**News in September 2022**

1. **Cardiovascular Imaging for Ischemic Heart Disease in Women: Time for a Paradigm Shift**

Heart disease is the leading cause of death among men and women. Women have a unique phenotype of ischemic heart disease with less calcified lesions, more nonobstructive plaques, and a higher prevalence of microvascular disease compared with men, which may explain in part why current risk models to detect obstructive coronary artery disease (CAD) may not work as well in women. This paper summarizes the sex differences in the functional and anatomical assessment of CAD in women presenting with stable chest pain and provides an approach for using multimodality imaging for the evaluation of suspected ischemic heart disease in women in accordance to the recently published American Heart Association/American College of Cardiology guidelines for the evaluation and diagnosis of chest pain. A paradigm shift in the approach to imaging ischemic heart disease women is needed including updated risk models, a more profound understanding of CAD in women where nonobstructive disease is more prevalent, and algorithms focused on the evaluation of ischemia with nonobstructive CAD and myocardial infarction with nonobstructive CAD.

2. **Body weight and physical fitness in women with ischaemic heart disease: does physical fitness contribute to our understanding of the obesity paradox in women?**

**Aims**

Body mass index (BMI) defined obesity is paradoxically associated with lower all-cause mortality in patients with known cardiovascular disease. This study aims to determine the role of physical fitness in the obesity paradox in women with ischaemic heart disease (IHD).

**Methods and Results**

Women undergoing invasive coronary angiography with signs/symptoms of IHD in the Women’s Ischemia Syndrome Evaluation (WISE) prospective cohort (enrolled 1997–2001) were analysed. This study investigated the longer-term risk of major adverse cardiovascular events (MACE) and all-cause mortality associated with BMI and physical fitness measured by Duke Activity Status Index (DASI). Overweight was defined as BMI ≥25 to 30 kg/m², obese as BMI ≥30 kg/m², unfit as DASI scores <25, equivalent to ≤7 metabolic equivalents. Among 899 women, 18.6% were normal BMI-fit, 11.4% overweight-fit, 10.4% obese-fit, 15.3% normal BMI-unfit, 23.8%
overweight-unfit, and 30.4% obese-unfit. In adjusted models compared to normal BMI-fit, normal BMI-unfit women had higher MACE risk [hazard ratio (HR) 1.65, 95% confidence interval (CI) 1.17–2.32; \( P = 0.004 \)]; whereas obese-fit and overweight-fit women had lower risk of mortality (HR 0.60, 95% CI 0.40–0.89; \( P = 0.012 \) and HR 0.62, 95% CI 0.41–0.92; \( P = 0.018 \), respectively).

**Conclusion**

To address the paradox of body weight and outcomes in women, we report for the first time that among women with signs/symptoms of IHD overweight-fit and obese-fit were at lower risk of long-term all-cause mortality; whereas normal BMI-unfit were at higher risk of MACE. Physical fitness may contribute to the obesity paradox in women, warranting future studies to better understand associations between body weight, body composition, and physical fitness to improve cardiovascular outcomes in women.

3. The fat but fit paradox: what do we know in women with heart disease

This editorial refers to ‘Body weight and physical fitness in women with ischaemic heart disease: does physical fitness contribute to our understanding of the obesity paradox in women?’, by O. Quesada et al., [https://doi.org/10.1093/eurjpc/zwac046](https://doi.org/10.1093/eurjpc/zwac046).

Overweight and obesity are well-established risk factors for cardiovascular disease (CVD) including canary heart disease (CHD) and major CVD risk factors such as hypertension, metabolic syndrome, diabetes.\(^1\)–\(^3\) Despite the strong association between excess adiposity and risk of CVD, growing evidence demonstrated that overweight and obesity were associated with decreased all-cause and CVD mortality in healthy people or people with chronic diseases including CHD, a phenomenon referred to ‘obesity paradox’.\(^1\)\(^2\)\(^4\) Many longitudinal studies demonstrate that high levels of cardiorespiratory fitness (CRF), might attenuate the adverse health consequences of obesity after adjusting some key potential confounders, which is referred as the ‘fat but fit’ phenomenon.\(^4\)–\(^6\)

