

## **News in January 2023**

### **1. 1975 to 2019 Saw Decrease in Stroke Mortality for Men, Women**

From 1975 to 2019, there was a decrease in age-standardized stroke mortality for men and women, according to a study recently published in the *International Journal of Epidemiology*.

Cande V. Ananth, Ph.D., M.P.H., from Rutgers Robert Wood Johnson Medical School in New Brunswick, New Jersey, and colleagues conducted a sequential time series analysis to examine stroke mortality trends among 4,332,220 people aged 18 to 84 years in the United States between 1975 and 2019. Trends in overall, ischemic, and hemorrhagic stroke were examined.

The researchers found that from 1975 to 2019, there was a decrease in age-standardized stroke mortality from 87.5 to 30.9 per 100,000 (incidence rate ratio, 0.27; average annual decline, -2.78 percent). Among men, the age-standardized mortality rate decreased from 112.1 to 38.7 per 100,000 (incidence rate ratio, 0.26; average annual decline, -2.80 percent). With increasing age, stroke mortality increased sharply. A steeper decline in ischemic than in hemorrhagic strokes was observed.

"The contribution of predisposing risk factors to declines in stroke mortality underscores opportunities to develop public health campaigns and interventions to reduce untoward behaviors that negatively affect stroke and metabolic health," the authors write.

### **2. Women With Cycle Disorders Across Their Life Span May Be at Increased Risk of Cardiovascular Disease**

Irregular and especially long menstrual cycles, particularly in early and mid adulthood, are associated with an increased risk for cardiovascular disease. This finding is demonstrated in a new analysis of the Nurses' Health Study II.

"To date, several studies have reported increased risks of cardiovascular risk factors or cardiovascular disease in connection with cycle disorders," wrote Yi-Xin Wang, MD, PhD, a research fellow in nutrition, and his team from the Harvard T. H. Chan School of Public Health in Boston, in [an article](#) published in *JAMA Network Open*.

Ute Seeland, MD, speaker of the Gender Medicine in Cardiology Working Group of the German Cardiology Society, told *Medscape Medical News*, "We know that women who have indicated in their medical history that they have irregular menstrual cycles, invariably in connection with polycystic ovary syndrome (PCOS), more commonly develop diabetes and other metabolic disorders, as well as cardiovascular diseases."

#### Cycle Disorders' Role

However, the role that irregular or especially long cycles play at different points of a woman's reproductive life span was unclear. Therefore, the research group investigated the associations in the Nurses' Health Study II between cycle irregularity and cycle length in women of different age groups who later experienced cardiovascular events.

At the end of this study in 1989, the participants also provided information regarding the length and irregularity of their menstrual cycle from ages 14 to 17 years and again from ages 18 to 22 years. The information was updated in 1993 when the participants were aged 29 to 46 years. The data from 2019 to 2022 were analyzed.

"This kind of long-term cohort study is extremely rare and therefore something special," said Seeland, who conducts research at the Institute for Social Medicine, Epidemiology, and Health Economics at the Charité – University Hospital Berlin.

The investigators used the following cycle classifications:

- very regular (no more than 3 or 4 days before or after the expected date)
- regular (within 5 to 7 days)
- usually irregular

- always irregular
- no periods

### **3. Sex-specific time trends in incident atrial fibrillation and the contribution of risk factors: the Tromsø Study 1994–2016**

#### **Aims**

To explore sex-specific time trends in atrial fibrillation (AF) incidence and to estimate the impact of changes in risk factor levels using individual participant-level data from the population-based Tromsø Study 1994–2016.

#### **Methods and results**

A total of 14 818 women and 13 225 men aged 25 years or older without AF were enrolled in the Tromsø Study between 1994 and 2008 and followed up for incident AF throughout 2016. Poisson regression was used for statistical analyses. During follow-up, age-adjusted AF incidence rates in women decreased from 1.19 to 0.71 per 1000 person-years. In men, AF incidence increased from 1.18 to 2.82 per 1000 person-years in 2004, and then declined to 1.94 per 1000 person-years in 2016. Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP), body mass index (BMI), physical activity, smoking and alcohol consumption together accounted for 10.9% [95% confidence interval (CI): -2.4 to 28.6] of the AF incidence decline in women and for 44.7% (95% CI: 19.2; 100.0) of the AF incidence increase in men. Reduction in SBP and DBP had the largest contribution to the decrease in AF incidence in women. Increase in BMI had the largest contribution to the increase in AF incidence in men.

#### **Conclusion**

In the population-based Tromsø Study 1994–2016, AF incidence decreased in women and increased following a reverse U-shape in men. Individual changes in SBP and DBP in women and individual changes in BMI in men were the most important risk factors contributing to the AF incidence trends.

