1. Deep neural networks reveal novel sex-specific electrocardiographic features relevant for mortality risk

Aims
Incorporation of sex in study design can lead to discoveries in medical research. Deep neural networks (DNNs) accurately predict sex based on the electrocardiogram (ECG) and we hypothesized that misclassification of sex is an important predictor for mortality. Therefore, we first developed and validated a DNN that classified sex based on the ECG and investigated the outcome. Second, we studied ECG drivers of DNN-classified sex and mortality.

Methods and results
A DNN was trained to classify sex based on 131,673 normal ECGs. The algorithm was validated on internal (68,500 ECGs) and external data sets (3303 and 4457 ECGs). The survival of sex (mis)classified groups was investigated using time-to-event analysis and sex-stratified mediation analysis of ECG features. The DNN successfully distinguished female from male ECGs {internal validation: area under the curve (AUC) 0.96 [95% confidence interval (CI): 0.96, 0.97]; external validations: AUC 0.89 (95% CI: 0.88, 0.90), 0.94 (95% CI: 0.93, 0.94)}. Sex-misclassified individuals (11%) had a 1.4 times higher mortality risk compared with correctly classified peers. The ventricular rate was the strongest mediating ECG variable (41%, 95% CI: 31%, 56%) in males, while the maximum amplitude of the ST segment was strongest in females (18%, 95% CI: 11%, 39%). Short QRS duration was associated with higher mortality risk.

Conclusion
Deep neural networks accurately classify sex based on ECGs. While the proportion of ECG-based sex misclassifications is low, it is an interesting biomarker. Investigation of the causal pathway between misclassification and mortality uncovered new ECG features that might be associated with mortality.
Increased emphasis on sex as a biological variable in artificial intelligence is warranted.

2. **Tolerability and Treatment Outcomes of COVID-19 Monoclonal Antibodies Administered During Pregnancy**

Monoclonal antibodies (mAb) for the treatment of COVID-19, which are available under emergency use authorization (EUA), prevent disease progression and reduce the risks of hospitalization and mortality when given early. Pregnancy is associated with increased rates of severe illness, intensive care unit (ICU) admission, mechanical ventilation, preterm birth, stillbirth, and death compared with nonpregnant women of reproductive age. Despite a paucity data on tolerability and outcomes, the American College of Obstetricians and Gynecologists and the Society of Maternal Fetal Medicine support the recommendation from the National Institutes of Health to offer mAb to pregnant individuals with mild-to-moderate COVID-19 infections. To date, there are only 2 published studies on mAb treatment outcomes during pregnancy. The objectives of this study were to evaluate the tolerability of mAb treatment during pregnancy and to assess the subjective improvement in symptoms, admission within 30 days for COVID or non-COVID reasons, and the pregnancy outcomes.

3. **N-Terminal Pro-B-Type Natriuretic Peptide Concentrations Vary Substantially by Sex and Race**

The absolute risk of heart failure (HF) associated with a given value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration varies substantially by sex and race, according to a study published in *JAMA Cardiology*.

Researchers assessed the extent to which interpreting NT-proBNP concentrations with sex and race may better predict absolute HF risk in these subgroups in midlife and late life.

In the ongoing prospective Atherosclerosis Risk in the Communities (ARIC) study, 12,750 participants without HF (aged mean 57.3±5.7 years; 45% men; 25% Black) at study visit 2 (1990-1992) were included for analysis in midlife. A
total of 5191 participants without HF (aged mean 76.0±5.2 years; 41% male; 20% Black) at visit 5 (2011-2013) were included for analysis in late life.

The primary outcome was incident HF among participants who were alive in the 5 years of follow-up after visits 2 and 5. All statistical analysis was performed from June 2018 to October 2021.

The investigators also assessed the generalizability of their findings in 3920 participants from the Cardiovascular Health Study (CHS) without HF and who had NT-proBNP measurements during their 1992 to 1993 study visit (aged mean 74.5±5.2 years; 61% women, 17% Black).

The 5191 participants at visit 5 had a median NT-proBNP concentration of 124 pg/mL (IQR, 64-239). At visit 5, the NT-proBNP level was 19% (95% CI, 14%-24%) lower in men compared with women ($P<.001$). After the investigators accounted for known determinants of NT-proBNP, the NT-proBNP concentrations were 39% (95% CI, 35%-45%) lower in men vs women ($P<.001$).

Black race was associated with a 30% (95% CI, 24%-36%) lower NT-proBNP concentration in multivariable models that accounted for known determinants of NT-proBNP and included an interaction between race and left ventricular volume.

Of the 12,750 participants at visit 2, the median (IQR) concentration of NT-proBNP was 30 (14-67) pg/mL for Black men, 46 (23-86) pg/mL for Black women, 39 (22-72) pg/mL for White men, and 70 (42-111) pg/mL for White women.

Of this group, 622 (4.9%) developed HF or died during the 5-year follow-up (incidence rate, 1.02 per 100 person-years [95% CI, 0.94-1.10]; 324 incident HF and 601 died). The incidence rate per 100 person-years was 1.72 (95% CI, 1.41-2.10) for Black men, 1.27 (95% CI, 1.13-1.43) for White men, 1.21 (95% CI, 1.01-1.46) for Black women, and 0.57 (95% CI, 0.48-0.67) for White women.

Increased concentrations of NT-proBNP were associated with a greater risk for incident HF or death after adjustment for age, sex, race, comorbidities, blood pressure, BMI, and estimated glomerular filtration rate (hazard ratio [HR] per doubling, 1.60; 95% CI, 1.52-1.68; $P<.001$). Stronger associations were found in White participants (HR, 1.71; 95% CI, 1.60-1.83) vs Black participants (HR, 1.49; 95% CI, 1.38-1.61; $P$ for interaction =.02).

The predicted risk corresponding with a given NT-proBNP concentration varied substantially between sex- and race-based categories. A guideline-recommended NT-proBNP threshold was associated with a 6.7-fold (95% CI, 4.6-9.9) difference in predicted rate of incident HF or death for White women compared with Black men. The differences in absolute predicted risk between sex- and race-based categories were greater for higher NT-proBNP concentrations.
For the CHS participants without HF, NT-proBNP levels greater than guideline-recommended thresholds were associated with a 4-fold lower difference in the incidence rate of HF or death for White women compared with Black men (incidence rate per 100 person-years, 2.8 [95% CI, 2.4-3.3] vs 11.0 [95% CI, 7.8-15.6]; rate ratio, 4.0; 95% CI, 2.7-5.8), with intermediate incidence rates among Black women and White men.

Among several study limitations, the number of Black participants was limited, and the population included participants in a community-based prospective cohort. In addition, the researchers did not have measurements of biologically active NPs, such as B-type NP and A-type NP.