In this issue, Quesada and colleagues examined joint effects of physical fitness and obesity in women undergoing invasive coronary angiography with signs and symptoms of ischemic heart disease (IHD) using data from Women’s Ischemia Syndrome Evaluation (WISE) prospective cohort in 1996–2000.\(^7\) A total of 899 women were included in this analysis. Obesity was assessed by body mass index (BMI), waist circumference (WC), and waist–hip ratio (WHR). BMI was
categorized into normal BMI (<25 kg/m²), overweight (25–29 kg/m²) and obese (≥30 kg/m²). WC (≤88 vs. > 80 cm) and WHR (≤0.85 vs. >0.85) were divided into two groups. Physical fitness was measured by Duke Activity Status Index scores (DASI), an assessment of functional capacity derived from self-reported ability to perform various activities. DASI score greater than 25 (>7METs) were considered as fit. The outcomes of interest were the first occurrence of major adverse cardiovascular events (MACE) and all-cause mortality.

A total of 245 women developed a MACE event at 5.8 years median follow up and 174 of the women died during 11 years of follow-up. After adjusting for potential confounding variables, the findings showed overweight- and obesity-fit women were associated with a significantly lower risk of mortality (HR 0.60, 95% CI 0.40–0.89; HR 0.62, 95% CI 0.41–0.92, respectively) compared to the normal BMI-fit group, supporting fat-but-fit hypothesis (Figure 1A and B). Conversely, unfit women across all BMI groups were associated with higher risk for MACE compared to women in the fit group. Notably, normal BMI but unfit women were 65% more likely to develop MACE (HR 1.65, 95% CI 1.17–2.32). When central measures of obesity, such as WC, waist-hip-ratio were used, the unfit group was associated with greater risk of MACE and mortality than the fit group, while there were no significant differences observed among fit women regardless of anthropometric methods.

Figure 1
Graphical illustration of joint effects of obesity and fitness in relation to major adverse cardiovascular events (MACE), cardiovascular disease (CVD) mortality and all-cause mortality in women and men from the studies. (A and B) Quesada et al 2012 on women with ischemic heart disease. (C) McAuley et al 2010 examined the fat-fit association in men with known or suspected heart disease using data from VETS. (D) McAuley 2012 examined the fat-fit association in men with known or suspected heart disease using data from ACLS.

The findings of this study used the DASI score as an assessment of joint effects of physical fitness and BMI were consistent with the previous studies using CRF in men. McAuley et al. have demonstrated joint impacts of CRF and BMI in a large cohort of middle-aged men with known or suspected CHD using data from Veterans Exercise Testing Study (VETS) (Figure 1C). They
found overweight- and obese-fit men had significantly lower all-cause mortality risk and were 48–57% less likely to die compared to normal-weight fit men. A comparable finding was found in the analysis of 9563 men with documented or suspected CHD in the Aerobics Centre Longitudinal Study (ACLS) using BMI and CRF (Figure 1D). The similar patterns were also observed in the adiposity exposures used WC or percent body fat for CVD mortality (Figure 1D). Collectively, these findings strongly support that high level of fitness may counteract the adverse effects of an excess of total and abdominal adiposity on the cardiovascular system in patients with known or suspected CHD in both men and women.

There are several explanations for this fat but fit paradox in the CVD population. For example, higher fitness is associated with a more favourable CV and metabolic risk factor profile, thereby lowering mortality risk. Overweight or obese people may receive medical check-ups more frequently or sooner, consequently, the disease may have been diagnosed and treated at earlier stages. Quesada et al. suggest the paradoxical association between BMI and mortality in fit women in current may be due to the fit individuals have lower body fat and higher lean mass requiring for further investigation.

The main strength of this study is the longitudinal design with a cohort of women with signs and symptoms of IHD who underwent coronary angiography. The limitation is the suboptimal assessment of fitness using DASI compared with gold standard measures using cardiopulmonary exercise. However, CRF measurements often require time, resource and trained personnel that often makes it less utilized in the clinical practice, while other conventional risk factors such as BP measure that can be routinely performed in the primary care setting for preventive screening. In this study, obesity was mainly assessed by BMI. BMI has often been criticized for failing to take account for fitness relate to the proposition of lean mass to adiposity. Despite many criticisms, BMI is the most commonly used anthropometric index in the studies and clinical settings. This study was strengthened by performing the additional analysis using direct measures of central fatness (WC, WHR).

Taken all evidence together, the present study provided important findings in women with IHD that supports two key health messages. Firstly, improving physical fitness and maintaining regular exercise to improve cardiorespiratory fitness have important long-term health benefits in women.
Second, lean but unfit women had the highest risk for MACE and all-cause mortality among all groups, suggesting being normal weight might not be enough to ensure optimal cardiovascular health, instead being fit plays an important role. Lean and unfit women particularly with signs and symptoms of IHD warrant further CVD screen and intervention.

