

# 9th Congress of the International Society of Gender Medicine

Gender and the Genome  
Volume 3: 1-36  
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DOI: 10.1177/2470289719881516  
journals.sagepub.com/home/gng



## The Intelligent Genome: What Mediates Adaptation?

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For decades, the historical division between the biomedical community and the scholars of social structure about how the final phenotype is shaped seemed irreducible. It produced particularly heated arguments within the discipline of gender-specific medicine. Clinical investigators insisted that the answers to what shaped function lay almost entirely within our biological sex while anthropologists, sociologists, and even epidemiologists maintained that biomedical investigators were ignoring the powerful impact of the environment on shaping the phenotype, that is, that “maleness” and “femaleness” are profoundly influenced by the environment. The only thing about which both camps agreed was that to separate the *individual* impact of the two—biology and environment—was an impossible task. It was the Gordian knot of gender-specific medical studies: Before the genomic era, lecture after lecture in conferences like these began with the effort to describe the distinction between “sex” and “gender.” With the discovery of the structure of the human genome less than 2 decades ago, a unifying hypothesis began to emerge. The first piece of data was that the human genome was 99.5% identical in all humans and that the actual number of individual genes was much smaller than had been predicted: 20 000 to 25 000 (Human Genome Project) and at a maximum, 46 000 (Stephen Salzberg). How did this explain the enormous variability- and adaptability-of humans both within and across generations? If biological sex is significantly restrictive for the phenotype, how do we explain memory, learning new skills, and adjustment to the world around us? The answer lies in how *genes are expressed*: their function is modified by actual chemical tags attached to the various components of the genome. These modifications do not change underlying structure, but profoundly modify the way genes are up or down regulated, modify mRNA, and even postrationally modify protein structure through folding, stabilization, and binding partners. The results are the precisely engineered components of the individual

human. Importantly, some of the epigenetic changes in the genome can be inherited by future generations in a sex-specific way. In short, the science of epigenetics knits the once separate findings of social scientists and biomedical investigators into a unified functional whole. We might well consider substituting *epigenetic medicine* for the term *gender-specific medicine*, a term that tells a more accurate and complete story and unites the 2 concepts that are no longer separable: sex and gender.

## Prioritising Sex and Gender Equity in Health in Europe

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The European Union can do more to prioritize women’s health in order to improve the health of all, targeting existing gaps and challenges. Action must be taken early and at critical points to ensure health and well-being from preconception to childhood through to old age. Biological and social influences are critical to health. Women face higher rates of diseases, such as in breast cancer, osteoporosis, and autoimmune diseases than do men. Other diseases affect men and women differently, including diabetes, depression, and cardiovascular disease. Women do not present the same for conditions and respond differently to treatment than do men. Strategies must account for these differences. Many factors outside of the health sector—such as socioeconomic status, education, culture, and ethnicity—affect behavior and resource access. Sex and gender have important implications for health-care delivery. Due to women’s reproductive role, their health affects the health of their unborn child and that of future generations. Health care and health systems should be highly responsive to women, but too often fail them. Translating the evidence from sex and gender research into regulatory practice leads to more targeted, safe, and effective opportunities for health and health care. Women are the heaviest medicine users, yet they are underrepresented in research and data. Consequently, the evidence base is weak for women as well as for older people. The Clinical Trials Regulation must be implemented in order to combat the underrepresentation of women in clinical trials. Health-care systems must be supported to systematically and more



effectively overcome sex and gender inequities. Treatments must be delivered, responding to differences, such as sex, gender, and age, and adapt treatment to ensure that all people and patients in Europe receive the best available care.

## Focusing on Women's Health: Policies That Work? Experiences From an Austrian Initiative

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After the highly successful Vienna Women's Health Program adopted in 1999 by the city parliament as a regional model of good practice, the Austrian Ministry of Women's Affairs and the Austrian Ministry of Health decided 2014/2015 to develop an Action Plan for Women's Health on the national level. Goals of the Action Plan mirror the different stages of life: girls and young women, working women, and elderly and old women.

Austrian Women's Health Action Plan was elaborated by interdisciplinary highly professional expert working groups. The Plan highlights and addresses critical issues of women's health based on a biopsychosocial view. Following this approach, the goals focus not only on women's health but furthermore on the social determinants of health such as poverty, equal pay, and gender roles. The Action Plan was adopted by the Austrian parliament and consists of 17 goals and proposes 40 measures on achieving these goals. To ensure the implementation and progress, the departments for health and the departments of women's affairs of all 9 counties were activated and as "Focal Points" established. These act as coordinating body within the 9 countries. The overall aim of the "Focal Points" is that all over Austria, in the cities as well as countryside, women's health issues are known, understood, and services for special issues like violence, body images, sexual health, reproductive health, and gender-specific chronic diseases are offered. To advance the process of the implementation, the focal points are establishing regional networks, 3 times a year Focal Point meetings are held to exchange experiences as well as an Austrian "Women's Health Dialogue" conferences for a broader audience. Summarizing these joint efforts, awareness for women's health has increased policies as well as in experts and the population. Therefore, it seems to be a model of good practice because it works.

## Chronotype, Gender, and Health

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The circadian preference (chronotype) reflects the individual's internal circadian rhythm that influences the sleep-activity

cycle in a 24-hour period. It can be self-assessed by the Morningness-Eveningness Questionnaire (MEQ), identifying Morning-types, Evening-types, and neither-types or Intermediate. Many genes participate in the determination of chronotype, and PERIOD2, a core molecular component of the circadian clock, seems to play active role. However, individual chronotype is not immutable, and varies with age and sex. Eveningness is more frequent in younger subjects, whereas morningness is greater in the advancing age. Men are typically later chronotypes than women before 40, but earlier types after 40. Moreover, environmental cues, for example light in particular, may play an important role. For billion years, the light/dark cycle determined by the sun has regulated the endogenous circadian rhythmicity in almost all life forms. From the XIXth century, the availability of incandescent light sources (ILSs), allowed humans to work over the 24-hour of a day, leading to a "shift-work desynchronization." Due to many advantages, that is, low energy consume and smaller size screen, light-emitting diodes (LEDs) have replaced ILS, becoming the dominant source for urban lighting and personal domestic devices, that is smartphones, tablets, so on. However, the LED-emitted blue light elicits a significant, dose-dependent, suppression of endogenous melatonin, with negative consequences on sleep. Light-at-night (LAN) has an impact on chronotype and health. A growing body of evidence indicates an association between eveningness and health problems, including (i) unhealthy habits and diet, more smoking, and alcohol drinking; obesity, metabolic syndrome, diabetes; (ii) psychological and psychological disorders, impulsivity, anger, depression, and anxiety (especially in women), risk taking behavior, psychopathology and personality traits, and (iii) sleep disorders, later bedtime and wake-up time, irregular sleep-wake schedule, subjective poor sleep, excessive daytime sleepiness and poor sleep quality (especially in women). These findings open new perspectives for prevention.

## The Biological Clock and Sleep

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Virtually all cells follow the 24-hour circadian rhythm of a hypothalamic master pacemaker that evolved in the natural light-dark cycle. Decoding this biologic clock, which is the prime regulator of sleep/wake, culminated in the Nobel Prize in Physiology or Medicine 2017 for the discovery of molecular mechanisms controlling the circadian rhythm. It is now recognized that a strong, unperturbed biologic clock is a hallmark of healthy aging. The introduction of electric light, however, presents unique challenges: Increases in the risk of major chronic disease and mortality have been associated with night work. Further, the ubiquity of light at night implicates potential risk not only for night workers but for everyone. Triggered by the melatonin hypothesis posed by Richard Stevens und Scott Davis in 1986, substantial effort has been put toward deciphering these negative health effects. In 2007, based on convincing

evidence from animal research, yet only a limited number of observational studies, the World Health Organization (WHO) classified nightshift work as a class 2A carcinogen (“probably carcinogenic”). A large body of additional evidence has now accumulated, giving rise to a WHO reassessment of the carcinogenicity of night shift work in June 2019. In this presentation, an overview and current status of the accumulated epidemiological evidence is provided, and future directions are discussed.

## Biological Clock and Sleep

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Sleep is important to our health and well-being and is essential to our homeostasis. The regulation of the sleep-wake cycle is governed by the circadian system. The circadian system acts as a “supra-physiological” system that coordinates and regulates many physiological functions on a 24-hour basis including core body temperature, hormone secretion, appetite, and the sleep-wake cycles. Proper organization of circadian rhythms is a key for normal function and disruption to the circadian rhythm leads to adverse consequences. The human circadian system actively synchronizes (entrains) to the 24-hour day via environmental signals (light and darkness). However, the entrainment of the circadian system to the 24-hour cycles is not constant. Differences between individuals in this phase of entrainment is shaped by genotype, environment, gender, and age leading to different phenotypes, known as chronotypes. There are several circadian sleep disorders including: shift work disorder, the relative new disorder called “social jet-lag,” delayed sleep phase syndrome, advanced sleep phase syndrome, irregular sleep-wake rhythm, and non-24-hour sleep-wake rhythm. An overview on these sleep disorders will be provided.

## Why so Slow? Content and Context in Gender Medicine

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Although the political and institutional support for sex and gender-sensitive medicine has significantly increased over the last decade, the implementation of its concepts into practice is lagging behind. General knowledge and single best practice examples are available, yet they are not widely adopted. Sex and gender-medicine is an innovative approach to medical

research, care, and teaching. Its implementation is a complex change process that questions the underpinnings of traditional androcentric medicine. Given the complexity of the process, its implementation can only be achieved through a systemic approach and the sole production of sex-specific knowledge will not lead to innovation. In this talk, I will briefly discuss 3 examples from the (a) academic, (b) organizational, and (c) societal context to demonstrate how content and context are interlinked. Starting with (a) a focus on sex and gender-sensitive medicine in Europe, I will highlight how the alignment of content, institutional, and sociopolitical context is needed to achieve implementation. I will then proceed to (b) the role of context in the establishment of organizational guidelines against gender discrimination and sexual harassment. Here again, perceived need, pressure groups, and institutional support are essential in mandating lasting institutional change. Last, I will point out (c) the role of context in the development of innovative health-care concepts for vulnerable populations. A detailed need analysis, stakeholder networks, and structural support are mandatory for the implementation of successful social innovations. All 3 examples demonstrate how the presence of innovative content and best practices alone does not suffice to achieve change. Only the alignment of knowledge, perceived need, and political will lead to rapid and effective implementation. Most intriguingly, however, the examples demonstrate that context can be shaped to favor adoption of innovation. These learnings could provide a blueprint to accelerate the implementation of sex and gender-sensitive medicine.