#### **4. What is the Impact of Isolated IHD on Outcomes in Pregnant Women During Delivery Hospitalization?**

Isolated pre-existing ischemic heart disease (IHD) in pregnancy is associated with worse outcomes at the time of delivery compared with patients with no cardiac diagnosis, with a level of risk similar to that associated with World Health Organization (WHO) class I-II cardiac diagnoses, according to a study published Dec. 14 in *JACC: Advances*.

**Anna E. Denoble, MD, MSCR**, et al., conducted a retrospective cohort study using data collected from

2015 to 2018 in the Nationwide Readmissions Database (NRD) to compare adverse pregnancy outcomes between those with isolated IHD and those with other cardiac diagnoses in the modified WHO classification (mWHO) and those without a cardiac diagnosis. The mWHO classification of maternal cardiovascular risk is widely used to counsel patients with pre-existing cardiac disease during pregnancy but does not include IHD.

Results showed that of 11,556,136 hospitalizations for delivery, IHD alone was identified in 3,009 and other cardiac diagnoses in 63,331. Patients with IHD were older and had higher rates of diabetes and hypertension.

Unadjusted analyses showed that adverse outcomes were more common among patients with isolated IHD. After adjustment, the risk of a primary outcome event, defined as severe maternal morbidity (SMM) or death during the delivery hospitalization, was higher among patients with IHD alone (adjusted relative risk [aRR]), 1.51; 95% CI, 1.19-1.92) vs. those without cardiac disease. Furthermore, the aRR was 1.90 for WHO class I-II diseases and 5.87 for WHO II/III-IV diseases.

Patients with isolated IHD were also at higher risk for nontransfusion SMM or death (aRR, 1.60) and cardiac SMM or death (aRR, 2.98).

The authors note that, to their knowledge, this is the largest analysis to date examining the risk of severe morbidity and mortality among pregnant people with IHD. The relative risk of SMM and mortality IHD compared with patients with no cardiac disease was similar with that for cardiac lesions classified as mWHO class I or II, suggesting that an IHD diagnosis should be considered for addition to mWHO class I or II to further refine the classification schema, and that these “data will aid clinicians in counseling patients with pre-existing IHD.”

### **5. Long-Term Health Consequences Seen for Stroke in Pregnancy**

Amy Y.X. Yu, M.D., from the University of Toronto and Sunnybrook Health Sciences Centre, and colleagues used administrative data to identify pregnant adults aged 49 years or younger with stroke between 2002 and 2020 and two comparison groups: nonpregnant women with stroke and pregnant patients without stroke. After propensity score matching, pregnant patients with stroke were compared to the two comparison groups for the composite outcomes of death and all-cause nonpregnancy readmission.

Data were included for 217 pregnant patients with stroke, 7,604 nonpregnant patients with stroke, and 1,496,256 pregnant patients without stroke. The researchers found that 41.6 percent of the 202 pregnant patients with stroke who survived the index stroke admission subsequently died or were readmitted during follow-up. At one-year follow-up, pregnant patients with stroke had a lower risk for death and all-cause readmission compared with nonpregnant patients with stroke (hazard ratio, 0.64); during longer-term follow-up, this association did not persist. In contrast, a higher risk for death and readmission was seen for pregnant patients with stroke versus pregnant patients without stroke at one year (hazard ratio, 5.70), and this association persisted for 10 years.

“Stroke during pregnancy is associated with long-term health consequences,” the authors write. “It is essential to transition care postpartum to primary or specialty care to optimize vascular health.”

## **6. Meta-Analysis: Men May Have Larger, More Pronounced Carotid Atherosclerotic Plaques**

A new meta-analysis suggests there may be sex differences in carotid atherosclerosis. Overall, men had more and larger plaques, and these plaques had more features than those in women, the analysis shows.

This information was reported by Dianne H.K. van Dam-Nolen, MD, of Erasmus University Medical Center in Rotterdam, the Netherlands, and colleagues in a manuscript published Monday online and in a special issue of *Stroke* focused on cerebrovascular diseases in women, published in conjunction with the American Heart Association’s [Go Red for Women initiative](#)

It is estimated that 10% to 15% of all ischemic strokes are caused by carotid atherosclerosis. Men are at greater risk for ischemic stroke over a lifetime, and are more likely to have large-artery related atherosclerosis, than women. Women are more likely to experience cardioembolic strokes. Women are also at higher risk for perioperative stroke and death, and benefit less from surgery overall.