4. Hypertensive Disorders of Pregnancy Up for Gen Z, Millennial

More recent birth cohorts of pregnant individuals have experienced a doubling of rates of hypertensive disorders of pregnancy, according to a study published online Aug. 24 in *JAMA Network Open*.

Natalie A. Cameron, M.D., from Northwestern University Feinberg School of Medicine in Chicago, and colleagues examined associations of delivery year and birth year of pregnant individuals with incident rates of hypertensive disorders of pregnancy. The analysis included data from 38.1 million nulliparous individuals (aged 15 to 44 years) with a singleton, live birth identified from the National Vital Statistics System (1995 to 2019).

After adjusting for age and birth year, the researchers found that among pregnant individuals who delivered in 2015 to 2019, the adjusted rate ratio (aRR) for the incidence of hypertensive disorders of pregnancy was 1.59 versus those delivering from 1995 to 1999. The aRR for the incidence of hypertensive disorders of pregnancy was 2.61 among pregnant individuals born from 1996 to 2004 versus those born from 1951 to 1959, when adjusting for age and year of delivery. In each birth cohort, the incidence of hypertensive disorders was higher among self-identified non-Hispanic Black individuals, with similar relative changes for year of delivery (aRR, 1.76) and birth year (aRR, 3.26) versus non-Hispanic White individuals (aRRs, 1.60 and 2.53, respectively).

“This study suggests that public health efforts increasing awareness of and focusing on prevention among younger individuals are needed to reverse adverse trends in hypertensive disorders of pregnancy,” the authors write.

5. COVID-19 Vaccination in Pregnancy Not Tied to Adverse Birth Outcomes

Deshayne B. Fell, Ph.D., from the Children’s Hospital of Eastern Ontario Research Institute in Ottawa, Canada, and colleagues conducted a population-based retrospective cohort study from May 1 to Dec. 31, 2021, involving all liveborn and stillborn infants from pregnancies conceived
at least 42 weeks before the end of the study period and with gestational age ≥20 weeks or birth weight ≥500 g.

The researchers found that 50.6 percent of 85,162 births occurred in individuals who received one dose or more of a COVID-19 vaccine during pregnancy (99.7 percent received an mRNA vaccine). There was no association observed between vaccination during pregnancy and any increased risk for overall preterm birth, spontaneous preterm birth, or very preterm birth. There was also no increase in the risk for small for gestational age at birth or stillbirth. The findings did not differ according to trimester of vaccination, mRNA vaccine product, or number of vaccine doses received during pregnancy.

“Our findings — along with extant evidence that vaccination during pregnancy is effective against COVID-19 for pregnant individuals and their newborns, and that COVID-19 during pregnancy is associated with increased risks of adverse maternal, fetal, and neonatal outcomes — can inform evidence based decision making about COVID-19 vaccination during pregnancy,” the authors write.

6. Risk of Preterm Birth, Small for Gestational Age at Birth, and Stillbirth After COVID-19 Vaccination During Pregnancy

OBJECTIVE

To assess the risk of preterm birth, small for gestational age at birth, and stillbirth after covid-19 vaccination during pregnancy.

DESIGN

Population based retrospective cohort study.

SETTING

Ontario, Canada, 1 May to 31 December 2021.

PARTICIPANTS
All liveborn and stillborn infants from pregnancies conceived at least 42 weeks before the end of the study period and with gestational age ≥20 weeks or birth weight ≥500 g.

MAIN OUTCOME MEASURES

Using Cox regression, hazard ratios and 95% confidence intervals were estimated for preterm birth before 37 weeks (overall and spontaneous preterm birth), very preterm birth (<32 weeks), small for gestational age at birth (<10th centile), and stillbirth. Vaccination against covid-19 was treated as a time varying exposure in the outcome specific risk window, and propensity score weighting was used to adjust hazard ratios for potential confounding.