## Reducing the Gender Gap in Medical Academic Activities in Japan

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According to the latest data released by the Japanese government, the percentage of women medical doctors (MDs) in Japan is 21.1%, which is the lowest among the Organization for Economic Co-operation and Development countries as of 2013. However, in 2016, the ratio of women MDs in their 20s reached 34.6% in Japan, which was the highest among all age groups. As with other occupations, the employment rate of Japanese women MDs shows an “M-shaped curve” due to the decrease in the rate that reflects maternity and childcare leave. According to a survey by the Ministry of Health, Labour and Welfare, the employment rate among women decreases to its lowest point (73%) at the 11th year after licensure (estimated age: 37 years), compared with 89.9% among men in the same age cohort. Although the employment rate increases to over 80% among women in their 50s, it remains lower than that among men of the same age. One way to address this issue is by promoting changes in health policies, the working environment, and established notions about women and childcare. Since around 2006, federal funding in the form of grants and incentives from the Ministry of Education, Culture, Sports,

Science and Technology and the Ministry of Health, Labour and Welfare has been allocated for activities that promote the career development of women MDs and prevent job abandonment. Furthermore, universities, academic societies, prefectural governments, and the Japan Medical Association and affiliated associations have been working to address these issues. We analyzed female participation in the Japanese Societies of Internal Medicine and Subspecialties. Especially, we conducted a detailed analysis of the Japan Endocrine Society. I would like to introduce the results of this analysis and our efforts to reduce the gender gap in academic activities over the past 10 years.

### **The 9th Congress of the International Society for Gender Medicine (2019) Sex and Gender in Cardiovascular Medicine**

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The importance of sex and gender differences has been emerging in all medical fields, including cardiovascular medicine. In our department, we have been conducting research for sex difference, ranging from basic to clinical and epidemiology research. We have demonstrated the importance of sex differences in ischemic heart disease, heart failure, pulmonary hypertension, arrhythmias, and even disaster medicine. In ischemic heart disease, we demonstrated that Rho-kinase, a molecular switch for vascular smooth muscle contraction, plays a central role not only in vasospastic angina but also in microvascular angina. The long-term prognosis of patients with vasospastic angina is deteriorated when coronary microvascular dysfunction is coexisted, both of which are mediated by Rho-kinase activation. Importantly, the expression of Rho-kinase is markedly suppressed by estrogen and enhanced by nicotine. Indeed, smoking is the strongest risk factor in postmenopausal women. In heart failure, we demonstrated the sex differences in terms of clinical characteristics, transition to symptomatic heart failure, and long-term prognosis. In pulmonary hypertension, it is widely known that the prevalence of the disorder is higher in females than in males, while the long-term prognosis is better in females than in males. We found that sex hormones may be differently involved in the development of pulmonary hypertension and right ventricular dysfunction. In arrhythmias, sex differences are also involved, especially in atrial fibrillation and Brugada syndrome. Finally, in 2011, we experienced the Great East Japan Disaster, where the City of Sendai was the center of the disaster. We found that although all types of cardiovascular diseases and pneumonia were increased in both sexes after the earthquake, post-traumatic stress disorder was associated with increased cardiovascular diseases, especially in female patients, after the earthquake. Thus, sex and gender differences are one of the most important points and therapeutic targets in cardiovascular medicine.

### **Sex and Gender in Arterial Vascular Stiffness—A Modern Management in Risk Assessment**

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Arterial stiffness is an important component of vascular ageing and a potent cardiovascular disease (CVD) risk predictor. The concept that “early vascular aging” (EVA) is better related to the prognosis of CVD compared to chronological age is rapidly evolving. Methods for assessing vascular ageing, for example, non-invasive measurement of pulse wave velocity (PWV) and augmentation index (AIx), are not yet established in clinical routine practice. Clinical data of 2 main studies will be presented by the author to elucidate the benefit of arterial vascular stiffness measurement for clinical practice both for general practitioners and gynaecologists: The “Berlin Risk Evaluation in Women” study was performed to measure the vascular health of women living in Berlin. The study tested the hypothesis that the measurement of AIx and PWV is useful in addition to that of traditional cardiovascular risk factors when assessing the risk of left ventricular diastolic dysfunction (LVDD). The study data show that the measurement of pathological aortic PWV values  $\geq 9.7$  m/s predict the risk of LVDD, in addition to the cardiovascular risk factors postmenopausal age and waist circumference  $> 80$  cm. The high prevalence of vascular dysfunction and arterial stiffness (45%) in this female cohort and the high prevalence of LVDD (31.7%) should encourage implementation of aortic PWV measurement to improve cardiovascular-risk assessment. The aim of the sub study of BASE-II was to examine age and sex differences of arterial wave reflection and to estimate associations with endogenous (estradiol)- and exogenous (oral contraceptives [OCP] and postmenopausal hormone therapy [HRT]) sex hormones. Pulse wave velocity and AIx were measured in 590 male and 400 female participants, recruited from 2 age-strata, 22 to 35 years and 60 to 82 years. The findings suggest important sex differences in measures of arterial wave reflection, with a higher mean AIx observed in women compared to men. Oral contraceptives promote the development of hypertension, maybe by increasing the AIx. Suppressed endogenous estradiol levels could be responsible for this increased arterial wave reflection, due to higher vasotonus of the small and medium arteries compared to the non-OCP users. Among postmenopausal women, no associations of HRT with estradiol level and measures of arterial stiffness were observed.

### **Sex Differences in Immunity and Immune-Mediated Diseases**

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Immune response differs between women and men at many levels. In general, females mount stronger innate and adaptive immune responses in comparison to males. In particular, women show more effective phagocytosis and antigen presentation, stronger production of inflammatory cytokines, higher absolute number of CD4+ T lymphocytes, higher levels of circulating antibodies, in comparison to men. Genetic, epigenetic, hormonal, and environmental factors contribute to sex differences in immune response. The strong immune response in women, on one hand, appears to be beneficial, leading to the reduction of pathogen load and accelerating pathogen clearance, but, on the other hand, it can be detrimental by causing autoimmune or inflammatory diseases. Accordingly, most autoimmune diseases (eg, rheumatoid arthritis, Sjögren syndrome, primary biliary cirrhosis, antiphospholipid syndrome, systemic sclerosis, multiple sclerosis, and systemic lupus erythematosus) are more prevalent in women than in men and symptoms, disease course, and response to therapy may also differ between males and females. The search for the mechanisms responsible for these differences could lead to the identification of sex-specific diagnostic, prognostic and predictive biomarkers, and to the identification of new therapeutic targets. Our studies focused on estrogen (ER) and vitamin D (VDR) receptors in T cells of men and women. We found that ER $\beta$  expression could be considered a marker of disease progression and represents a potential therapeutic target in systemic autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. We also observed that VDR expression is significantly different in T lymphocytes from women and men and its activation significantly inhibited IL-17 and TNF- $\alpha$  production. In conclusion, ER and VDR could represent important biomarkers and therapeutic target in autoimmune diseases opening new perspective in the application of a gender-specific, personalized treatment.

### Sex Differences in Invisible Illnesses: Chronic Pain, Fibromyalgia, and Hypermobility Disorders

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Recent research suggests that chronic pain conditions like hypermobile spectrum disorder (HSD) and hypermobile Ehlers Danlos syndrome (hEDS), which are considered invisible illnesses, occur fairly often in the population; 255 million or 3.5% people affected worldwide. Based on Mendelian genetics, the sex ratio of hEDS patients is expected to be 1:1, but in fact the disease affects females more than males. Fibromyalgia is an illness associated with chronic pain and estimated to occur in 2% of the population (9:1, W: M). In spite of the large number of patients with these conditions, the pathogenesis of disease remains largely unknown. We performed a retrospective study examining sex and age difference, presence of comorbidities, vitals and labs in around 8000 patients from the Mayo Clinic EMR who were diagnosed with one of these chronic pain condition. We found that HSD, hEDS, and fibromyalgia occur more often in women with hEDS occurring more often in premenopausal women and fibromyalgia occurring more often in postmenopausal women. Comorbidities that were examined include fatigue, migraine, IBS, chronic pain, and depression. We also found that sex differences occur in common comorbidities such as migraines. We found that females with fibromyalgia had more migraines and depression compared to males, whereas males had more fatigue. When we examined comorbidities according to age using age 50 as a surrogate for menopause status, we found that women under 50 were more likely to have migraines while women over 50 were more likely to have hypertension. Knowing common comorbidities and/or vital/lab trends affecting patients could lead to a better understanding of the pathogenesis of disease and lead to better treatment strategies for patients. Our findings highlight the importance of studying sex and age differences in disease and provide insight on factors that may contribute to chronic pain in patients with these conditions.

### Blood Sera of Women Affected by Fibromyalgia: An NMR Metabolomics Analysis

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Fibromyalgia syndrome (FMS) is a female prevalent chronic pain disease. Timely diagnosis and accurate monitoring are decisive to improve the accuracy of therapy. In the present work, we present an NMR-based metabolomic study of blood sera of FMS patients. Spectral analyses of samples were conducted using a 600 MHz <sup>1</sup>H nuclear magnetic resonance (NMR) spectrometer; data processing and analyses were performed using Bayesil and MetaboAnalyst software.

Unsupervised and supervised multivariate analyses distinguished control and FMS patient groups. Sample of patients analyzed versus control according to age and gender led to the identification of a characteristic metabolomic profile that can be a useful tool to classify FMS affected women. Nuclear magnetic resonance based metabolomic analysis confirms to be a suitable tool to explore the metabolite information in order to improve existing medical practice and planning personalized therapies.