“Important sex- and race-based differences in risk of HF or death exist and NT-proBNP is not a reliable equalizer of risk across these important demographic subgroups,” the investigators concluded. “Consideration of NT-proBNP values in the context of sex and race allows for more uniform prediction of absolute risk across sexes and races.”

4. Oral Contraceptive Use, Hormone Replacement Therapy, and Stroke Risk

BACKGROUND

Millions of women worldwide use exogenous hormones as oral contraceptives or hormone replacement therapy. Still, time-dependent and long-term consequences of exogenous hormones on stroke risk remains unclear.

METHODS

We examined the association between self-reported oral contraceptive and hormone replacement therapy use and stroke risk in 257,194 women from the UK Biobank, born between 1939 and 1970. Outcomes included any type of stroke, ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. Exposures were analyzed as time-varying variables in Cox regression models.

RESULTS

During first year of oral contraceptive use, an increased event rate of any stroke was observed (hazard ratio [HR], 2.49 [95% CI, 1.44-4.30]), while the hazards were found to be comparable during remaining years of use (HR, 1.00 [95% CI, 0.86-1.14]), compared with nonusers. Similarly, first year of hormone replacement therapy use was associated with higher hazard rates of any stroke (HR, 2.12 [95% CI, 1.66-2.70]), as well as cause-specific stroke, including ischemic stroke (HR, 1.93 [95% CI, 1.05-3.57]) and subarachnoid hemorrhage (HR, 2.17 [95% CI, 1.25-3.78]), which remained increased for any stroke during
remaining years of use (HR, 1.18 [95% CI, 1.05-1.31]), and after discontinuation (HR, 1.16 [95% CI, 1.02-1.32]).

CONCLUSIONS

Oral contraceptive use and hormone replacement therapy were associated with an increased risk of stroke, especially during the first year of use, possibly due to immediate changes in hemostatic balance. This study provides new insights on the effects of hormone exposure on stroke risk and provide evidence of not only an overall risk but also a pronounced effects seen in the beginning of treatment.

5. Age- and Gender-Based Trends in Schizophrenia Onset

A study found that schizophrenia onset among men had a 2-modal peak pattern and among women, a 3-modal pattern. These findings were published in the Journal of Psychiatric Research.

Investigators at the University of Melbourne in Australia evaluated data collected for the 2010 Australian Survey of High Impact Psychosis (SHIP) study. SHIP was a population-based study of nearly 1.5 million adults and was conducted at 7 sites across Australia. Participants were screened for psychosis and the subset of participants with schizophrenia underwent an additional interview and data collection phase. For this study, age- and gender-based predictors of schizophrenia onset were evaluated using a hierarchical clustering method.

Study participants (N=857) were stratified by gender. Men (n=612) and women (n=245) were aged mean 34.1±9.0 and 39.0±11.5 years with the earliest recall of schizophrenia symptoms at 21.7±10.9 and 25.5±9.7 years of age, respectively.

Men were observed to have a 2-cluster solution for age at onset with early onset occurring at a mode of 18 years and late onset at 40 years. For women, early onset occurred at a mode of 21 years, intermediate onset at 26 years, and late onset at 42 years.

Stratified by early and late onset, significant group differences among men with schizophrenia were observed for parental separation in childhood (42.4% vs 15.8%; \( P = .002 \)), cannabis abuse (80.8% vs 50.0%; \( P = .004 \)), age at school leaving (mean, 16.2 vs 16.4 years; \( P = .009 \)), childhood temperament or personality difficulties (64.8% vs 45.9%; \( P = .033 \)), and family history of psychosis (52.4% vs 34.2%; \( P = .044 \)), respectively.

For women, early, intermediate, and late onset cohorts differed for migration status (10.6% vs 27.5% vs 18.2%; \( P = .005 \)), family history of psychosis (63.6% vs 47.3% vs 36.4%; \( P = .010 \)), alcohol or drug abuse (40.9% vs 39.6% vs 9.1%; \( P = .015 \)), poor premorbid social adjustment (43.9% vs 27.5% vs 22.7%; \( P = .017 \)), poor premorbid work adjustment (35.6% vs 24.2% vs
9.1%; \( P = .018 \), premorbid personality disorder (12.9% vs 3.3% vs 4.5%; \( P = .033 \)), and first-degree or other close relative death in childhood (48.1% vs 47.8% vs 19.0%; \( P = .039 \)), respectively.

The major limitation of this study was recruiting participants through specialized mental health services, so individuals who could manage their disease using less intensive services were likely not represented.

The study authors concluded, “Distal factors occurred more commonly in the early onset group of both sexes, and somewhat more frequently in early onset males. Genetic effects, early developmental difficulties and psychosocial trauma contributors may possibly sensitize individuals to a future onset of psychosis. [...] Proximal factors occurred somewhat more commonly in earlier rather than later onset females, but there were mostly no statistically significant differences in the occurrence of proximal factors between the early and late onset male groups. A slightly different pattern of characteristics with less premorbid impairment may be evident in middle to later onset female cases.”

6. hs-Troponins and the Chest Pain Guidelines: Experts Call for Clarification

Guidelines on the evaluation and diagnosis of stable chest pain put out last year by the American College of Cardiology and American Heart Association (ACC/AHA) may have endorsed the use of high-sensitivity cardiac troponin (hs-cTn) testing as the preferred biomarker, but a group of concerned physicians says the document is lacking detailed advice as to how to incorporate this assay in clinical practice.

In their paper, published online last week in *Circulation*, Yader Sandoval, MD (Mayo Clinic, Rochester, MN), and colleagues outline several analytical aspects of hs-cTn testing as well as issues with the commonly used thresholds for diagnosing myocardial injury, among other areas in need of clarification.

“This is an appraisal that is trying, without calling names or suggesting any degree of bad intentions, to point out that there were some major areas that really weren’t as good as they could have been in these guidelines,” senior author Allan S. Jaffe, MD (Mayo Clinic), told TCTMD. “We felt that we should, in the interest of helping clinicians, point out some of these errors so that they would not be promulgated by clinicians who might be using these guidelines.”

Further, he continued, while more data are needed in areas such as hs-cTn testing in patients with type 2 MI as well as sex-specific 99th percentiles effect
on outcomes, “there are other places where there is more than enough data and the data were either ignored or at times put in in a way that made it confusing at best and maybe even inaccurate.”

Taken as a whole, the guidelines do not offer guidance “that can be functionally operationalized in any way,” Jaffe said.

In response, writing committee chair Martha Gulati, MD (Cedars-Sinai Medical Center, Los Angeles, CA), told TCTMD that while she considers this paper “a good supplement,” guidelines in general “have to be practical and simple and understandable to everyone who reads them. And not everybody who reads our guidelines is a biomarker expert.”