RESULTS

Among 85,162 births, 43,099 (50.6%) occurred in individuals who received one dose or more of a covid-19 vaccine during pregnancy-42,979 (99.7%) received an mRNA vaccine. Vaccination during pregnancy was not associated with any increased risk of overall preterm birth (6.5% among vaccinated v 6.9% among unvaccinated; adjusted hazard ratio 1.02, 95% confidence interval 0.96 to 1.08), spontaneous preterm birth (3.7% v 4.4%; 0.96, 0.90 to 1.03), or very preterm birth (0.59% v 0.89%; 0.80, 0.67 to 0.95). No increase was found in risk of small for gestational age at birth (9.1% v 9.2%; 0.98, 0.93 to 1.03) or stillbirth (0.25% v 0.44%; 0.65, 0.51 to 0.84). Findings were similar by trimester of vaccination, mRNA vaccine product, and number of doses received during pregnancy.

CONCLUSION

The findings suggest that vaccination against covid-19 during pregnancy is not associated with a higher risk of preterm birth, small for gestational age at birth, or stillbirth.

7. Hypertensive disorders of pregnancy and onset of chronic hypertension in France: the nationwide CONCEPTION study

Aims

Hypertensive disorders of pregnancy (HDP) are a leading cause of maternal and foetal morbidity and mortality. We aimed to estimate the impact of HDP on the onset of chronic hypertension in primiparous women in the first years following childbirth.

Methods and results
This nationwide cohort study used data from the French National Health Data System (SNDS). All eligible primiparous women without pre-existing chronic hypertension who delivered between 2010 and 2018 were included. Women were followed up from six weeks post-partum until onset of hypertension, a cardiovascular event, death, or the study end date (31 December 2018). The main outcome was a diagnosis of chronic hypertension. We used Cox models to estimate hazard ratios (HRs) of chronic hypertension for all types of HDP. Overall, 2 663 573 women were included with a mean follow-up time of 3.0 years. Among them, 180 063 (6.73%) had an HDP. Specifically 66 260 (2.16%) had pre-eclampsia (PE) and 113 803 (4.27%) had gestational hypertension (GH). Compared with women who had no HDP, the fully adjusted HRs of chronic hypertension were 6.03 [95% confidence interval (CI) 5.89–6.17] for GH, 8.10 (95% CI 7.88–8.33) for PE (all sorts), 12.95 (95% CI 12.29–13.65) for early PE, 9.90 (95% CI 9.53–10.28) for severe PE, and 13.17 (95% CI 12.74–13.60) for PE following GH. Hypertensive disorders of pregnancy exposure duration was an additional risk factor of chronic hypertension for all PE subgroups. Women with HDP consulted a general practitioner or cardiologist more frequently and earlier.

Conclusion

Hypertensive disorders of pregnancy exposure greatly increased the risk of chronic hypertension in the first years following delivery.
8. Impact of hypertensive disorders of pregnancy: lessons from CONCEPTION

This Focus Issue on hypertension contains the Special Article entitled ‘Hypertension in children and adolescents: a consensus document from ESC Council on Hypertension, European Association of Preventive Cardiology, European Association of Cardiovascular Imaging, Association of Cardiovascular Nursing & Allied Professions, ESC Council on Cardiology Practice and Association for European Paediatric and Congenital Cardiology’ by Giovanni de Simone from the Federico II University Hospital in Naples, Italy, and colleagues. The authors note that the definition and management of arterial hypertension in children and adolescents are uncertain, due to different positions of current guidelines. The ESC task force, constituted by Associations and Councils with interest in arterial hypertension, has reviewed current literature and evidence, to produce a consensus document focused on aspects of hypertension in the age range of 6–16 years, including definitions, methods of measurement of blood pressure, clinical evaluation, assessment of hypertension-mediated target organ damage, evaluation of possible

9. Hypertension in children, adolescents, and pregnant women: challenges and opportunities
vascular, renal, and hormonal causes, assessment and management of concomitant risk factors (with specific attention on obesity), and antihypertensive strategies, especially focused on lifestyle modifications. The Consensus Panel also suggests aspects that should be studied with high priority, including generation of multiethnic sex-, age-, and height-specific European normative tables, implementation of randomized clinical trials (RCTs) on different diagnostic and therapeutic aspects, and long-term cohort studies to link with adult cardiovascular risk. Finally, suggestions for the successful implementation of the contents of the present consensus document are also given.