## Gender and Pain: Theoretical Foundations and Practical Applications

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The gender differences in experience of pain became a burning issue in current years. Women are corroborated to be at a higher risk of chronic pain compared to men and even suffer from more severe aches. Gender divergences in pain perception are hypothesized to be based on the modifying impact of gonadal hormones on the neural substrate. The existing evidence on the distribution of sex hormones and their receptors in the areas of the central and peripheral nervous system engaged with the nociceptive transmission revealed causal pathways. The peculiarities of both personalities: a health-care worker and a patient evidently contribute to gender bias in pain therapy. Various biological, psychological, and social factors (genetics, endogenous opioid system, sex hormones, gender roles, pain relieving models, and catastrophizing) are involved as well. Furthermore, the gender discrepancies in responses to the medicinal and nonmedicinal pain treatment are discovered, whereas the findings may fluctuate in relation to the definite methods of treatment and characteristics of pain. As far as prescribed doses of remedies are calculated on a model of 70 kg weighing man, female patients may be posed at risk of either enlarged therapeutic or adverse effects of the drug. The predispositions are explained by lower mean body weight paralleling a higher average percentage of body fat that leads to elevated average drug concentrations in women in comparison with male patients. The pain management cannot be adjusted in accordance with gender specificity nowadays. Hence, further researches clarifying the mechanisms defining gender differences in pain responses for the purpose of personalized therapy are warranted.

## Clinical Feature of Coronary Artery Disease in Japan

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The incidence of angina pectoris in women increases after 60 years of age in Japan as other western countries. Coronary

spasm has been reported to play an important role in the pathogenesis of ischemic heart disease in general, including acute coronary syndrome. Approximately 40% of angina pectoris is related to coronary spasm in Japan. Impairment of endothelial function as well as the hypercontractile response of smooth muscle in coronary artery may play an important role the genesis of coronary spasm. A hyperventilation test is a specific test for coronary spastic angina (CSA). Estrogen replacement prevents the hyperventilation-induced attacks in postmenopausal women with CSA. Thus, estrogen may prevent coronary spasm. Even though a lot of perimenopausal women have chest symptoms in Japan, most of those patients do not go to hospital, or do not receive any treatment due to be diagnosed as cardioneurosis or unknown. These facts are not good for women's health. Internists must be aware of this lapse and need to induce these women that estrogens may be efficacious and effective.

## Sex Differences in the Management of Heart Failure

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Heart failure (HF) is a global pandemic in Asia and Western countries. Sex is an important contributor to the phenotypic heterogeneity of HF. Women with HF are typically older, and more often have hypertension, preserved left ventricular ejection fraction, and less ischemic heart disease as compared with men. The significant underrepresentation of women in clinical trials limits the capacity to evaluate the extent of sex-related differences in HF. The Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study is a multi-center, prospective cardiovascular observational study in Japan (NCT 418 041). Among 4736 consecutive HF patients (mean age, 69 years) in the CHART-2 Study, crude mortality rate was comparable between women and men (52.4/1000 and 47.3/1000 person-year for women and men, respectively,  $P = .225$ ), but women had a reduced risk of mortality after adjusting for potential confounders (adjusted HR: 0.791; 95% CI: 0.640-0.979,  $P = .031$ ). The incidence of cardiovascular death, particularly that due to HF, was significantly higher in women than men. We also found sex difference in prognostic importance of statin therapy in patients with history of myocardial infarction ( $n = 3124$ ): statin therapy was comparably related with reduced incidence of death between both sexes but associated with reduced incidence of HF admission only in men but not in women (men: HR = 0.70,  $P < .001$ ; women: HR = 0.98,  $P = .92$ ,  $P$  for interaction = 0.07). These observations indicate that consideration of sex differences may provide more precise cares for HF patients. In this session, we will discuss the current insights into management of HF to maximize treatment benefits with a special reference to sex difference.

## Multicenter Studies in Japan on Subjective Symptoms and Diagnosis at Internal Medicine in Consideration of Sex, Gender and Age Differences in Medicine

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The General Internal Ambulatory Department plays a very important role in local hospitals and the demand among the inhabitants in Japan. We present hereby the second report where we considered the problem of patients at the Internal Medicine Ambulatory department from the standpoint of sex, gender, and age. This is a cross-sectional retrospective study conducted in the form of a unified medical examination sheet questionnaire. We studied 6 local hospitals/infirmaries near the metropolitan area, presenting us with data of new patients all in the field of internal medicine. Thus, between June 15 and July 15, 2011 (summer period), and between January 16 and February 15, 2012, we collected data from 4424 individuals. Those individuals whose complaints we could analyze we grouped according to sex and gender, age, and encoded according to the Element No 1 of the second edition of International Classification of Primary Care. Of all, 3976 individuals were analyzed, 1335 in summer, 2641 in winter, 46.8% were male, mean age  $51.7 \pm 19.6$  years. A split up according to complaints yielded 43.3% "Respiratory," which was the highest value followed by "General and unspecified" (35%), "Digestive" (30.9%), "Neurological" (22.2%), and "Musculoskeletal" (12.1%) in this order. Female patients had significantly more troubles with digestive organs than men. The younger the patients were the more they suffered from locally unspecified troubles (or over the whole body), problems with digestive tract, nerves, and respiratory organs. On the other hand, the older the patients were the more they suffered from circulatory dysfunctions. We studied the complaints of patients at the Ambulatory Departments of community-based hospitals. We are continuing our research about prognoses, diagnostic name, and appropriate treatment at the time of the first examination.

## Sex, Hormones and Macrophage Activation in Cardiovascular Disease

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**Introduction:** Aging is associated with deterioration of the physiological function, leading to systemic inflammation and mitochondrial dysfunction that promote the development of cardiovascular diseases. Sex differences in cardiovascular diseases have been postulated. However, the exact mechanism of these differences remains unclear. In the current study, we aimed to investigate, whether there are sex and aged-induced differences in the inflammation. We propose sex differences in the Sirt1-AMPK axis and expression of mitochondrial proteins in young hearts and that this differences are lost in age. Furthermore, we propose a decreased mitochondrial biogenesis in aged female hearts that promotes pro-inflammatory actions in old women. **Methods:** Male and female human nondisease lateral left ventricular wall tissue (men = 16 and female = 15) were used for qRT-PCR, Western blot analysis, and immunohistochemistry. Sirt1, AMPK, pAMPK, ac-Ku70, TFAM, PGC-1 $\alpha$ , Sirt3, SOD2, and catalase were used as parameters for mitochondrial biogenesis. CD68 was used as marker for macrophages and the ratio of IL-12:IL10 was used to examine the inflammatory stage in the heart. **Results:** Sirt1 expression was significantly higher in young females compared to young males ( $P < .05$ ), whereas in aged hearts Sirt1 expression was significantly downregulated in females ( $P < .05$ ). Accordingly to the Sirt1 downregulation in aged females, Ku70 acetylation in aged female hearts was significantly elevated ( $P < .05$ ). The activity of AMPK was significantly decreased in aged individuals; however, no sex differences in the AMPK expression or activity were found in young or in old individuals. The expression of TOM40, SOD2, and Sirt3 was significantly upregulated in young female compared to young male ( $P < .05$ ), while in aged female hearts SOD2 and TOM40 were downregulated. In addition, the expression of catalase, a key cytosolic and mitochondrial antioxidative enzyme was significantly higher in young females ( $P < .05$ ) and this female sex benefit was lost in aged hearts. In addition, the number of cardiac macrophages was significantly increased in old female hearts ( $P < .05$ ). Accordingly with this, we found differences in the IL12/IL10 ratio in young female cardiac tissue in favor of the anti-inflammatory mediator IL-10 (ratio 1:4) compared to young males (ratio 1:1). The anti-inflammatory environment in the heart was lost in aged females (ratio 1:1). **Conclusion:** We conclude that aging leads to a significant downregulation of Sirt1 expression and elevated acetylation of Ku70 in female, but not in male hearts. Furthermore, a beneficial upregulation of mitochondrial and antioxidative proteins in young females is lost with aging. Moreover the malfunctions in the Sirt1 expression and mitochondrial proteins in aged female hearts is accompanied by a significant pro-inflammatory shift, leading to an increase incidence of cardiovascular diseases in old women.

## Development of AI Diagnostic Navigation System (WaiSE) for Women's Medical Care Assistance

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Women, especially at perimenopausal phase, often present with a wide range of psychosomatic symptoms. Limited examination time often prevents a final diagnosis from being determined in general clinics. Therefore, women tend to repeatedly visit multiple clinics with nonspecific symptoms. In Japan, an estimation showed 18.8 billion yen spent annually on medical expenses for perimenopausal women. Comprehensive support that focuses on sex, gender, and age differences is desired. Since 2007, Tokyo Women's Medical University has provided comprehensive women's medical care based on gender medicine, and diagnoses specific diseases in 27% of women with nonspecific complaints. Therefore, based on our experience with gender medicine, we decided to develop a tool using artificial intelligence (AI) and a chatbot to support interview-taking and diagnosis for women with nonspecific symptoms. In April 2019, we began developing an AI diagnosis navigation system "WaiSE" with support from the Japan Agency for Medical Research and Development (AMED). WaiSE is an application for patients and physicians that incorporates a chatbot system with a diagnostic algorithm based on our clinical experience. In order to elucidate the pathology and establish evidence for appropriate diagnosis and treatment for women's nonspecific symptoms, we will analyze data from 61 983 medical records of 5241 patients who visited our Women's Specific Clinic at Tokyo Women's Medical University over the past 10 years. WaiSE reproduces inquiries of Women's Specific Clinic experts in dialogue form through an AI chatbot system to organize complaints and guide users to the necessary information for diagnosis. Women can use WaiSE to review information about their chief complaint before attending a clinic and know candidate of disease to be distinguished. They can share that information with physicians in order to get differential diagnoses and treatments. WaiSE is expected to improve patient satisfaction, reduce medical expenses, and help women's health through more accurate diagnoses.

