provides a more accurate reflection of how expressions of SLD may arise from “distinct or coexisting etiologies,” the researchers wrote. Cheng et al noted that although heterogeneity between men and women in SLD is well recognized, it is still not well understood. The new concepts, according to the authors, provide a unique opportunity for research that explores how SLD phenotype prevalence and

ultrasonography findings or essential covariate data, the final cohort numbered 10 007. Researchers followed participants for all-cause mortality, reviewing National Death Index records through December 31, 2019.¹

Using criteria for the new naming convention, study definitions were as follows¹:

- **Presence of MASLD:** steatosis in the presence of any cardiometabolic risk trait
- **Presence of ALD:** steatosis in the presence of consuming greater

FIGURE. Prevalence of SLD Phenotypes¹

	Men	Women	Sex difference
MASLD	18.5%	10.3%	
MetALD	3.2%	1.2%	<i>P</i> < .001 for all
ALD	1.7%	0.3%	

than 420 g of alcohol/week for men, greater than 350 g/week for women.

- **Presence of MetALD:** a distinct group of patients with MASLD who consumed 210 to 420 g of alcohol/week for men and 140 to 350 g/week for women

FINDINGS

Participants' mean age was 42 years, and 50.3% of the cohort were women. Based on the revised SLD nomenclature, 1461 were identified as having MASLD, 225 as having MetALD, 105 as having ALD, and 180 had other types of SLD. The remaining 8036 participants were classified as having no SLD. Cheng et al reported 2495 deaths over the median follow-up of 26.7 years.¹

The investigators found that the prevalence of SLD phenotypes differed significantly between men and women (**FIGURE**).¹

MASLD was not significantly associated with all-cause mortality for either sex in multivariable-adjusted survival analyses, according to the results. As noted, however, the HR for MetALD-associated all-cause mortality for women was 1.83 (95% CI, 1.29-2.57) but was not significantly associated with mortality in men (sex difference *P* = .005).¹

Cheng et al reported further that the association of all-cause mortality with the presence of ALD, while significant for both

sexes, was far greater among women (HR, 3.49; 95% CI, 1.86-6.52) than men (HR, 1.89; 95% CI, 1.42-2.51; sex difference *P* = .080).¹

A limitation of the study, the researchers pointed out, was that the data from NHANES III were collected between 1988 and 1994. It is likely that the prevalence of metabolic dysfunction and patterns of alcohol use have changed over the 3 decades since, so additional research will be needed to validate their results. The team does plan to investigate further the differential hepatic impact of alcohol in men and women and to focus on behavioral change that might reduce ALD risk in the latter.¹

“Because alcohol consumption is modifiable, limiting alcohol intake particularly in women at risk for SLD could be critical as part of efforts to mitigate mortality risk in patients with SLD,” the researchers concluded.¹ ■

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