The issue also contains a co-published Special Article entitled ‘Harmonization of the American College of Cardiology/American Heart Association and European Society of Cardiology/European Society of Hypertension Blood Pressure/Hypertension Guidelines: comparisons, reflections, and recommendations’ by Paul K. Whelton from the Tulane University School of Medicine in New Orleans, LA, USA and colleagues. The authors indicate that the 2017 American College of Cardiology/American Heart Association and 2018 European Society of Cardiology/European Society of Hypertension clinical practice guidelines for management of high blood pressure/hypertension are influential documents. Both guidelines are comprehensive, were developed using rigorous processes, and underwent extensive peer review. The most notable difference between the two guidelines is the blood pressure cut-off point recommended for the diagnosis of hypertension. There are also differences in the timing and intensity of treatment, with the American College of Cardiology/American Heart Association guidelines recommending a somewhat more intensive approach. Overall, there is substantial concordance in the recommendations provided by the two guideline-writing committees, with greater congruity between them than their predecessors. Additional harmonization of future guidelines would help to underscore the commonality of their core recommendations and could serve to catalyse changes in practice that would lead to improved prevention, awareness, treatment, and control of hypertension worldwide.

In a State of the Art Review article entitled ‘Research strategies in treatment of hypertension: value of retrospective real-life data’, Giovanni Corrao and Giuseppe Mancia from the University of Milano-Bicocca in Italy discuss the limitations of data collected by RCTs in relation to their applicability to daily life clinical management. In the article the authors argue that these
limitations are only partially overcome by modifications of RCT design and conduct (e.g. ‘pragmatic trials’) while being substantially attenuated by real-life-derived research, which can fill many gaps left by trial-collected evidence and thus have an important complementary value. The focus is on the real-life research approach based on the retrospective analysis of the now widely available healthcare utilization databases (formerly known as administrative databases), which are discussed in detail for their multiple advantages as well as challenges. Emphasis is given to the potential of these databases to provide low-cost information over long periods on many different healthcare issues and drug therapies. This review also mentions that thanks to the current availability of these data in electronic format, results can be obtained quickly, helping timely decisions in emergencies. The potential shortcomings of this approach (confounding by indication, misclassification, and selection bias) are also discussed along with their possible minimization by suitable analytic tools. Finally, examples of the contributions of studies on hypertension and other cardiovascular risk factors are offered based on retrospective healthcare utilization databases that have provided information on real-life cardiovascular treatments unavailable via RCTs.

Beyond its role as an atherosclerotic risk factor, hypertension contributes an estimated 40% to heart failure (HF) risk, making it a significant public health burden. While adverse left ventricular remodelling and hypertrophy are well-recognized intermediate phenotypes for HF, overt myocardial structural changes are late-stage findings that are not universally present in all patients with hypertensive heart disease, thus highlighting the need for improved understanding of the pathophysiological mechanisms of hypertensive heart disease-associated HF. Coronary microvascular dysfunction, even in the absence of obstructive epicardial coronary artery disease, has long been recognized as a central mechanism in several cardiovascular diseases. In a Clinical Research article ‘Low coronary flow relative to myocardial mass predicts heart failure in symptomatic hypertensive patients with no obstructive coronary artery disease’, Jenifer M. Brown from the Harvard Medical School in Boston, MA, USA, and colleagues hypothesized that insufficient perfusion to match global metabolic demand, reflected by a low ratio of myocardial blood flow to global myocardial mass, may be a HF risk marker. A retrospective cohort \( n = 346 \) of patients with hypertension who underwent clinical positron emission tomography (PET) myocardial perfusion imaging for chest pain and/or dyspnoea at Brigham and Women's Hospital (Boston, MA, USA) were studied. Patients without obstructive coronary artery
disease by history or PET perfusion, HF, cardiomyopathy, or ejection fraction (EF) <40% were followed for HF hospitalization (primary outcome), all-cause death, and their composite. Myocardial blood flow, left ventricular (LV) mass, volumes, and EF were obtained from PET, and a ‘flow/mass ratio’ was determined as hyperaemic myocardial blood flow over LV mass indexed to body surface area. A lower flow/mass ratio was independently associated with larger end-diastolic (β = −0.44, P < 0.001) and end-systolic volume (β = −0.48, P < 0.001) and lower EF (β = 0.33, P < 0.001). A flow/mass ratio below the median was associated with an adjusted hazard ratio (HR) of 2.47 (P = 0.01) for HF hospitalization, 1.95 (P = 0.02) for death, and 2.20 (P < 0.001) for the composite.