### **Sex Differences in Myocarditis and DCM: A Personalized Medicine Approach for Men and Women**

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Heart failure due to nonischemic dilated cardiomyopathy (DCM) contributes significantly to the global burden of cardiovascular disease. Myocarditis is, in turn, a major cause of acute DCM in both men and women. However, recent clinical and experimental evidence suggests that the pathogenesis and prognosis of myocarditis and DCM differs between the sexes. Men have an increased incidence and severity of most cardiovascular diseases including atherosclerosis, myocardial infarction, myocarditis, DCM, and heart failure, with the exception of hypertension, which is higher in women. A recent study found that myocarditis is 3.5 times more common in men than women and DCM, regardless of cause, is around 2 times more common in men. Men are more likely to require a heart transplant following myocarditis and are at increased risk of death compared to women. Animal models have provided valuable information about the mechanisms that lead to more severe myocarditis, DCM, and heart failure in men than women. We recently showed that the biomarker sST2 only indicates risk of heart failure in men under the age of 50 but not in women and not in men over 50. This study highlights the need to examine diagnostic and risk biomarkers and clinical end points according to sex and age. Considering that sex hormones alter gene expression that influences basic organ physiology, the immune response to infection and damage, drug dose effects, and thus symptoms and outcomes of therapy, a personalized approach to medicine that incorporates the sex and age of the patient is essential in order to provide effective health care.

### **Sex Differences in Mitochondrial Function**

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Mitochondria are unique organelles present in almost all cell types. They are involved not only in the supply of energy to the host cell but also in multiple biochemical and biological processes like calcium homeostasis, production and regulation of reactive oxygen species (ROS), pH control, or cell death. The importance of mitochondria in cell biology and pathology is increasingly recognized. Being maternally inherited, mitochondria exhibit a tissue-specificity, because most of the mitochondrial proteins are encoded by the nuclear genome. This renders them exquisitely well adapted to the physiology of the host cell. It is thus not surprising that mitochondria also show a sexual dimorphism as that they are also prone to the influence of sex chromosomes and sex hormones. Sexual dimorphism of mitochondria involve mainly oxidative capacities, calcium handling, and resistance to oxidative stress in a tissue-specific manner. In turn, sex hormones regulate mitochondrial function and biogenesis. Estrogens affect mitochondria through multiple processes involving membrane and nuclear estrogen



receptors (ERs) as well as more direct effects through signaling pathways. Moreover, estrogen receptors have been identified within mitochondria. Mitochondrial dysfunction is also an important parameter for a large panel of pathologies including neuromuscular disorders, encephalopathies, cardiovascular diseases, metabolic disorders, neuropathies, renal dysfunction and so on. Many of these pathologies present sex/gender specificity. We will discuss the sexual dimorphism of mitochondria from different tissues and how this dimorphism takes part in the sex-specificity of important pathologies, mainly cardiovascular diseases and neurological disorders.

## La Pura Women's Health Resort: Healthy Aging and Well-Being Exclusively for Women

Sabine Fröhlich, MD<sup>1</sup>

<sup>1</sup>Medical Director of *la pura*, Women's Health Resort, Gars am Kamp, Austria

In the idyllic Gars am Kamp region, *la pura* presents itself as a site of strength and energy only for women who consider a healthy lifestyle just as important as ambiance. *La pura* is the only resort just for women in all of Europe. It was founded 2011 and belongs to the VAMED company. Our gender medicine programs have been developed in cooperation with Alexandra Kautzky-Willer, Professor of Gender Medicine and Head of the Division of Endocrinology & Metabolism of the Medical University of Vienna. The Gender Institute in Gars enables sex and gender-based research at *La pura*. The medical team at *la pura* consists of general practitioners and specialists for trauma surgery and orthopedics with additional education in osteopathy, FX Mayr medicine, traditional Chinese Medicine, homeopathy, and minimal aesthetic intervention and sports experts as well as psychologists. The nutritional concept at *la pura* is the GourMed<sup>®</sup> Cuisine. Valuable regional food products are prepared in a gentle way, using organic and seasonal products. With our medical programs, we focus on prevention of chronic diseases, a healthier lifestyle including individualized healthy nutrition, exercise, and healthy aging and mental health. As well we provide medical help and advice for women-specific problems and female life-phases. We offer detox programs for weight management and the FX Mayr cure for regeneration of the digestive system—all under medical supervision. Our healthy aging program includes 2 epigenetic tests, on the one hand a metabolic panel and on the other hand a biological age panel to find out any predispositions and risks to premature aging. All programs are being perfected continuously based on current evaluation and new knowledge to further improve health and well-being of our female guests.

## Inflammaging and Gender Differences

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Human aging is characterized by a chronic, low-grade inflammation. This phenomenon has been called *inflammaging*, defined as the chronic low-grade inflammation which is an important risk factor for morbidity and mortality in the old people. Most if not all age-related diseases have an inflammatory pathogenesis. Gender differences in prevalence/incidence of diseases, clinical manifestations, prevention strategies as well as in pharmacological needs are very important. This may be most dependent on differences in the inflammaging process. Is there a relationship between inflammaging and Frailty? And is there a difference between males and females? Frailty is a state of reduced physiological reserve and increased vulnerability for poor resolution of homeostasis after a stressor event. The male-female health survival paradox may bound to the fact that at any given age females have higher Frailty Index (FI) scores than males. However females live longer than males but with poorer health. In many papers a relationship between frailty and cardiovascular diseases is described with higher incidence but less mortality in females who are more affected by obesity, diabetes, metabolic syndrome, coronary calcifications, carotid plaques. Several papers conclude that biological, behavioural, and social factors underpin sex differences in frailty. However a great importance may be due to different inflammaging processes: women have a lower susceptibility and higher resistance to infection diseases in the first years of life, due to a higher inflammation capacity. However in the adult and late life, the high inflammation reaction of women leads more often to immunological, atherosclerotic diseases, as well as to the so called “degenerative” diseases (as osteoarthritis and dementia). Longevity is a good balance between pro- and anti-inflammatory stimuli. And genetic component and great individual variability influences frailty or robustness.

## Sex and Gender Specific Phenotypes in Alzheimer's Disease—the Gateway to Precision Medicine

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Sex differences in neurological and psychiatric diseases, notoriously heterogeneous in biology, clinical presentation and disease progression, have just started to be investigated and their significance is currently debated. In this talk, I will provide an overview of the literature documenting the occurrence and role of sex differences in dementia, with a focus on Alzheimer's disease. Sex-differences in symptoms, biomarkers, risk factors, and in response to medical intervention will be discussed. Failing to recognize and appropriately consider sex and gender differences might compromise the development and validation of optimal diagnostic and therapeutic tools for highly heterogeneous diseases, such as Alzheimer's. The Women's Brain Project advocates for more basic and clinical research into this topic, in the context of a precision medicine approach that will benefit both men and women.

## Metabolomic Profiles Differentiate Men and Women in Accordance With Metabolic Disease

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There is evidence that pathophysiology of metabolic syndrome (MetS) differ between men and women. Sixty-six (33 female, 33 male) patients aged 60.3 to 62.5 years with (n = 57) and without (n = 9) MetS, but without diabetes, were included in the study. Each patient performed an oral glucose tolerance test (oGTT). Untargeted metabolomics were measured fasting and 120 minutes after intake of 75 g glucose. Metabolic syndrome was diagnosed by NCEP-ATIII criteria. Branched-chain amino acids (BCAA) and fatty acids (FA) could be selected by a VIP plot for MetS. A coefficients plot showed FA negatively correlated with MetS and BCAA positively correlated. Individual amino acids (AA) were clustered in MetaFA and MetaBCAA. Men had fewer MetaFA than women at time point 0 (LSD Intervals: -0.6 vs 0.5); after 120 minute men had more MetaFA than women (LSD intervals: 0.6 vs -0.4). Women had fewer MetaBCAA at time point 0 (-0.5 vs 0.5) and after 120 minutes (-1 vs 0.9) after oGTT and MetaBCAA dropped, while MetaBCAA in men rose after glucose intake. A boxplot showed that MetaBCAA in women without MetS differed significantly compared to MetaBCAA in women with MetS, whereas no such difference could be shown for MetS in men. Men had less MetaFA than women at time point 0 (-0.7 vs 0.5), after glucose MetaFA increased in men (0.4) but decreased in women (-0.5). Men without MetS had a significant different MetaFA profile than men with MetS, whereas this could not be detected in women. Women without insulin resistance (IR) had significant lower MetaBCAA than women with IR (-1 vs 1); men showed no differences in MetaBCAA regarding IR; women with IR had more MetaBCAA than men with IR (1 vs -0.3). Men with IR had significantly fewer MetaFA than women with IR (-1 vs 1.3). Spearman rank correlations of single AA showed differences in untargeted metabolomics between men and women. These results indicate that metabolomics can distinct (patho)mechanisms of components of MetS that differ between men and women. More detailed analysis and exact requests in homogenous groups are needed.

## The Nuclear Membrane Estrogen Receptors Define the Diagnosis and Treatment of Gender Specific Medicine Disease

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Gender specific medicine (GSM) no longer is limited to hypothesizing from observations of statistically significant correlation between mankind's gender and appearance of diseases. Pierdominici's discovered that loss of the estrogen receptor-beta (ER $\beta$ )/estrogen receptor-alpha (ER $\alpha$ ) ratio correlated directly with 90% of flairs of Crohn disease. Therefore, researchers and clinicians have a reproducible biomarker that directly links inflammation, hormones, GSM observations, and treatments. Homeostatic ER $\beta$  signaling maintains the anti-inflammatory humoral state of IL-6, IL-10, and TNF $\alpha$ . As ER $\beta$  is a testosterone receptor, our clinical research directly links loss of bioavailable testosterone in both sexes with loss of ER $\beta$  homeostasis and disease. In women with severe endometriosis, the ER $\beta$ /ER $\alpha$  ratio is increased up to 100-fold. Considering endometriosis as a GSM diseases limited to only women, the prescribe anabolic steroids, actions similar to danazol, reset the ER $\beta$ /ER $\alpha$  ratio biomarkers downward. The 2 biomarkers used are bioavailable testosterone (Free Androgen Index) and the ER $\beta$ /ER $\alpha$  ratio. This differs from Crohn disease in which men and women are both affected, yet, remissions have occurred in both sexes with anabolic medications that reset the low ER $\beta$ /ER $\alpha$  ratio, upward. This information has almost unlimited applications: the clinician defines the disease, measures the aforementioned serum biomarkers, and treats the patient in parallel to the in vitro findings from the individual's T-lymphocytes tissue culture. The ER $\beta$ /ER $\alpha$  ratio and 8 cytokines testing are repeated 8-weeks after various drug therapies. This is the future of precision medicine: direct treatment individually based on in vitro biomarkers. The ER $\beta$ /ER $\alpha$  ratio should be adopted as the biomarker for all GSM research: it separates diseases limited to only women such as endometriosis, breast and ovarian cancer, and directs a new course of understanding and potential future treatments in diseases that affect both sexes.