She hopes that laboratories which process hs-cTn assays are aware of all the details discussed by Sandoval et al, but “that was too much information for us to put into the guidelines.”

**What Level to Use?**

For example, while the guidelines advocate for the use of single-sample rule out—ruling out MI in a patient with chest pain who has a very low level of troponins on admission—both the ACC/AHA and European Society of Cardiology guidelines suggest using a value below the limit of detection (LoD) of the assay. However, the US Food and Drug Administration prohibits clinical reporting below a slightly higher threshold called the level of quantification (LoQ).

“For many assays, the value that allows you to exclude MI is much higher than the limit of detection,” Jaffe explained. “So the idea that you have to use the limit of detection, which you can’t do, and therefore making this suggestion unusable is really not only incorrect but misses the fact that for a large number of assays one can’t use values that are allowed to be reported by the FDA.”

He cited his recently published study that demonstrated that using a concentration of less than 6 ng/L—higher than the LoQ—in conjunction with a normal ECG was safe to rapidly triage patients without acute MI using the hs-cTnT assay.

Further, the authors point out that the guidelines don’t give enough recommendations for patients with both unstable angina as well as type 2 MI, which may outnumber type 1 MIs in the US.

“Unstable angina is diagnosed less frequently using hs-cTn assays, but the entity has not yet disappeared,” Sandoval and colleagues write. “Education on this fact would be helpful because it alerts clinicians that although hs-cTn assays are excellent in ruling out acute MI, unstable angina presentations and severe stable obstructive coronary artery disease still occur.”
As for risk stratification, the ACC/AHA guidelines suggest imaging for all patients deemed to be at intermediate risk. “Well, the reality is that you could get to be intermediate risk, for example, by having a high risk score . . . or you could be at intermediate risk because your troponin is elevated,” Jaffe said. “We would argue strongly that the latter is a situation which is much more associated with information that suggests markedly abnormal risk than the situation where the risk score pins somebody as intermediate.”

The problem with sending patients with normal or even low troponins for imaging is that it will only “delay the ability of people to move out of the emergency room,” he continued. “One of the best benefits of high-sensitivity assays has been the ability to rapidly triage people and move them out quickly, reducing overcrowding.” However, with a lack of “precision” in the guidelines about what to do for a patient considered intermediate risk solely by a risk score, “you actually might lose a lot of that,” Jaffe argued.

There are likely subsets of patients—perhaps those with an elevated troponin—who would benefit from imaging, he said, but these are fundamentally different from “the group that reaches that intermediate status by having a higher risk score but has totally normal troponins.”

**Appropriate Metrics**

Sandoval and colleagues also highlight the use of appropriate metrics for hs-cTn assays, which they claim are glossed over by the guidelines.

The guidelines do endorse use of the 99th percentile upper reference limit, but the authors point out that these thresholds have varied in many studies depending on patient selection. “Support by the guidelines for a consistent approach in this area would have helped the standardization of the 99th percentile upper reference limits,” they write.

The lack of advocacy for sex-specific cutoffs was also disappointing, Jaffe said. “It would have been good for them to have embraced the idea that men and women need different metrics. They sort of talked about it, but they never said it,” he said. “Many of us believe that that would improve care of women.”

Here, Gulati specifically agreed with Sandoval and colleagues, saying that the guidelines writing committee did debate this issue. “We felt like we at the time when we wrote these, we didn’t have a lot of information in the United States yet,” she said. “When we started writing these guidelines, that’s when troponins were being rolled out.”

Gulati said that, in her view, “we should have sex-specific cutoffs,” which is why she was happy to at least have a class 1b recommendation to acknowledge them. “We just know that a lot of places aren’t doing it, and if we could just start
communicating in one manner and we have solid evidence in the United States, perhaps it would be more endorsed,” she added.

Ultimately, “we're interested in helping clinicians get it right. Whether the guidelines [authors] choose . . . to update things that we point out might be done better is their decision, not ours,” Jaffe said. “What's really important is not whether they change or don't change, but that clinicians understand how to do this properly and how to implement these guidelines.”

Gulati acknowledged that if the guidelines are updated, “there's probably a few things I would take from this to add into our update.”

The paper was endorsed by the International Federation of Clinical Chemistry and Laboratory Medicine Committee on the Clinical Application of Cardiac Biomarkers, an entity focused in part on setting global standards for laboratory tests in collaboration with other international organizations.

7. **Association Among Infertility, Recurrent Pregnancy Loss, and Risk of Stroke**

**OBJECTIVE**

To examine the associations of infertility, recurrent miscarriage, and stillbirth with the risk of first non-fatal and fatal stroke, further stratified by stroke subtypes.

**DESIGN**

Individual participant pooled analysis of eight prospective cohort studies.

**SETTING**

Cohort studies across seven countries (Australia, China, Japan, Netherlands, Sweden, the United Kingdom, and the United States) participating in the InterLACE (International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events) consortium, which was established in June 2012.

**PARTICIPANTS**

618,851 women aged 32.0-73.0 years at baseline with data on infertility, miscarriage, or stillbirth, at least one outcome event (non-fatal or fatal stroke), and information on covariates were included; 93,119 women were excluded. Of the participants, 275,863 had data on non-fatal and fatal stroke, 54,716 only had data on non-fatal stroke, and 288,272 only had data on fatal stroke.

**MAIN OUTCOME AND MEASURES**
Non-fatal strokes were identified through self-reported questionnaires, linked hospital data, or national patient registers. Fatal strokes were identified through death registry data.

RESULTS

The median follow-up for non-fatal stroke and fatal stroke was 13.0 years (interquartile range 12.0-14.0) and 9.4 years (7.6-13.0), respectively. A first non-fatal stroke was experienced by 9265 (2.8%) women and 4003 (0.7%) experienced a fatal stroke. Hazard ratios for non-fatal or fatal stroke were stratified by hypertension and adjusted for race or ethnicity, body mass index, smoking status, education level, and study. Infertility was associated with an increased risk of non-fatal stroke (hazard ratio 1.14, 95% confidence interval 1.08 to 1.20). Recurrent miscarriage (at least three) was associated with higher risk of non-fatal and fatal stroke (1.35, 1.27 to 1.44, and 1.82, 1.58 to 2.10, respectively). Women with stillbirth were at 31% higher risk of non-fatal stroke (1.31, 1.10 to 1.57) and women with recurrent stillbirth were at 26% higher risk of fatal stroke (1.26, 1.15 to 1.39). The increased risk of stroke (non-fatal or fatal) associated with infertility or recurrent stillbirths was mainly driven by a single stroke subtype (non-fatal ischaemic stroke and fatal haemorrhagic stroke), while the increased risk of stroke (non-fatal or fatal) associated with recurrent miscarriages was driven by both subtypes.