Various studies have tackled the question of sex differences in carotid atherosclerosis, addressing symptomatic vs. nonsymptomatic patients, mild vs. severe cases and overall assessment of plaques in the disease. This study focused on reviewing the literature on sex differences in carotid atherosclerosis and providing a comprehensive summary of the findings.

PubMed, Embase, Web of Science, Cochrane Central and Google Scholar were used to find the 42 studies analyzed in this review. The studies had to include reports of calcifications, lipid-rich necrotic core, intraplaque hemorrhage, thin or

ruptured fibrous cap, plaque ulceration, degree of stenosis, plaque size or plaque inflammation. Studies using ultrasonography were excluded.

Compared with women, men had larger plaques and plaques with calcifications more often (odds ratio [OR]=1.57; 95% confidence interval [CI]=1.23–2.02) as well as lipid-rich necrotic core (OR=1.87, 95% CI=1.36–2.57), and intraplaque hemorrhage (OR=2.52, 95% CI=1.74–3.66) or an ulcerated plaque (OR=1.81, 95% CI=1.30–2.51). Symptomatic participants demonstrated more sex differences for lipid-rich necrotic core than asymptomatic participants.

No sex differences were found in the normalized wall index. All three measures of plaque size (one-, two- and three-dimensional) were sex-dependent, with men having larger plaque sizes. Some mechanisms have been proposed to underly the differences between men and women in carotid atherosclerosis, such as sex hormones, systemic inflammation and genetics. The gut microbiome has also been a focus of study for prevention of cardiovascular disease, and may play its role as a mediator in the development of carotid atherosclerosis, the authors wrote.

The investigators concluded that sex is an important variable to consider in clinical and research settings. Every type of plaque feature — including lipid-rich necrotic core, intraplaque hemorrhage and calcification—was more common in men compared with women. They noted that future studies should focus on sex-specific stroke risks and review plaque composition.

## **7. Gender Disparity Persists in Leadership of Stroke-Related Trials, Analysis Shows**

Leadership of stroke-related clinical trials still is weighted more heavily toward men, despite women making gains in neurology faculty over the last decade, new study results show.

Bharat Rawley, MBBS, of the State University of New York Upstate Medical University, Syracuse, and colleagues, reported these findings in a manuscript published Monday online and in a special issue of *Stroke* focused on cerebrovascular diseases in women, published in conjunction with the American Heart Association's Go Red for Women initiative.

Studies show differences in stroke rate and consequences between men and women, and both sex and gender can influence clinical treatment of stroke. While efforts have been made to recruit more female patients into clinical trials, the presence of a gender cap in stroke-related clinical trial leadership in North America had not previously been reported.

The authors, therefore, examined gender disparity in stroke-related clinical trial leadership from 2011 to 2020 by analyzing the gender of trial principal investigators and authors.

Rawley and colleagues analyzed 821 clinical trials registered on ClinicalTrials.gov and 110 published on PubMed. Their analysis showed that the gender disparity among principal investigators and first and last authors of manuscripts was maintained throughout the 2010s and that there was not a significant trend toward parity.

Men were overrepresented among principal investigators (78.11% vs. 21.87%;  $p < 0.01$ ) as well as leaders of trials studying acute stroke (86.04% vs. 13.89%;  $p < 0.01$ ). The study also showed that a lower proportion of female neurology residents pursued vascular neurology fellowships during the decade (33.5% vs. 42.5%;  $p < 0.05$ ). This was despite the percentage of women in neurology faculty rising from 34.6% in 2011 to 42.56% in 2020.

The authors noted that the persistent gender gap in clinical trial leadership is “not exclusive to the stroke field and represents broader, interacting, and social cultural factors that have been barriers against women in science,” which



were reported by the National Academies of Science, Engineering, and Medicine in 2007.

Despite this, Rawley and colleagues noted that the proportion of women leading stroke-related clinical trials that were funded by the National Institutes of Health or other federal agencies fared better than that of overall stroke-related trials, which they said, “is likely reflective of the initiatives taken towards supporting the advancement of women faculty and increasing their academic productivity.”

The authors said their findings show “a more comprehensive, multifaceted and inclusive effort” to increase access to funding for women and underrepresented minorities is warranted. Such an effort should include the “creation of flexible policies that cater to some of the disproportionate challenges women face, such as access to childcare support, allowing for re-entry and re-integration into the academic sphere, flexibility in promotion tracks,” and that it should be supplemented by mentorship, additional training “and identifying diverse candidates when opportunities for promotion and speaking engagements arise,” Rawley and colleagues wrote.