## Large-Scale Screening of Organ-Specific Autoantibodies in Patients With Autoimmune Thyroid Diseases

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**Background:** Multiple autoimmune syndromes (MAS) are diseases characterized by autoimmune activity against more than one endocrine organs, although nonendocrine organs can be affected. Four types of MAS have been described: MAS type

1 (at least 2 among chronic candidiasis, chronic hypoparathyroidism, Addison's disease); MAS type 2 (Addison's disease plus autoimmune thyroid disease [ATD] and/or diabetes mellitus type 1); MAS type 3 (ATD plus other autoimmune diseases); and MAS type 4 (association of diseases that do not fit in type 1, 2, and 3). It is well recognized the prevalence of female in the MAS, but an analysis of the frequency of the single antibodies in female and male has never been reported in literature. The aim of our study was to establish the prevalence of organ-specific autoantibodies: antiadrenal (ACA), antiovary (StCA), antipituitary (APA), antiparietal gastric cells (PCA), antitransglutaminase (AtTG), antiglutamic acid decarboxylase (GAD), and antimuscle nicotinic acetylcholine receptor (ARAb) in patients with ATD. **Experimental methods:** A total of 1629 patients (1419 F, 210 M, age:  $50.6 \pm 14.7$ ) with ATD have been prospectively enrolled. ACA, StCA, APA, and PCA were measured by indirect immunofluorescence assay (Euroimmun, Germany), AtTG by a fluorescence enzyme immunoassay (Phadia, Sweden), GAD by an enzyme immunoassay (Technogenetics, Italy), and Arab by a radioimmunoassay (RSR, United Kingdom). **Results:** Antiadrenal autoantibodies were positive in 11 patients (10 F, 1 M), StCA in 6 F, APA in 9 patients (8 F, 1 M), PCA in 151 patients (129 F, 22 M), GAD in 67 patients (51 F, 16 M), AtTG in 11 female, and ARAb in 5 patients (4 F, 1 M). Only GAD was significantly associated with males ( $P = .015$ ). **Conclusions:** Our results show that there is no difference of the prevalence of the analyzed organ-specific autoantibodies in patients with ATD regarding gender, as already reported, except for GAD.

### Gender Differences in Osteoporosis

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**Background:** Osteoporosis is characterized by low bone mineral density (BMD) and increased risk of fractures. In Italy osteoporosis affects about 5 000 000 people, of which 80% are postmenopausal women. Men are underdiagnosed and inadequately treated, although osteoporotic fractures in men are accompanied by greater mortality compared to women. **Objectives:** To assess gender differences in BMD, bone remodeling serum markers and fractures in subjects observed at the outpatient Center for Osteoporosis of L'Aquila University. **Methods:** We evaluated 749 females ( $65.29 \pm 10$  years) and 43 males ( $66.62 \pm 10.99$ ). Calcium (Ca), phosphorus (P), parathyroid hormone (PTH), 25(OH) vitamin D (vit D), beta-cross laps (CTX), osteocalcin, bone alkaline phosphatase (BAP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and lumbar/femoral BMD (T-score) were measured. **Results:** Women showed lower vit D, CTX, and PTH serum levels than men ( $25.31 \pm 15.17$  ng/mL vs  $32.97 \pm 21.90$  ng/mL,  $389.07 \pm 453$  pg/mL vs  $441.28 \pm 343.37$  pg/mL and

$59.82 \pm 39.18$  pg/mL vs  $60.17 \pm 43.11$  pg/mL, respectively;  $P < .01$ ). Serum P levels and ESR were lower in men than women ( $2.90 \pm 0.56$  mg/dL vs  $3.37 \pm 0.52$  mg/dL and  $14.59 \pm 12.31$  mm/h vs  $19.85 \pm 14.36$  mm/h, respectively;  $P < .01$ ). No difference in the other parameters was observed. Bone mineral density was lower in females (mean T-score level  $-2.33 \pm 1.14$ ) compared to males ( $-31 \pm 1.55$ ;  $P < .01$ ). The prevalence of osteoporosis (T-score  $< -2.5$ ) was higher in females compared to males (51.26% vs 27.90%;  $P < .05$ ), whereas the percentage of fractured patients was higher in osteoporotic men than women (50% vs 30.72%). **Conclusions:** Bone mineral density is higher in men than women of comparable age. However, osteoporotic fractures are higher in men than women. CTX, PTH, and vit D are lower and ESR is higher in women than men.

### Sex Differences in Gastrointestinal Cancers

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So far, oncology has been largely sex- and gender-blind. However, together with the interest in personalized oncology and our improved understanding of cancer biology, sex differences in cancer epidemiology and distribution of molecular subtypes of various cancer types (eg, gastroesophageal cancer) as well as patient outcome are gaining increasing attention. In addition, recent evidence suggests significant sex differences in efficacy and toxicity of certain chemotherapies, alone or when used in combination with biologicals. The European Society for Medical Oncology (ESMO) is addressing this challenge. After an initial workshop "Gender medicine meets oncology" held in 2018, ESMO created a multidisciplinary task force which will define key research projects to investigate the effect of sex and gender on cancer epidemiology and outcomes, as well as treatment effects and communicate relevant findings at future meetings.

### Drug-Utilization Pattern of Non Small Cell Lung Cancer Patients Related to Gender at the University Hospital of Siena, Italy

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Lung cancer is the third most commonly occurring cancer in females. Non-small cell lung cancer (NSCLC) represents about 85% of all cases of lung cancer. Recently, treatment guidelines for NSCLC have changed due to the introduction of new drugs for patients with advanced stage of the disease. The aim of the study was to analyze the treatment patterns of patients diagnosed with NSCLC between 2009 and 2017 at the University Hospital of Siena (UHS), focusing on gender difference in drug utilization. Patients with NSCLC diagnosis were identified by records in the pathology registry (PR) of UHS. Pathology registry data of NSCLC patients were anonymized and linked to the administrative health-care database of Tuscany region. Advanced stage patients were defined as those without surgical intervention (NO-SUR patients). A total of 2003 NSCLC patients were identified. There was a statistically significant upward trend ( $P = .0177$ ) in the incidence in women, rising from 25% in 2009 to 38% in 2017. The average age of patients was 69 years and 45.3% were aged between 50 and 69 years; NO-SUR were the 57.1% of the study cohort ( $n = 1144$ ). This cohort was divided in elderly, aged  $\geq 70$  years ( $n = 587$ ), and young patients, aged 18 to 69 years ( $n = 557$ ). In the 6 months following the index date, the percentage of subjects who received both immunotherapy and target therapy was higher among young patients, 5.9% vs 1.7% and 13.1% vs 11.1%, respectively and increased from 2.8% to 28.2% in young patients ( $P < .001$ ) and from 1.4% to 6.9% in elderly patients between 2015 and 2017. In this cohort, the proportion of women increased. Data will be presented on the pattern of drug utilization and outcome in relation to gender. Real-world data on the pattern of drug utilization provide important information for clinician and health provider both in terms of appropriateness and economic sustainability of care.

### **X-Chromosome-Linked miR-548am-5p Is a Key Regulator of Mitochondria-Mediated Apoptosis and Is Implicated in XX and XY Cell Disparity**

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The relevance of sex dimorphism in cell response to stress has previously been investigated by different research groups. It has been reported that, under the same stressing conditions,

XY cells easier undergo cell death in comparison with XX cells that easier undergo cytoprotection by autophagy. This dimorphism could be due, at least in part, to regulatory elements such as microRNAs (miRs). In order to point out miR expression differences, we took advantage of specialized databases to identify X chromosome-encoded miRs potentially escaping X chromosome inactivation (XCI). One of these, the MiR-548am-5p, was found as a potential XCI escaper. This MiR is also deeply related to cell fate paths. We found that experimentally induced overexpression of miR548am-5p in XY cells by lentivirus vector transduction decreased apoptosis susceptibility, whereas its downregulation in XX cells enhanced apoptosis susceptibility. These data suggest that miR identified with this approach, miR548am-5p, can account, at least in part, for sex-dependent differences observed in the susceptibility to mitochondria-mediated apoptosis of human cells. More in general, these results also underscore the relevance of X chromosome-encoded miRs escaping XCI in cell pathology and the possible key roles of epigenetic mechanisms in determining XX and XY cell fate disparity.

### **Global Health and Gender Education: A Multidisciplinary Approach**

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Global Health is a concept that apply to the vision of health and disease as a result of many factors related to biological or individual characteristics but also to social, economic, and environmental conditions. Introducing gender issues in educational programs for health professionals may be useful but global health may be improved only through a multidisciplinary commitment aimed at creating a wider gender perspective about access to health care, decent work, and representation in political and economic decision-making processes. In the Global Gender Gap Index 2018, Italy ranks 82nd out of 144 Countries and 118th in economic participation and opportunity subindex. “Gender equality” is the fifth out of 17 goals of the UN 2030 Agenda for Sustainable Development. Based on the premises that global health inequalities cannot be overcome by simply focusing on medical field but that an encompassing cultural change is needed, a group of teachers of different Departments (Law, Social sciences, Medicine) of the University of Siena decide to run the first comprehensive educational program addressed to students, both graduated and undergraduated, and to University and Municipality staff. Following presentations of statistics, scientific data and academic research in various disciplines, students were invited, also through non formal education tools, to openly discuss about their beliefs, feelings, and “unconscious” gender stereotypes to enhance their critical thinking skills. The exams’ results of the pilot course held in May demonstrate students’ increased interest

and understanding of the multiple levels of gender issues and the need for gender mainstreaming in all fields of social life.