CONCLUSION

A history of recurrent miscarriages and death or loss of a baby before or during birth could be considered a female specific risk factor for stroke, with differences in risk according to stroke subtypes. These findings could contribute to improved monitoring and stroke prevention for women with such a history.

8. Possible Causal Relationship Between COVID-19 and Gestational Diabetes Onset

A possible causal relationship was observed in which COVID-19 infection increased the risk for gestational diabetes mellitus (GDM) and GDM increased the risk for COVID-19 infection, according to results of a study published in *Diabetes & Metabolism*.

This case-control study reviewed records of 75 women who received care for COVID-19 infection during pregnancy at the Hospital of Bern in Switzerland between 2020 and 2021. Each patient was matched in a 1:2 fashion against an historical cohort (controls) of women (n=149) who were pregnant and delivered between 2016 and 2019.
Among patients in the COVID-19 and control groups, the mean age was 30.76 and 30.62 years, BMI was 26.27 and 25.91 kg/m², 80% and 80% were White, and 17.3% and 7.6% delivered preterm (\(P=.04\)), respectively.

Among patients with COVID-19 infection during pregnancy, 14.66%, 25.33%, and 49.33% were diagnosed in the first, second, and third trimesters, respectively. Of these patients, most (89.33%) had asymptomatic, mild, or moderate infection, and few (n=4) had severe disease requiring transfer to an intensive care unit and/or mechanical ventilation. No deaths were observed.

The researchers found that GDM occurred more frequently among patients in the COVID-19 group vs those in the control group (34.7% vs 16.1%; \(P=.002\)). Among patients in the COVID-19 group, 35.7% were diagnosed with GDM after recovering from the infection.

Among 9 patients with COVID-19 infection who were hospitalized, 4 required ICU transfer. Of these 4 patients, 2 had GDM. Using multivariate logistic regression, the researchers found that positive COVID-19 infection (odds ratio [OR], 2.79; 95% CI, 1.42-5.47; \(P=.003\)) and BMI (OR, 1.12; 95% CI, 1.05-1.19; \(P=.001\)) significantly increased the risk for GDM.

After the researchers performed a regression analysis for factors associated with inpatient vs outpatient COVID-19 management, no significant differences were observed for GDM (OR, 1.14; 95% CI, 0.22-5.80; \(P=.88\)), time of COVID-19 infection onset (OR, 1.08; 95% CI, 0.98-1.20; \(P=.12\)), or BMI (OR, 1.07; 95% CI, 0.91-1.25; \(P=.41\)).

This study was limited by its small sample size, and patients were not matched on the basis of potential comorbidities or socioeconomic status.

These data underscore the importance of vaccination and taking precautions to prevent COVID-19 infection during pregnancy. These results also suggest a “possible causal relationship between COVID-19 [infection] and onset of GDM,” the researchers concluded.

9. Zulresso Indication Expanded to Include Younger Patients With Postpartum Depression

The Food and Drug Administration (FDA) has approved the supplemental New Drug Application (sNDA) for Zulresso (brexanolone) to include patients 15 years of age and older with postpartum depression. Previously, the treatment was approved only for adults 18 years of age and older.

The expanded approval was based on safety data from an open-label study in 20 patients aged 15 to 17 years with postpartum depression. Patients were titrated
to a target dosage of 90mcg/kg/hour and were then followed for 4 weeks. Results showed that the adverse reactions reported in this patient population were generally similar to those observed in clinical studies of Zulresso in adults with postpartum depression. Additionally, brexanolone pharmacokinetics in patients 15 to 17 years old were found to be comparable to those in adults.

Zulresso, a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator, is intended for continuous intravenous infusion over a total of 60 hours following a titration schedule. It must be administered by a health care provider in a certified health care facility under close monitoring. Zulresso should not be given to patients with end stage renal disease due to the potential accumulation of the solubilizing agent, betadex sulfobutyl ether sodium.

Zulresso carries a Boxed Warning associated with the risk of excessive sedation or sudden loss of consciousness during administration. Due to these risks, the product is only available through a restricted program called the Zulresso REMS Program. The most common adverse reactions associated with treatment include sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

Zulresso is a Schedule IV controlled substance. The 100mg/20mL strength preservative-free solution is supplied in single-dose vials that require dilution.

10. Prevalence of Cancer Among Pregnant Patients on the Rise

The prevalence of pregnant patients with cancer is on the rise in the United States, and these patients have a significantly increased risk of poor outcomes, according to data published in *JAMA Oncology*.

Researchers found that the prevalence of pregnancy with cancer increased 13.8% from 2016 to 2019.

In addition, pregnant patients with cancer had significantly higher risks of severe maternal morbidity and death during their hospital stay, when compared with non-cancer patients.

To uncover these findings, researchers conducted a population-based study using data from the National Inpatient Sample. The data included more than 14.6 million deliveries from January 2016 through December 2019.

The prevalence rate of pregnancy with cancer was 69.3 cases per 100,000 deliveries. The prevalence increased from 64.5 cases per 100,000 deliveries in 2016 to 73.4 per 100,000 in 2019 (*P* < .001).
The most common cancer types recorded were breast cancer, lymphoma, leukemia, and gynecologic cancers. Over the period studied, there was an increased incidence of cancers of the skin, soft tissue, breast, and oral cavity/pharynx.

The researchers compared outcomes of patients with and without cancer. After accounting for potential mediators between cancer and adverse outcomes, the data showed that patients with cancer were more likely to experience severe maternal morbidity and death during the index hospital stay for delivery.

The prevalence of severe maternal morbidity was 97.4 per 1000 deliveries among cancer patients and 17.3 per 1000 deliveries among non-cancer patients (adjusted odds ratio [aOR], 3.63; 95% CI, 3.42-3.84).

The prevalence of death during the hospital stay for delivery was 2.2 per 1000 deliveries among cancer patients and less than 0.1 per 1000 deliveries among non-cancer patients (aOR, 13.34; 95% CI, 8.72-20.39).

The researchers noted several limitations to this study, including a lack of information on cancer stage, anticancer treatment, and disease status at the time of delivery. In addition, the dataset did not include information on the cause of death, oncologic outcomes, neonatal outcomes, or information after discharge.

11. Obesity Status and Sex Affect Eating Behavior in Patients With NAFLD
Men and women with obesity and nonalcoholic fatty liver disease (NAFLD) have significantly higher scores on restrained and emotional eating scales compared with control individuals, according to a study in *Human Nutrition & Metabolism*.

The findings are based on an evaluation of the features and tendencies of eating behaviors in patients with NAFLD compared with patients without NAFLD.

Researchers conducted a cross-sectional study in 103 patients with NAFLD, who were enrolled from a hospital in Japan from May 2015 to July 2016. Patients were then categorized into an obese NAFLD group (body mass index [BMI] ≥25.0 kg/m²; n=68; 35 women) and a nonobese NAFLD group (BMI <25.0 kg/m²; n=35; 18 women).