The authors conclude that an integrated physiological measure of insufficient myocardial perfusion to match global metabolic demand identifies subclinical hypertensive heart disease and elevated risk of HF and death in patients with hypertension but without flow-limiting coronary artery disease. The article is accompanied by an Editorial by Antoni Bayés-Genís from the Universitat Autònoma de Barcelona, and Javier Díez from the University of Navarra, in Spain. Bayés-Genís and Díez note that notwithstanding limitations, this work is a step forward on the bumpy road cardiologists are facing towards precision medicine. Oncologists have already demonstrated that personalized therapies based on a refined histological and molecular phenotyping of tumours translate into improved individualized outcomes. The authors of this Editorial strongly believe that a similar approach is necessary not only for treating but also for preventing HF in patients with hypertension and/or other risk factors. The time has come for a precision medicine-based approach to cardiovascular patients that includes knowledge of the histological, molecular, and metabolic changes occurring at the myocardial level that are responsible for progressive impairment of LV morphology and function, with further translation to non-invasive biomarkers and novel preventive and therapeutic strategies.

Figure 1
Analysis of 25 years of follow-up data from Atherosclerosis Risk in Communities studies reveals increased risk to develop heart failure (HF) and left ventricular hypertrophy (LVH) among study participants with middle age serum sodium >142 mmol/l. Left panels (beginning of the study): participants are divided into four groups based on serum sodium levels. Middle panels (follow-up: time-to-event analysis): increased incidence of HF in higher sodium groups with adjusted hazard ratio reaching 1.39 when serum sodium exceeds 143 mmol/l. Right panels (end of the 25 years follow-up: 70- to 90-year-old participants): increased prevalence of HF and LVH and accelerated hypertrophic left ventricular remodelling in higher sodium groups.14

With increasing prevalence of HF owing to the ageing population, identification of modifiable risk factors is important.12-13 In a mouse model, chronic hypohydration induced by lifelong water restriction promotes cardiac fibrosis. Hypohydration elevates serum sodium. In a Clinical Research article entitled ‘Middle age serum sodium levels in the upper part of normal range and risk of heart failure’, Natalia I. Dmitrieva from the National Heart Lung and Blood Institute in Bethesda, MD, USA, and colleagues evaluate the association of serum sodium at middle age as a measure of hydration habits with risk of developing HF.14 The authors analysed data from the Atherosclerosis Risk in Communities study with middle age enrolment (45–66 years) and 25 years of follow-up. Participants without water balance dysregulation and with the following characteristics were selected: serum sodium within the normal range (135–146 mmol/L), not
diabetic, not obese, and free of HF at baseline \((n = 11,814)\). In time-to-event analysis, HF risk was significantly increased by 39% if middle age serum sodium exceeded 143 mmol/L corresponding to a 1% body weight water deficit (HR 1.39). In a retrospective case–control analysis performed on 70- to 90-year-old attendees of Visit 5 \((n = 4961)\), serum sodium of 142.5–143 mmol/L was significantly associated with a 62% increase in odds of left ventricular hypertrophy (LVH) diagnosis \([\text{odds ratio (OR)} 1.62]\). Serum sodium >143 mmol/L was significantly associated with a 107% increase in odds of LVH \([\text{OR} 2.07, 95\% \text{ confidence interval (CI) 1.30–3.28}]\) and a 54% increase in odds of HF \((\text{OR} 1.54)\). As a result, prevalence of HF and LVH was increased among 70- to 90-year-old participants with higher middle age serum sodium \((\text{Figure 1})\).

Dmitrieva et al. conclude that middle age serum sodium >142 mmol/L is a risk factor for LVH and HF. Maintaining good hydration throughout life may slow down the decline in cardiac function and decrease the prevalence of HF. This contribution is accompanied by an Editorial by Friedrich C. Luft from the Experimental and Clinical Research Center and Charité Medical Faculty in Berlin, Germany. Luft notes that the bottom-line message could be just, ‘drink up’. However, are the increased sodium concentrations merely a function of decreased water intake and from where does the sodium come? Sodium metabolism is more complex than previously thought. For instance, the skin (negatively charged glycosaminoglycans) has been rediscovered as a sodium storage site, regulated by immune cells under the control of NFAT5. Hypertonic microdomains were identified with hypertonicity, with sodium playing a role in immune cell activation. The storage site was found to be relevant to blood pressure. In man, sodium magnetic resonance imaging serves to make this site visible. Mobilization of sodium occurs as dramatically in patients treated for acute HF as in dialysis patients undergoing renal transplantation. Salt storage in the skin may serve to buffer free extracellular sodium and macrophage modulation of the extracellular matrix and lymphatics. This view supposes that body electrolyte homeostasis cannot be achieved by renal regulation alone and that extrarenal regulatory mechanisms play a role.