### Focus Gender—Medical Students Gender Specific Perception and Attitudes Towards Burdens of the Everyday Student Life

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The aim of this study was to investigate whether female and male medical students perceive burdens differently and whether students of both sexes assess their capability to stand performance pressure differently. In 2017, second (n = 424, 53% female) and sixth (n = 161, 46.6% female) year students at the medical university of Vienna were surveyed using a fully structured questionnaire. In second year, female students felt significantly more often that they could not measure up to study requirements than male students (87.5% vs 94.4%). Performance pressure was perceived as major problem by male (45.5%) and female (50.9%) students, while in sixth year the number was only half as high than in second (24%, 18.4%). In sixth year, significantly more female than male students were complaining about competition between students (33.3% vs 8%). Half of the students shared the view that there is no difference between men and women in the capability to deal with performance pressure. Most of the other half state that men are superior to women in handling performance pressure. In both groups, significantly more male than female students were convinced that they are superior to the other sex in handling performance pressure. Perception of problems is similar in male and female students. While in objective assessments, female students perform equally to male students they consider themselves less competent and are more inclined to doubt their capability.

### Gender Integration in the Pregraduate Medical Curricula: A Swiss Perspective

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**Introduction:** Integrating gender perspective in the medical curricula has been proved to be of the utmost value in order to address the health inequities created by gender bias. Following the insertion of gender sensitive objectives in the 2018-revised Swiss catalog of medical learning objectives (Profiles), the integration of gender in the medical curricula of the University of Lausanne has been facilitated. This integration process, driven by the Gender and Medicine Unit, focuses on 2

axes: content (evidence-based gendered medicine) and form (gender neutral/nonstereotyped teaching material). **Hypothesis:** Using a multilevel strategy in clinically relevant medical education disciplines facilitates the integration process. **Project Description:** First, a Gender and Medicine Commission composed of 12 academic representatives from different medical disciplines has been created. Then, information about the new gender objectives set in the profiles was sent to every discipline leader. Integration was progressively launched through a strategic selection of disciplines (cardiology, abdominal surgery, oncology, pediatrics, and psychiatry) based on 2 facilitating factors: pertinence in gender integration and available literature; and a listing of gender supportive faculty members or teachers. Subsequently, we conducted a review of literature and teaching material to address predefined disciplines' leaders and teachers in order to provide specific and practical material for gender integration. This project aims to communicate broadly on the processes and outputs in order to incite other disciplines to endorse evidence-based gender integration. **Conclusion:** As shown by previous international experiences, gender integration is effective but requires a multilevel strategy. The focus on pregraduate students is pertinent as it will ultimately improve care for all patients.

### Integrating a Gender Perspective into Core Curriculum of Medical Students

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Integrating gender issues into curriculum and underlining the influence of gender in personal and professional choices is necessary to promote gender equality in medicine. Several years ago, an optional course on Gender Medicine was run at the University of Siena on request of a teacher who aimed to raise awareness about the influence of gender on health and illness, choice of specialization, professional and social relationships. Following students' interest, "Gender health" was then introduced into the second year core curriculum as a module within the Integrated Course of "Medico-scientific methodology, human sciences and health promotion." A gender perspective was applied in reviewing the medical literature, discussing the role of women in the history of medicine and surgery and the concept of gender as a determinant of health and a topic of scientific relevance. The final examination consisted of a written paper on the treated topics with a free-form reflection. Afterward, according to the Faculty policy, all students must fill out an online anonymous, semistructured satisfaction questionnaire. In all, 658 students (404 F; 254 M) attended the MSSUP from 2016 to 2019 and most of them stated their satisfaction with the course as a whole. The module of "Gender Health" received the highest rating in all 3 years

(4.8 in a 5 level scale). Students of both sexes declared great interest for gender issues that were referred to as relevant for their clinical practice and social commitment. Young people have a desire to learn and fertile minds. Persons in leadership positions have to be engaged to introduce a gender perspective in formal education. Competent and gender sensitive teachers are important as well. All staff and educators have to become aware of scientific relevance of gender differences to integrate such knowledge in every class and discipline.

## A Conceptual Framework: Gender Medicine Versus Gender of Medicine

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In this study, the physicians' opinions about "Gender of Medicine" and "Gender Medicine" were evaluated from the answers of the survey question conducted for physicians and medical faculty students. Over the years, the effects of gender on medicine became more observable. It has been possible for women to be involved in the medical profession just in the last centuries. Like women, LGBT+ individuals also experience various problems in medical practice. On the other hand, in every step of medical practices Gender Medicine Vision's significance is a crystal-clear fact. In this descriptive study, the universe is the physicians in Turkey; sample size is not calculated and purposive and snowball sampling methods were used. Through social media and communication tools, open access online questionnaire was shared and volunteers answered. This study conducted via the last question which is "In your opinion, what is the difference between 'Gender of Medicine' and 'Gender Medicine.'" Of all, 908 people participated in the questionnaire, and the 2 conceptual frame, from the view of semantics, inference and differences were discussed with the coding of answers. As a result of coding, few main themes were revealed as Medicine is a little Man growing with patriarchy, doctor's sexual identity versus Patients'. The main outcome point of this research is that physicians may differ in their perception of the gender of their own professional discipline and knowledge of "Gender Medicine" that may shed light on the future of medical practices.

## Reflexivity on Gender Bias in Clinical Practice: A Tool for Medical Education Implemented in Switzerland

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The Medical School of Lausanne, Switzerland, includes a gender medicine theoretical teaching that aims at "fixing the

knowledge" on sex and/or gender differences in medicine. In 2019, a pilot project was introduced to integrate reflexivity on the influence of gender in clinical practice. The aim was to raise students' awareness on gender bias and the potential effect on patients' management. Reflexivity is the ability to critically reflect on and assess one's own presuppositions and social experiences that shape one's perceptions and actions. By reflecting on one's gender perceptions, the hypothesis is that gender bias (gender stereotyping [treating men and women differently but not clinically relevant] or gender blindness [treating men and women equally when clinical differences exist]) may be reduced in clinical practice. During their internship, medical students discuss the case management an encountered clinical case with a chief resident, in small groups. A gender lens was introduced whereby students are asked to discuss the case considering potential gender bias, with support from a gendered medicine expert. In a second step, students are asked to fill an online reflexivity sheet, presenting their discussed clinical case and reflecting individually on potential gender bias and lessons learned. Their assessment is commented and validated by a gendered medicine expert. Topics discussed in groups and in reflexivity sheets can be grouped in different categories: the relevance and use of epidemiological data (gender difference in disease prevalence) for patient management; medical knowledge on evidence-based gender differences, by pathology; gender bias at different steps of a consultation: anamnesis (gender stereotypes assessing psychosocial background); clinical exams (influence of gender on clinician-patient interactions); differential diagnosis (driven by evidence-based or stereotyped-gender differences); treatment (gender differences in pain management). Reflexivity is a powerful tool to raise awareness on one's own gender perceptions and potential bias that may impact clinical practice.

## The Relevance of Hidden Curriculum in Health Professional Formation

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**Background:** Gender awareness is mandatory to improve medical practice and to maintain good relationships with patients and colleagues. Different strategies have been proposed to integrate gender issues in formal medical education but the hidden curriculum, conveyed by official and unofficial teachers, is important as well. **Aim of the Study:** To assess gender sensitivity and basic knowledge about gender differences in medicine in persons involved in formal and nonformal training of health-care professionals (HP). **Methods:** An anonymous, semistructured questionnaire has been e-mailed to 1975

HP of the University Hospital of Siena where HP trainees attend for internship. **Results:** A complete questionnaire was returned by 148 (7.49%) HP (39 M, 139 F). One fourth of respondents have a teaching assignment at the University of Siena and half of them claims to have introduced gender issues in class: 45% of those who do not state the topic is not relevant for their discipline. Slight differences between men and women are noted in answers related to knowledge of gender differences in the incidence of breast (17%), colorectal (37%), and lung cancer in never-smokers (8%); < 12% knows that scientific studies have been mostly conducted on men, male animals, and male cells; 52% are aware that woman's symptoms of the same disease are often different from a man's; 75% believe that her perception of illness may be different. Stereotypical thinking about communication style of both patients and doctors and between them is also shown. **Conclusions:** Increasing gender sensitivity in HP is necessary not only to improve quality of care but also to avoid that prejudices and stereotypical thinking may be transmitted to younger generation through the hidden curriculum. Commitment of hospital managers in addition to that of Faculty Members is of utmost importance.

### Gender Medicine in the Programs of the Italian Public Institutions: The Role of FNOMCeO

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**Background:** About 400 000 active medical doctors of the Italian health system did not receive any pregraduate education on Health and Gender Medicine. Since June 13, 2019 in Italy we have, first country in Europe, a specific law for the application and diffusion of Gender Medicine in the National health system. FNOMCeO (National Federation of the Orders of Doctors and Dentists) is a public Institution, subsidiary of the State, whose main purpose is to update the Code of Ethics for Italian physicians and to check that they respect it. According to the Code of Ethics, the post graduated-education on Gender Medicine is mandatory. **Methods:** Both FNOMCeO and the Provincial Medical Councils are accredited providers for Continual Medical Education and they have been organizing residential postgraduate training courses for several years. In 2014, FNOMCeO set up a specific Committee for Health and Gender Medicine composed of both experts and Presidents or Vice-Presidents of the Local Medical Councils. The aims of the Committee are to plan postgraduate training courses, to inform citizens, to take part to the National and International Network for Gender Medicine, to cooperate with other Italian Public Institutions, and to encourage clinical research. **Results:** Since 2014, this Committee has been organizing 20 residential

courses, workshops, and it has been taking part of symposia organized by the most important National Scientific Societies (eg, general practitioners, hospital doctors, etc). In the last 10 months, Italian medical doctors or dentists have received more than 28 000 CME credits through a FNOMCeO Course in Distance Learning (F.A.D.). **Conclusions:** In consideration to the need of implementing postgraduate education on health and Gender Medicine for Italian physicians, FNOMCeO is cooperating with other Public Institutions (University, Scientific Societies, Regional and National Governments, etc) to promote an adequate post graduated-education on Gender Medicine.