The control individuals had voluntarily received an annual clinical examination in June 2015 and from March to April 2017 (n=74; 51 women).

The study participants were asked to complete an eating behavior questionnaire (EBQ), which included a restrained eating scale, an emotional eating scale, and an external eating scale.
Because significant differences were found in women regarding age, the researchers selected participants aged 50 years and older in each group who showed no statistically significant difference for age.

For men in the NAFLD group, the obese NAFLD group, the nonobese NAFLD group, and the control group, the emotional and external eating scales had significant positive correlations ($r=0.515, P<.001$; $r=0.463, P=.008$; $r=0.598, P=.014$; and $r=0.593, P=.004$, respectively). For the control group, the restrained eating scale and BMI had a significantly positive correlation ($r=0.619, P=.002$).

Among women, the emotional and external eating scales had significant positive correlations in the NAFLD group ($r=0.535, P<.001$), obese NAFLD group ($r=0.518$ and $P=.004$), and control group ($r=0.512, P=.004$). A significantly positive correlation was observed between the emotional eating scale and BMI in the NAFLD group ($r=0.480, P=.001$).

Study limitations included use of the self-administered EBQ questionnaire, with the potential for recall bias and response errors. Also, all study participants were Japanese, and the results in women were limited to those aged 50 years and older.

“Overall, these findings suggest that eating behavior in patients with NAFLD might vary based on sex and obesity status; therefore, a suitable treatment approach may involve individualized support for effective diet therapy,” the researchers concluded.

**Disclosure:** One study author declared affiliations with biotech, pharmaceutical, and/or device companies. Please see the original reference for a full list of authors’ disclosures.

### 12. ACCEL Lite: Pre-Eclampsia: Maternal Red Flag of Risk

Women with preeclampsia and related hypertensive disorders of pregnancy have increased risk of heart disease compared with women who experienced uncomplicated pregnancy. Women should ensure treating clinicians know their reproductive history, and clinicians should work to aggressively prevent and treat development of cardiovascular risk factors in women with a history of preeclampsia.

In this interview, Michael Honigberg, MD, MPP, FACC and Glenn A. Hirsch MD, MHS, FACC, with Yuvraj Chowdhury MD, discuss Pre-Eclampsia: Maternal Red Flag of Risk.
13. Association of In Utero Exposure to COVID-19 With Risk of Neurodevelopmental Disorder in the First Year of Life

IMPORTANCE
Epidemiologic studies suggest maternal immune activation during pregnancy may be associated with neurodevelopmental effects in offspring.

OBJECTIVE
To evaluate whether in utero exposure to SARS-CoV-2 is associated with risk for neurodevelopmental disorders in the first 12 months after birth.

DESIGN, SETTING, AND PARTICIPANTS
This retrospective cohort study examined live offspring of all mothers who delivered between March and September 2020 at any of 6 Massachusetts hospitals across 2 health systems. Statistical analysis was performed from October to December 2021.

EXPOSURES
Maternal SARS-CoV-2 infection confirmed by a polymerase chain reaction test during pregnancy.

MAIN OUTCOMES AND MEASURES
Neurodevelopmental disorders determined from International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) diagnostic codes over the first 12 months of life; sociodemographic and clinical features of mothers and offspring; all drawn from the electronic health record.

RESULTS
The cohort included 7772 live births (7466 pregnancies, 96% singleton, 222 births to SARS-CoV-2 positive mothers), with mean (SD) maternal age of 32.9 (5.0) years; offspring were 9.9% Asian (772), 8.4% Black (656), and 69.0% White (5363); 15.1% (1134) were of Hispanic ethnicity. Preterm delivery was more likely among exposed mothers: 14.4% (32) vs 8.7% (654) (P = .003). Maternal SARS-CoV-2 positivity during pregnancy was associated with greater rate of neurodevelopmental diagnoses in unadjusted models (odds ratio [OR], 2.17 [95% CI, 1.24-3.79]; P = .006) as well as those adjusted for race, ethnicity, insurance status, offspring sex, maternal age, and preterm status (adjusted OR, 1.86 [95% CI, 1.03-3.36]; P = .04). Third-trimester infection was associated with effects of larger magnitude (adjusted OR, 2.34 [95% CI, 1.23-4.44]; P = .01).

CONCLUSIONS AND RELEVANCE
This cohort study of SARS-CoV-2 exposure in utero found preliminary evidence that maternal SARS-CoV-2 may be associated with neurodevelopmental sequelae
in some offspring. Prospective studies with longer follow-up duration will be required to exclude confounding and confirm these associations.

14. Guiding Principles and Member Guidance: Maternal CV Care

Background:

The ACC has long advocated for patients engaging with their doctor and the cardiovascular care team about their heart health and related risks. Shared decision-making is an essential tool in helping to navigate the risks and benefits of all treatment options, taking into account the latest science and medical evidence, social determinants of health, emphasis on health equity, and the patient’s own beliefs and goals.

While the ACC has no official policy on abortion, clinical practice guidelines and other clinical guidance tools address the dangers of pregnancy in certain patient populations at higher risk of death or serious cardiac events. As such, the College is deeply concerned about the potential implications of the Supreme Court decision regarding Dobbs vs. Jackson on the ability of patients and clinicians to engage in important shared discussions about maternal health, or to remove previously available health care options, especially given the alarming maternal health crisis in the U.S.

Similar to topics like gun violence that impact the broader medical community and the patients we serve, the ACC will continue to work with the larger House of Medicine to address specific laws and policies as they move forward that would threaten or criminalize patient-clinician discussions regarding maternal cardiovascular care.

Guiding Principles:

ACC’s mission is to transform cardiovascular care and improve heart health. We are patient-centered in our decisions and value teamwork, collaboration, professionalism and excellence.

1. Cardiovascular disease is the leading cause of maternal mortality, a substantial and growing problem in the US. A recent study noted a 33% increase in US maternal mortality during the pandemic.
2. Cardiovascular professionals are experts in the care of women with cardiovascular disease who are or may become pregnant.
3. The field of cardio-obstetrics is one of the fastest growing fields in CV medicine, and has developed a growing body of medical science, scientific literature, and practice standards (e.g. JACC five-part Cardio-Obstetrics Focus Seminar).
4. Cardiovascular professionals bear professional responsibility to women with a variety of cardiovascular diseases which may create substantial risk of morbidity and mortality during pregnancy.

5. Our standards of practice include counseling and shared decision-making with our patients regarding use of contraception and pregnancy termination. Important components of these decisions include knowledge of maternal risks associated with certain cardiovascular conditions and patients' values, goals and willingness to take risk. These are among the hardest conversations that we undertake as cardiovascular professionals.