Figure 2
Hypertensive disorders of pregnancy increase the risk of developing chronic hypertensions in primiparous women in the early years after delivery by O’Donnell et al.\textsuperscript{18}

Hypertensive disorders of pregnancy (HDP) are a leading cause of maternal and foetal morbidity and mortality.\textsuperscript{16-17} In a Clinical Research article entitled ‘\textit{Hypertensive disorders of pregnancy and onset of chronic hypertension in France: the nationwide CONCEPTION study}’, Pauline Boucheron from the Santé publique France, and colleagues aimed to estimate the impact of HDP on the onset of chronic hypertension in primiparous women in the first years following childbirth.\textsuperscript{18} This nationwide cohort study used data from the French National Health Data System. All eligible primiparous women without pre-existing chronic hypertension who delivered between 2010 and 2018 were included. Women were followed up from 6 weeks post-partum until onset of hypertension, a cardiovascular event, death, or the study end date (31 December 2018). The main outcome was a diagnosis of chronic hypertension. The authors used Cox models to estimate HRs of chronic hypertension for all types of HDP. Overall, 2 663 573 women were included, with a mean follow-up time of 3.0 years. Among them, 6.73% had an HDP. Specifically, 2.16% had pre-eclampsia (PE) and 4.27% had gestational hypertension (GH). Compared with women who had no HDP, the fully adjusted HRs of chronic hypertension were 6.03 for GH, 8.10 for PE (all sorts), 12.95 for early PE, 9.90 for severe PE, and 13.17 for PE following GH.
The authors conclude that HDP exposure greatly increases the risk of chronic hypertension in the first years following delivery. The contribution is accompanied by an Editorial by Anastasia S. Mihailidou from the Macquarie University from Sydney, Australia, along with Martha Gulati. They observe that as we continue to understand the interconnectedness of cardiovascular health and pregnancy, we are now developing a greater understanding of not just how HDP increases the risk of chronic hypertension, but also how the duration of gestational hypertension prior to pre-eclampsia may further increase the risk. Our future work must focus on understanding the impact of treatment and lifestyle interventions in preventing the development of permanent hypertension and cardiovascular disease in these high-risk women. Whether the conception of permanent hypertension following complicated pregnancies is inevitable or preventable is the question we need to answer.

The issue also contains a Viewpoint article entitled ‘Settling the controversy of salt substitutes and stroke: sodium reduction or potassium increase?’ by Franz H. Messerli from the University Hospital Berne in Switzerland, and colleagues. The authors conclude that the SSaSS trial demonstrates that moving from a ‘low potassium, high sodium’ diet toward an average potassium/but persistently high sodium intake (an intake numerically still higher than the average consumption in Switzerland and in the USA) prevents stroke, cardiovascular events, and death. These data, therefore, provide reassurance about the efficacy and safety of increasing potassium intake.

10. Traffic-Related Air Pollution May Impact Women More

The impact of breathing diesel exhaust fumes may be more severe among women than men, according to a study presented at the European Respiratory Society International Congress 2022, held from Sept. 4 to 6 in Barcelona, Spain.

Hemshekhar Mahadevappa, Ph.D., from the University of Manitoba in Winnipeg, Canada, and colleagues examined sex-related differences in plasma profile in response to low, real-world concentrations of diesel exhaust. Analysis included data from five male and five female healthy, never-smokers who were exposed to either filtered air or diesel exhaust (20, 50, 150 μg PM2.5/m³) for four hours, with a four-week washout period between each exposure.
The researchers found that the abundance of 52 proteins in men and 153 proteins in women were significantly altered in plasma following exhaust exposure versus filtered air. For 91 exhaust-related proteins, sex was a significant effect modifier broadly within functional groups of inflammation, oxidative stress, hemostasis, cardiovascular disease, and host defense peptides. Some of these sex effects were concentration dependent, which were robust at 150 μg PM$_{2.5}$/m$^3$ of diesel exhaust.

"This is important as respiratory diseases such as asthma are known to affect females and males differently, with females more likely to suffer severe asthma that does not respond to treatments," a coauthor said in a statement. "We need to know a lot more about how females and males respond to air pollution and what this means for preventing, diagnosing and treating their respiratory disease."