### Health and Gender Medicine: a Cutting-Edge Formative Experience Promoted by the University of Florence

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**Background:** There has been an increased awareness that gender-specific issues influence women's and men's health more broadly and with a higher impact than previously recognized. These differences are not limited to reproductive health, but extend to almost every other organ and tissues. The University of Florence promoted education in health and gender medicine, which is targeted at students of bachelor and master programs as well as at postgraduate students, clinicians, academicians, and researchers. **Methods:** In the pregraduate education, gender medicine has been recognized as an integral and suggested part of the core curriculum for students in all medical schools; it is represented in the teaching programs of the School of Medicine and Surgery in Italy. In postgraduate education, master is an example of truly interdisciplinary collaboration, staffed by academics from a range of disciplines, each bringing their specific expertise to bear on the topics under discussion. It is intended for all health science professionals with a university master degree in medicine, dentistry, pharmacy, biology, nutritional sciences, nursing, psychology or sociology, interested in gender-specific health issues and its program features 4 taught modules, followed by an experimental thesis. **Results:** From 2017, School of Medicine of Florence initiated pregraduate education by in-room teaching, several educational courses, and workshops. From 2016 to 2018, 17 professionals brilliantly completed their postgraduate course of studies. In the academic year 2018-2019, 10 participants are obtaining specific expertise on health and gender medicine topics. **Conclusion:** The implementation of gender medicine into clinical practice is dependent on the adaptation of pregraduate and postgraduate medical education to these principles. The education in this field is the keystone for understanding and applying gender medicine principles. The University of Florence paved the

way to support and encourage the development of gender medical clinical and preclinical research.

## Gender Medicine Multimedia Library: An Apulian Experimental Project

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**Background:** The Multimedia Library of Gender Medicine is a new section of Apulian Regional Council Library “Teca del Mediterraneo” created by GiseG (“Gruppo Italiano Salute e Genere”), in collaboration with Apulian Regional Council, with the aim of become an efficient, qualified, and reliable cultural reference center for gender medicine in terms of information, research, and documentation.

The main objectives of this structure are:

- develop knowledge of gender issues and undertake health education initiatives
- promote scientific and research activities
- carry out training programs for professional development and ongoing training
- correctly inform citizenship of related issues through the use of correct information dissemination channels
- construct a qualified gender point of view on the set of pathologies affecting women and men
- highlight the centrality of the “gender approach” in medicine.

**Methods:** The project involves the collection and cataloging of the available literature on gender medicine and the availability of online material for both health workers and citizens interested in the subject. In addition to the scientific

material, the multimedia library will also offer training and information spaces, with educational material, training courses, and events on the subject, both for those who work in the health sector and for citizens who want to learn more about the subject. Will be available, for example, short informative videos, “Pills” of gender medicine. **Results:** On September 1, 2018, a protocol on gender medicine was signed between the GISeG and the Regional Council of Apulia. The multimedia library is now online and available at this link: <http://biblioteca.consiglio.puglia.it/dettaglio/menu/4522/Medicina-di-genere> [Accessed Jun 29, 2019]. **Conclusion:** We hope the library will play an important role in increasing and supporting participation in gender medicine projects, becoming a service center for information and advices to any public or private subject interested in the subject.

## Reporting of Sex-Specific Outcomes in Trials on Cardiovascular Disease: Where Is the Progress?

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**Background:** Past decade attention of the importance of sex and gender-specific medicine has increased. However, whether this has led to tangible results regarding reporting sex and gender in publications is uncertain. Our aim is to determine whether reporting efficacy and safety data stratified by sex in major cardiovascular trials has increased between 2010 and 2017. **Methods:** We reviewed the availability of sex-specific data of the publications of cardiovascular drug trials which were presented during the “Hotline sessions” of the conference

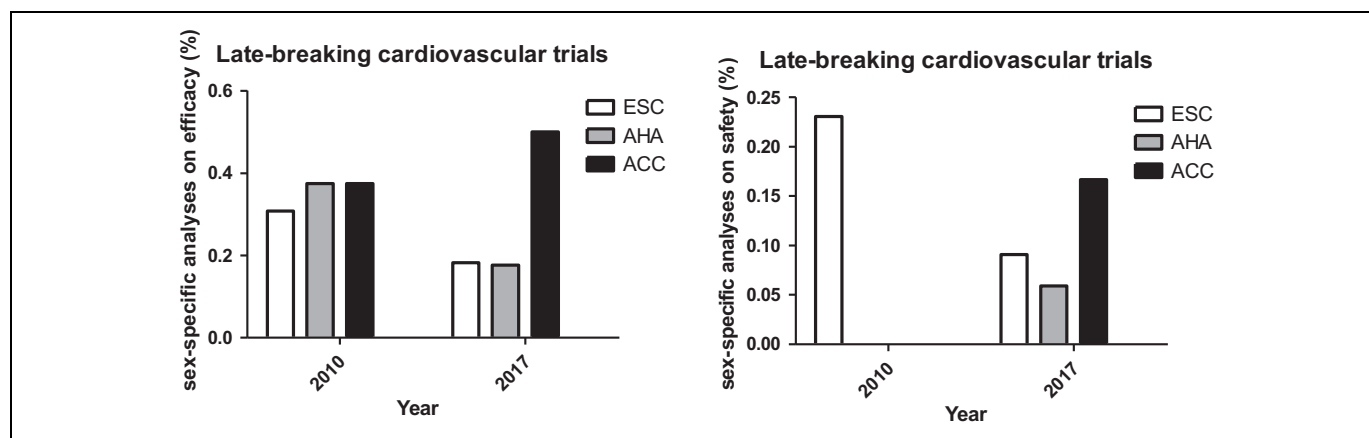


Figure 1. Sex-specific analyses on efficacy and safety.



of the European Society of Cardiology (ESC), the “Late Breaking Clinical Trials” of the American Heart Association (AHA) and the American College of Cardiology (ACC) in 2010 and compared these with 2017. Sex-specific data was assessed separately for efficacy and safety (adverse events) end points. Moreover we assessed the percentage of sex-specific data per publishing journal, conference, and sex of the first author. **Results:** In total, we included 29 in 2010 and 34 trials in 2017. The mean percentage of female participants was 32.8% in 2010 vs 33.4% in 2017. In 2010, efficacy and safety end points were reported per sex in 34.5% and 11.1% of the trials vs 23.5% and 8.8% of the trials in 2017. Only ACC showed improvement in reporting of sex-specific efficacy end points (37.5% to 50%) (Figure 1). Of the journals, the *New England Journal of Medicine* had the highest percentage of studies reporting sex-specific end points (2010: 41.7% vs 2017: 54.5%). Studies with a female first author did not report more often sex-specific data compared to those with a male first author. **Conclusion:** Despite the growing awareness of the importance of sex and gender, reportage of sex-specific efficacy and safety in cardiovascular drug trials has not improved. Specific guidelines and checklists issued by scientific societies and journals regarding reporting sex and/or gender specific data could help to improve this shortcoming.

### Role of Endometriosis in Defining Cardiovascular Risk in Women: An Interdisciplinary Approach of Gender Medicine

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**Background:** The relationship between endometriosis and subclinical atherosclerosis represents an emergent topic in women’s health, as women with endometriosis are at higher risk of cardiovascular (CV) disease later in life. **Objective:** We investigated metabolic and endothelial markers of atherosclerosis, and the association between atherosclerotic burden and clinical endometriosis degree. **Methods:** The study population comprised 660 women framed for CV risk. **Results:** In all, 109 women (16.5%) had endometriosis and showed an altered lipid profile, and increased homocysteine values in comparison to that observed in women without endometriosis. By analyzing CV profile according to degree of endometrial involvement, 92 women (84.4%) had stage III/IV, whereas 15.6% had stage I/II. We observed a significant difference of lipid profile in stage III/IV in comparison to that observed in stage I/II of endometriosis ( $P < .05$ ), as well as lower vitamin

B6 and folate ( $P = .01$  and  $P = .03$ , respectively) values, and higher hs-CRP concentrations ( $P = .04$ ). After adjustment for traditional CV risk factors (OR = 5.24,  $P = .02$ ), the worsen lipid profile remained significantly associated with severity of endometriosis. **Conclusions:** Our findings provide evidence of an unfavorable vascular profile related to pictures of accelerated atherosclerosis, possibly representing the common mechanism shared by a gynecological disorder and CV disease, and contributing to clarify the role of endometriosis as a gender-specific CV risk factor. The clinical relevance of our study lies in identify women with stage III/IV of endometriosis at higher risk of atherosclerotic disease, who could have a greater benefit for an early CV screening for controlling future CV risk.