6. We have a common interest in ensuring that cardiovascular professionals can continue to provide optimal cardiovascular care to produce the best possible outcomes for our pregnant patients with cardiovascular disease.

7. The law must allow space for cardiovascular professionals to provide counseling to pregnant patients with cardiovascular disease that includes all medically-appropriate options, as established by medical science and practice standards.

**Member Guidance:**

1. Cardiovascular professionals caring for pregnant women with heart disease should work in multi-disciplinary teams, with the patient at the center of each team. These teams are more common in large hospital systems or multispecialty clinics.

2. Health care professionals managing the care of pregnant women with cardiovascular disease who are not supported by a large enterprise should consider referring these patients to larger systems with more layers of support and experience.

3. In states currently or imminently restricting abortion, clinicians caring for pregnant women with heart disease should seek the counsel of risk management experts within their system and their hospital staff leadership. They should also work with their state medical societies and state representatives for the American College of Obstetrics and Gynecology (ACOG) to understand the relevant laws in their state.

4. Cardiovascular professionals providing telehealth consultations for pregnant women with cardiovascular disease across state lines should obtain legal support from counsel in the state where the patient resides as well as their home state/institution.

5. Cardiovascular professionals who provide care to women of childbearing age should understand the tools used to predict risk conferred by various types of cardiovascular disease and pregnancy and understand which forms of contraception are safe to use. Clinicians without relevant expertise or experience should identify the cardio-obstetric and women's heart health programs best suited to provide care to their patients.

6. Individual hospitals and health systems should communicate with their state medical societies and ACOG chapters concerning this issue. **Angela**
Shuman, ACC Director of State Government Affairs, and her team can facilitate contact with the state medical society's staff as needed.

7. The ACC's Cardio-Obstetrics Work Group will be developing a set of educational tools that can be used for the following purposes:
   a. Formal educational presentations to colleagues
   b. Educational materials for PCP and ObGyns and other medical team members
   c. Educational materials which can be used to educate elected state officials (via email, social media and in-person visits)
   d. Patient education materials about heart disease and pregnancy risk, cardiovascular health promotion, and wellness

15. Contributions of the Women’s Health Initiative to Cardiovascular Research: JACC State-of-the-Art Review

Abstract

The WHI (Women’s Health Initiative) enrolled 161,808 racially and ethnically diverse postmenopausal women, ages 50-79 years, from 1993 to 1998 at 40 clinical centers across the United States. In its clinical trial component, WHI evaluated 3 randomized interventions (menopausal hormone therapy; diet modification; and calcium/vitamin D supplementation) for the primary prevention of major chronic diseases, including cardiovascular disease, in older women. In the WHI observational study, numerous clinical, behavioral, and social factors have been evaluated as predictors of incident chronic disease and mortality. Although the original interventions have been completed, the WHI data and biomarker resources continue to be leveraged and expanded through ancillary studies to yield novel insights regarding cardiovascular disease prevention and healthy aging in women.

Highlights

• The WHI included 3 randomized trials and a parallel observational study addressing pivotal questions pertaining to the cardiovascular health of postmenopausal women.

• Data from wearable technologies, collected biological specimens, and embedded pragmatic trials will enrich the already extensive WHI resources.
• Long-term follow-up of women enrolled in the large WHI cohort provides insights into cardiovascular resiliency and healthy aging.

16. Sex-related differences in the management and outcomes of patients hospitalized with ST-elevation myocardial infarction: a comparison within four European myocardial infarction registries

Aims

Data on how differences in risk factors, treatments, and outcomes differ between sexes in European countries are scarce. We aimed to study sex-related differences regarding baseline characteristics, in-hospital managements, and mortality of ST-elevation myocardial infarction (STEMI) patients in different European countries.

Methods and results

Patients over the age of 18 with STEMI who were treated in hospitals in 2014–17 and registered in one of the national myocardial infarction registers in Estonia ($n=5817$), Hungary ($n=30787$), Norway ($n=33054$), and Sweden ($n=49533$) were included. Cardiovascular risk factors, hospital treatment, and recommendation of discharge medications were obtained from the infarction registries. The primary outcome was mortality, in-hospital, after 30 days and after 1 year. Logistic and cox regression models were used to study the associations of sex and outcomes in the respective countries. Women were older than men (70–78 and 62–68 years, respectively) and received coronary angiography, percutaneous coronary intervention, left ventricular ejection fraction assessment, and evidence-based drugs to a lesser extent than men, in all countries. The crude mortality in-hospital rates (10.9–15.9 and 6.5–8.9%, respectively) at 30 days (13.0–19.9 and 8.2–10.9%, respectively) and at 1 year (20.3–28.1 and 12.4–17.2%, respectively) after hospitalization were higher in women than in men. In all countries, the sex-specific differences in mortality were attenuated in the adjusted analysis for 1-year mortality.

Conclusion

Despite improved awareness of the sex-specific inequalities on managing patients with acute myocardial infarction in Europe, country-level data from this study show that women still receive less guideline-recommended management.
17. Infertility, Miscarriage Linked to Increased Risk for Stroke

Infertility, recurrent miscarriage, and stillbirth are associated with an increased risk for stroke, according to a study published online June 22 in *The BMJ*.

Chen Liang, from the University of Queensland in Brisbane, Australia, and colleagues examined the associations of infertility, recurrent miscarriage, and stillbirth with the risk for first nonfatal and fatal stroke using individual participant pooled data from eight prospective cohort studies. A total of 618,851 women aged 32 to 73 years at baseline were included, with follow-up of a median of 13.0 years for nonfatal stroke and 9.4 years for fatal stroke.

Infertility was associated with an increased risk for nonfatal stroke (hazard ratio, 1.14), while recurrent miscarriage (at least three) was associated with an increased risk for nonfatal and fatal stroke (hazard ratios, 1.35 and 1.82, respectively). The risk for nonfatal stroke was increased for women with stillbirth (hazard ratio, 1.31), while those with recurrent stillbirth had an increased risk for fatal stroke (hazard ratio, 1.26). A single stroke subtype was the main driver for the increased risk for stroke associated with infertility or recurrent stillbirths (nonfatal ischemic stroke and fatal hemorrhagic stroke, respectively), while both subtypes drove the increased risk for stroke associated with recurrent miscarriages.

18. Maternal Mortality Up by One-Third During the Pandemic

Maternal mortality significantly increased during the COVID-19 pandemic, according to a research letter published online June 28 in *JAMA Network Open*.

Marie E. Thoma, Ph.D., from University of Maryland in College Park, and Eugene R. Declercq, Ph.D., from Boston University, analyzed deidentified U.S. National Center for Health Statistics mortality and natality files from 2018 to 2020 to examine the pandemic’s role in 2020 maternal death rates.