## **8. Prognostic implications of myocardial perfusion imaging by 82-rubidium positron emission tomography in male and female patients with angina and no perfusion defects**

### **Aims**

Myocardial perfusion imaging with 82-rubidium positron emission tomography (<sup>82</sup>Rb-PET) is increasingly used to assess stable coronary artery disease (CAD). We aimed to evaluate the prognostic value of <sup>82</sup>Rb-PET-derived parameters in

patients with symptoms suggestive of CAD but no significant reversible or irreversible perfusion defects.

### **Methods and results**

Among 3726 consecutive patients suspected of stable CAD who underwent  $^{82}\text{Rb}$ -PET between January 2018 and August 2020, 2175 had no regional perfusion defects. Among these patients, we studied the association of  $^{82}\text{Rb}$ -PET-derived parameters with a composite endpoint of all-cause mortality, hospitalization for unstable angina pectoris, acute myocardial infarction, heart failure, or ischaemic stroke. During a median follow up of 1.7 years (interquartile range 1.1–2.5 years), there were 148 endpoints. Myocardial blood flow (MBF) reserve (MFR), MBF during stress, left ventricular ejection fraction (LVEF), LVEF-reserve, heart rate reserve, and Ca score were associated with adverse outcomes. In multivariable Cox model adjusted for patient and  $^{82}\text{Rb}$ -PET characteristics, MFR < 2 (hazard ratio (HR) 1.75, 95% confidence interval (CI) 1.24–2.48), LVEF (HR 1.38 per 10% decrease, 95% CI 1.24–1.54), and LVEF-reserve (HR 1.19 per 5% decrease, 95% CI 1.07–1.31) were significant predictors of endpoints. Results were consistent in subgroups defined by gender, history of ischaemic heart disease, low LVEF, and atrial fibrillation.

### **Conclusion**

MFR, LVEF, and LVEF-reserve derived from  $^{82}\text{Rb}$ -PET provide prognostic information on cardiovascular outcomes in patients with no perfusion defects. This may aid in identifying patients at risk and might provide an opportunity for preventive interventions.

## **9. Rural Residence Tied to Higher Risk for Heart Failure for Women, Black Men**

Rural residence is associated with an increased risk for heart failure among women and Black men, according to a study published online Jan. 25 in *JAMA Cardiology*.

Sarah E. Turecamo, from the U.S. National Institutes of Health in Bethesda, Maryland, and colleagues assessed whether rurality is associated with an increased risk for heart failure. The analysis included data from 27,115 participants (68.8 percent Black; median age, 54 years) in the Southern Community Cohort Study.

The researchers found that during a median 13-year follow-up, age-adjusted heart failure incidence was 29.6 per 1,000 person-years for urban participants and 36.5 per 1,000 person-years for rural participants. A greater risk for incident heart failure existed for rural versus urban participants even after adjusting for demographic information, cardiovascular risk factors, health behaviors, and socioeconomic status. There was variance seen in rurality-associated risk across race and sex. Risk was greatest among Black men, followed by White women and Black women. Rurality was not associated with a greater risk for incident heart failure for White men.

"This inequity points to a need for additional emphasis on primary prevention of heart failure among rural populations," the authors write.

## **10. Causes of SCD According to Age and Sex in Persons Aged 1 to 49 Years**

### BACKGROUND

Knowledge of causes of sudden cardiac death (SCD) according to age is important in clinical decision making and to lower the risk of SCD in family members of the deceased.

### OBJECTIVE

The purpose of this study was to report overall and sex-stratified causes of SCD according to age in persons aged 1-49 years.

## METHODS

The study population consisted of all persons in Denmark aged 1-35 years in 2000-2009 and 36-49 years in 2007-2009, which equals 27.1 million person-years. Danish death certificates, discharge summaries, autopsy reports, and data from nationwide registries were used to identify all SCD cases. The SCD cases were divided into 5-year age groups.

## RESULTS

In the 10-year study period, there were 14,294 deaths, of which 1362 (10%) were classified as SCD. Potentially inherited cardiac disease accounted for a high proportion (43%-78%) of autopsied SCD in all age groups. A significant proportion (19%-54%) of SCD was caused by sudden arrhythmic death syndrome in all age groups. Autopsy rates in both sudden unexpected death cases and SCD cases declined significantly with increasing age (74% in the youngest age group vs 35% in the oldest).

## CONCLUSION

The proportion of SCD cases that were identified with a potentially inherited cardiac disease postmortem was high in all studied age groups, while autopsy rates in sudden and unexpected death cases declined markedly with increasing age. Our findings indicate that diagnoses of inherited heart disease are likely missed in some SCD cases, along with the opportunity for treatment and prevention in surviving relatives.