The researchers found 18.8 maternal deaths per 100,000 live births before the pandemic versus 25.1 per 100,000 during the pandemic (April to December 2020), a relative increase of 33.3 percent. There was a 41 percent increase seen in late maternal mortality. Both absolute and relative changes were highest for Hispanic (8.9 per 100,000 live births and 74.2 percent, respectively) and non-Hispanic Black (16.8 per 100,000 and 40.2 percent, respectively) versus non-Hispanic White women (2.9 per 100,000 and 17.2 percent, respectively). For quarters 2 to 4 in 2020, a secondary code for COVID-19 was listed in 14.9 percent of maternal deaths versus zero in quarter 1. The largest relative increase in underlying cause-of-death codes was among indirect causes (56.9 percent), specifically other viral diseases (2,374.7 percent), diseases of the respiratory system (117.7 percent), and diseases of the circulatory system (72.1 percent). It was common for COVID-19 to be listed as a secondary condition with other viral
diseases (16 of 16 deaths) and diseases of the respiratory system (11 of 19 deaths).

“In the United States, maternal deaths increased substantially (33.3 percent) after March 2020, corresponding to COVID-19 onset, a figure higher than the 22 percent overall excess death estimate associated with the pandemic,” the authors write.

19. Maternal Vaccination and Risk of Hospitalization for COVID-19 Among Infants

BACKGROUND

Infants younger than 6 months of age are at high risk for complications of coronavirus disease 2019 (Covid-19) and are not eligible for vaccination. Transplacental transfer of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after maternal Covid-19 vaccination may confer protection against Covid-19 in infants.

METHODS

We used a case-control test-negative design to assess the effectiveness of maternal vaccination during pregnancy against hospitalization for Covid-19 among infants younger than 6 months of age. Between July 1, 2021, and March 8, 2022, we enrolled infants hospitalized for Covid-19 (case infants) and infants hospitalized without Covid-19 (control infants) at 30 hospitals in 22 states. We estimated vaccine effectiveness by comparing the odds of full maternal vaccination (two doses of mRNA vaccine) among case infants and control infants during circulation of the B.1.617.2 (delta) variant (July 1, 2021, to December 18, 2021) and the B.1.1.259 (omicron) variant (December 19, 2021, to March 8, 2022).

RESULTS

A total of 537 case infants (181 of whom had been admitted to a hospital during the delta period and 356 during the omicron period; median age, 2 months) and 512 control infants were enrolled and included in the analyses; 16% of the case infants and 29% of the control infants had been born to mothers who had been fully vaccinated against Covid-19 during pregnancy. Among the case infants, 113 (21%) received intensive care (64 [12%] received mechanical ventilation or vasoactive infusions). Two case infants died from Covid-19; neither infant's mother had been vaccinated during pregnancy. The effectiveness of maternal vaccination against hospitalization for Covid-19 among infants was 52% (95% confidence interval [CI], 33 to 65) overall, 80% (95% CI, 60 to 90) during the delta period, and 38% (95% CI, 8 to 58) during the omicron period. Effectiveness was 69% (95% CI, 50 to 80) when maternal vaccination occurred after 20 weeks of pregnancy and 38% (95% CI, 3 to 60) during the first 20 weeks of pregnancy.
CONCLUSIONS

Maternal vaccination with two doses of mRNA vaccine was associated with a reduced risk of hospitalization for Covid-19, including for critical illness, among infants younger than 6 months of age. (Funded by the Centers for Disease Control and Prevention.).

20. Hematopoietic Loss of Y Chromosome Leads to Cardiac Fibrosis and Heart Failure Mortality

The Y chromosome is good for something after all!

Loss of Y and cardiac fibrosis and outcomes

We increasingly recognize previously unsuspected links across aging, cancer, and genetic abnormalities that elevate the risk of cardiovascular disease.\textsuperscript{1-3} Certain acquired genetic abnormalities accumulate with age, distinct from germline mutations inherited from our parents, and can contribute to this nexus. People can have various portions of circulating leukocytes that bear these genetic alterations, yielding a mixed genetic state known as mosaicism. The Walsh laboratory has studied one of these age-related acquired genetic issues caused by casting off of the Y chromosome, the signature package of genetic information found in biological males, in some of the white cells in blood.\textsuperscript{4} This condition, known as “Loss of Y,” is associated with various diseases in ways that have remained incompletely understood.

This new study, performed in mice, is a systematic and comprehensive evaluation of Loss of Y using genetic manipulations.\textsuperscript{3} The authors found that the experimentally induced Loss of Y increased mortality, impaired heart function, and increased fibrous tissue in the heart. The authors also interrogated a large database derived from apparently well people in the United Kingdom, the UK Biobank, and found an increase in death and cardiovascular disease in men with Loss of Y roughly proportional to the burden of cells that have lost this chromosome.

Further studies on the cells derived from these mice engineered to have Loss of Y implicated a known pathway that causes fibrosis — an action of the protein transforming growth factor beta. Administering an antibody to block transforming growth factor beta ameliorated some of the ill effects on the heart. Curiously, the interleukin beta proinflammatory pathway implicated in augmented cardiovascular risk due to certain acquired mutations in leukemia driver genes (eg, TET2) actually declines in the mice with experimental Loss of Y.

From a cardiologic viewpoint, it would be interesting to know whether individuals with heart failure with preserved ventricular function have a higher prevalence
of Loss of Y due to the augmented myocardial fibrosis. While this form of heart failure is more common in women, perhaps the Loss of Y predisposes this type of heart failure in men.

This study provides new insight into this nexus between aging and acquired genetic abnormalities that accumulate during life, which are not at all uncommon in the older population. As transforming growth factor beta is a “double-edged sword” that can exert anti-inflammatory as well as profibrotic actions, its blockade will not likely be a viable therapy in humans with Loss of Y. However, these new data do suggest a hint regarding the development of more targeted approaches to mitigate some of the adverse consequences of this acquired condition.

While oncologists have used genetic data to target specific therapies for over 20 years, the cardiovascular field has lagged in this respect despite widespread and often successful use of this approach in cancer management. Studies such as this one point towards adopting genetically (or cytogenetically) targeted therapeutic interventions in cardiovascular medicine.

21. Contributions of the Women’s Health Initiative to Cardiovascular Research: JACC State-of-the-Art Review

Abstract

The WHI (Women’s Health Initiative) enrolled 161,808 racially and ethnically diverse postmenopausal women, ages 50-79 years, from 1993 to 1998 at 40 clinical centers across the United States. In its clinical trial component, WHI evaluated 3 randomized interventions (menopausal hormone therapy; diet modification; and calcium/vitamin D supplementation) for the primary prevention of major chronic diseases, including cardiovascular disease, in older women. In the WHI observational study, numerous clinical, behavioral, and social factors have been evaluated as predictors of incident chronic disease and mortality. Although the original interventions have been completed, the WHI data and biomarker resources continue to be leveraged and expanded through ancillary studies to yield novel insights regarding cardiovascular disease prevention and healthy aging in women.

Highlights

• The WHI included 3 randomized trials and a parallel observational study addressing pivotal questions pertaining to the cardiovascular health of postmenopausal women.
• Data from wearable technologies, collected biological specimens, and embedded pragmatic trials will enrich the already extensive WHI resources.

• Long-term follow-up of women enrolled in the large WHI cohort provides insights into cardiovascular resiliency and healthy aging.

22. Peripartum Cardiomyopathy: A Cardiologists Perspective

Peri-partum cardiomyopathy is a form of heart failure affecting young mothers during later stages of pregnancy or early post-partum. Medical management should be tailored to improving the mother’s health while ensuring safety of the baby.

Which of the currently available heart failure drugs are safe in pregnancy and during breast feeding? What are the outcomes of women with peripartum cardiomyopathy, who undergo LVAD implantation or heart transplantation?

In this interview, Dharini Ramu, MD, FACC and Spencer B. King III, MD, MACC, with Yuvraj Chowdhury MD, discuss Medical and Advanced Heart Failure Therapies in Peri-partum cardiomyopathy: A Cardiologist’s Perspective.

23. BBs, ACEI/ARBs to Prevent LV Dysfunction Due to Breast Cancer Drugs

Study Questions:

Are beta-blockers (BBs) and renin-angiotensin system blockers effective at preventing the decline in ejection fraction (EF) of women with breast cancer receiving trastuzumab, anthracyclines, or both?

Methods:

This study is a meta-analysis assessing the effect of BBs and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) on left ventricular ejection fraction (LVEF) in patients treated with either trastuzumab, anthracyclines, or both. Meta-analyses estimated the pooled mean difference (MD) of LVEF at the follow-up time and associated 95% confidence intervals (CIs) between the group randomized to either BB or ACEI/ARB treatment versus a control group receiving placebo.
Results:

A total of nine randomized controlled trials (n = 1,362) were included in the analysis; three studies examined the preventive effect of heart failure treatments with trastuzumab and six with anthracycline treatments. Sample size varied from 45 to 469 patients. Two thirds of studies had high risk of bias and moderate to high heterogeneity. All patients were women. Mean age varied from 40.8 to 53.6 years. The baseline LVEF means varied between 59.5% and 66.0%. ACEI/ARB therapy irrespective of concomitant anthracycline or trastuzumab therapy was not significantly associated with improved LVEF compared to placebo (MD, 1.5; 95% CI, −0.6 to 3.7; p = 0.11; $I^2 = 52\%$). In contrast, BB therapy preserved LVEF significantly better compared with placebo (MD, 2.4; 95% CI, 0.3–4.5; p = 0.033; $I^2 = 82\%$). Both ACEI/ARBs and BBs were associated with preservation of LVEF compared to placebo in recipients of trastuzumab alone (MD, 2.3; 95% CI, 0.0–4.6; p = 0.047; $I^2 = 72\%$), but not anthracycline alone (MD, 1.9; 95% CI, −0.5 to 4.2; p = 0.096; $I^2 = 77\%$). Whether LVEF was a primary outcome or not did not influence the MD (p = 0.65), nor did the imaging modality.

Conclusions:

This meta-analysis suggests BBs and ACEI/ARBs may be effective in preventing decline in LVEF in women with breast cancer undergoing treatment with trastuzumab and/or anthracyclines.

24. **Sex steroids and markers of micro- and macrovascular damage among women and men from the general population**

**Aims**

The contribution of sex hormones to micro- and macrovascular damage might differ among women and men. In particular, little is known about the association between sex hormones and small vessel disease. Therefore, we examined the association of total oestradiol, total testosterone, free-androgen index (FAI), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione levels with micro- and macrovascular diseases.

**Methods and results**

This cross-sectional study included 2950 women and 2495 men from the population-based Rotterdam Study. As proxy of microvascular damage, we measured diameters of retinal arterioles and venules. Markers of macrovascular damage included carotid intima-media thickness and carotid plaque, coronary artery calcification (CAC), and peripheral artery disease. Linear and logistic
regression models were used and adjusted for age, cardiovascular risk factors, and years since menopause. **Associations with microvasculature:** In women, total testosterone [mean difference per 1-unit increase in natural-log transformed total testosterone (95% confidence interval, CI): 2.59 (0.08–5.09)] and androstenedione [4.88 (1.82–7.95)] and in men DHEAS [2.80 (0.23–5.37)] and androstenedione [5.83 (2.19–9.46)] were associated with larger venular caliber. **Associations with markers of large vessel disease:** In women, higher total testosterone [−0.29 (−0.56 to −0.03)], FAI [−0.33 (−0.56 to −0.10)], and androstenedione levels [−0.33 (−0.64 to −0.02)] were associated with lower CAC burden and FAI [odds ratio (95% CI): 0.82 (0.71–0.94)] was associated with lower prevalence of plaque.

**Conclusion**
A more androgenic profile was associated with more microvascular damage in both women and men. Among women, however, higher androgen levels were also associated with less macrovascular damage. Our findings suggest that androgens might have distinct effects on the vasculature, depending on the vascular bed and stages of the atherosclerosis process.

**25. Endometriosis Linked to Greater Risk for Stroke**

Women with laparoscopically confirmed endometriosis may have an increased risk for stroke, according to a study published online July 21 in *Stroke*.

Leslie V. Farland, Sc.D., from the University of Arizona in Tucson, and colleagues followed participants in the Nurses' Health Study II from 1989 when they were aged 25 to 42 years until 2017 for development of incident stroke. The association between laparoscopically confirmed endometriosis and risk for incident stroke was examined, with adjustment for potentially confounding variables.

The researchers identified 893 incident cases of stroke during 2,770,152 person-years of follow-up. In multivariable-adjusted models, the risk for stroke was significantly increased for women with laparoscopically confirmed endometriosis versus those without a history of endometriosis (hazard ratio, 1.34). The largest proportion of the total association of endometriosis with the risk for stroke was attributed to hysterectomy/oophorectomy and hormone therapy (39 and 16 percent mediated, respectively). There were no differences seen in the association...
between endometriosis and stroke based on age, history of infertility, body mass index, or menopausal status.

"These results do not indicate that women who have endometriosis will have a stroke. Instead, these findings signify only an association of moderate relative risk. The absolute risk of stroke in women is low," a coauthor said in a statement. "Women with endometriosis should pay attention to their whole body and discuss added risks and preventive options with their health care team."

Several authors disclosed financial ties to the pharmaceutical, medical device, and health technology industries.