### Sex Differences in Prognostic Impacts of Serum Uric Acid Levels in Heart Failure—Insights From the CHART-2 Study

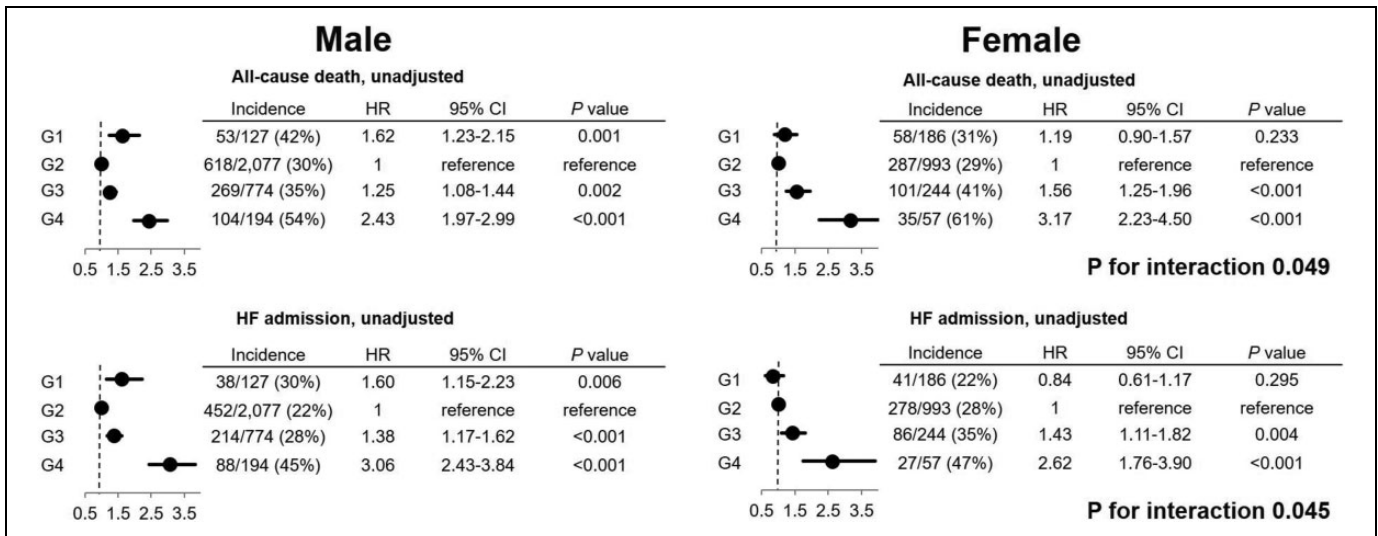
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**Background:** Prognostic impacts of serum uric acid (SUA) levels in patients with heart failure (HF) still remain unclear. We examined the relationship between SUA levels and the prognosis of patients with chronic HF (CHF) with a special reference to sex. **Methods and Results:** We classified 4652 consecutive CHF patients registered in our Chronic Heart Failure Registry and Analysis in the Tohoku District-2 (CHART-2) Study (N = 10 219) into 4 groups based on their baseline SUA levels by the Classification and Regression Tree; G1 (<3.8 mg/dL), G2 (3.8 to 7.1 mg/dL), G3 (7.2 to 9.2 mg/dL), and G4 (>9.2 mg/dL). In G1, G2, G3, and G4, mean age was  $71 \pm 12$ ,  $68 \pm 11$ ,  $66 \pm 13$ , and  $67 \pm 16$  years in males, and  $71 \pm 13$ ,  $71 \pm 12$ ,  $73 \pm 12$ , and  $77 \pm 9$  years in females, respectively (both  $P < .001$ ). Figure 1 shows the incidence rates during the median 6.3-year follow-up and hazard ratios for death and HF hospitalization in each group. Univariable Cox proportional hazards models showed the U-shaped relationship between SUA levels and prognosis in males, while not in females ( $P$  value for interaction 0.049 for all-cause death and 0.045 for HF admission); compared with G2 (reference), G1, G3, and G4 had significantly increased risks for all-cause death and HF admission in males, while G3 and G4, but not G1, did so in females. However, in multivariable Cox models with clinically important covariates, both males and females had the U-shaped relationship between SUA levels and prognosis ( $P$  value for interaction 0.541 for all-cause death and 0.445 for HF



**Figure 1.** Prognostic impacts of serum uric acid levels (Cox proportional hazard model).

admission). **Conclusions:** Sex difference exists in the relationship between SUA levels and prognosis in CHF patients, which was mainly attributable to the difference in G1. It is important to note that low SUA level is predictive of worse prognosis in males, but not in females, in the secondary prevention setting of CHF patients.

### Daylight Saving Time and Circulatory Deaths: Are There Differences By Sex? Data From the Veneto Region of Italy

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Some years ago, a study by the Karolinska Institutet first reported an association between daylight saving time transitions and an increased frequency of acute myocardial infarction (AMI) after the spring shift, and the effect was somewhat more pronounced in women than in men. A recent meta-analysis by our group, based on the available further studies, did not find differences by sex. We aimed to verify this observation in Veneto, a large region of North-Eastern Italy, with a total population of about 4 900 000 inhabitants. We performed a retrospective analysis on the regional archive of mortality records, years 2000 to 2015. For death classification, we utilized the ICD-9 and ICD-10 categories used in standard reports of mortality statistics. The number of deaths observed in each of the 7 days after the spring and the autumn shift (posttransitional weeks) was compared with the mean number of deaths registered in the corresponding week-day of the 2 weeks before and the 2 weeks after the posttransitional week (reference period).

During the study period, a total of 10 387 circulatory deaths were registered in the Spring and Autumn posttransitional weeks. No overall excess mortality was found in the posttransitional weeks with respect to the reference period in both Spring and Autumn. When analyzing the day-of-week pattern of mortality on total population, although a statistically significant excess of deaths ( $P = .011$ ) was observed on Tuesday only after the Spring post-transitional week, no differences by subgroups by sex were found. This study provides further confirmation of the existence of a modest, but significant, excess of death on the first days of the week, only after the Spring shift but with no differences by sex subgroups. It is likely that phase advance, sleep deprivation, and disruption of circadian rhythms could play some role, but these mechanisms need further investigation.

### Gender Differences of an Impact of Variant Mitochondrial Dehydrogenase Type2 Genotype in Patients With ST-Elevated Myocardial Infarction

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**Background:** Mitochondrial aldehyde dehydrogenase type 2 (ALDH2) removes toxic aldehydes, generated and released on ischemia/reperfusion injury (IRI). The deficient variant genotype (*ALDH2\*2*) is prevalent among East Asians and the allele is randomized at conception (Mendelian randomization). It is unknown whether the *ALDH2\*2* is associated with the severity of IRI in ST-segment elevation myocardial infarction (STEMI) patients. **Hypothesis:** The IRI is exacerbated in STEMI patients with variant the *ALDH2\*2* compared to wild *ALDH2\*1/\*1*. **Methods and Results:** The study subjects comprised consecutive 219 (167 men and 52 women) Japanese STEMI patients who underwent successful primary percutaneous coronary intervention (PCI) within 12 hours after onset. Of the study patients, 112 (51.1%) carried variant *ALDH2\*2* and the remaining 107 (48.9%) wild *ALDH2\*1/\*1*. There were no differences in clinical features between the *ALDH2\*2* and *ALDH2\*1/\*1* group except lower alcohol habit (14.7 vs 54.4%,  $P < .001$ ) in the *ALDH2\*2* group. However, the peak plasma levels of creatine phosphokinase (CK) and creatine phosphokinase isoenzyme muscle/brain (CK-MB) were significantly higher in the *ALDH2\*2* than *ALDH2\*1/\*1* group (2186 vs 1610 U/L,  $P = .001$  and 208 vs 147 U/L,  $P = .036$ , respectively). Further analysis revealed that peak CK and CK-MB were more significantly elevated (2455 vs 1595 U/L,  $P < .001$ , 222 vs 146 U/L,  $P = .004$ , *ALDH2\*2* and *ALDH2\*1/\*1* group, respectively) in males but not in females (1482 vs 1705 U/L,  $P = .949$ , 152 vs 171 U/L,  $P = .6$ , *ALDH2\*2* and *ALDH2\*1/\*1* group, respectively). Multivariable logistic regression analysis revealed that *ALDH2\*2*, and *ALDH2\*2* plus males were significant risk factor for severe IRI (OR = 2.13;  $P = .012$ ; OR = 3.05;  $P < .001$ , respectively). **Conclusions:** The peak CK and CK-MB were significantly elevated in the *ALDH2\*2* compared with *ALDH2\*1/\*1* STEMI patients preferentially in males. The deficient ALDH2 activity therefore exacerbates IRI in STEMI patients.

### Relationship Between Uric Acid, Renal Dysfunction, and Left Ventricular Remodeling in Hypertensive Women

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**Background:** Left ventricular (LV) hypertrophy is a strong predictor of cardiovascular mortality in women, and, in particular, concentric hypertrophy is associated with poor prognosis in hypertensive patients. The aim of this study was to elucidate the gender difference in the relationship between CKD, UA,

and LV geometry patterns. **Methods and Results:** A total of 682 (461 men, 221 women) consecutive patients with essential hypertension were evaluated using echocardiography. We investigated the relationship between estimated glomerular filtration rate and UA with LV hypertrophy according to the 4 different patterns of LV geometry: normal geometry, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy. Concentric hypertrophy was present in 151 (68%) hypertensive women and in 230 (50%) hypertensive men ( $P < .001$ ). Estimated glomerular filtration rate was lower in hypertensive women with concentric hypertrophy than in hypertensive women with normal geometry (60.7 vs 79.7 mL/min/1.73 m<sup>2</sup>;  $P < .05$ ). UA was higher in hypertensive women with concentric hypertrophy than in hypertensive women with normal geometry (5.6 vs 4.1 mg/dL;  $P < .05$ ). In patients with concentric hypertrophy, LV mass index inversely correlated with eGFR and positively correlated with UA in women ( $r = -0.20$ ,  $P = .016$ ;  $r = .44$ ,  $P < .0001$ , respectively) but not in men. **Conclusions:** Concentric hypertrophy was significantly more prevalent in hypertensive women than in hypertensive men. Furthermore, renal function and UA were associated with LV hypertrophy in hypertensive women with concentric hypertrophy.

### Sex Differences and Real World Registry in a Cryptogenic Ischemic Stroke via Patent Foramen Ovale

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It was shown as robust evidence in a multicentre, randomized, open-label trial that device closure of a patent foramen ovale (PFO) significantly reduces recurrent ischemic strokes compared to medical therapy alone. Therefore, it is expected that the specified PFO occluder will be soon reimbursed also in Japan following the United States. In addition, a recent meta-analysis of those randomised controlled trials revealed that device closure was more beneficial in men, implying the sex differences in a cryptogenic ischemic stroke via PFO. However, the Risk of Paradoxical Embolism (RoPE) score, which currently guides the decision of which patients benefit from PFO closure, includes only age, hypertension, diabetes, a history of stroke, smoking, and type of stroke, but not sex. On the other hand, we have shown in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 Study that 19.4% of the patients with stage C/D chronic heart failure complicated stroke at baseline. However, the systematic collaboration by stroke specialists and cardiologists has been absent in our hospital, in evaluating the etiology, demographics, and treatment options of stroke associated with heart disease. Recently, we

have established the Brain-Heart Team with the stroke specialists in our hospital. Now, we are planning to expand our Brain-Heart Team to the high volume centres of strokes in the whole Tohoku District, to establish multicenter, real world registry of a cryptogenic ischemic stroke. In this session, we would like to discuss the impact of the sex differences in a cryptogenic ischemic stroke and PFO closure by introducing our real world registry.

### Capillaroscopic Alterations in the Phenomenon of Raynaud in Men and Women

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Raynaud phenomenon (RP) is a pathological condition of vasospasm in response to cold or emotional stimulation, affecting the extremities, mainly the fingers. Clinically, it is characterized by 3 successive phases: the white (ischemic) phase, the cyanotic (deoxygenation) phase, and the red (reperfusion) phase. Raynaud phenomenon is often secondary to autoimmune diseases, exhibiting typical microvascular alterations. In the absence of diseases able to cause it, RP is called primitive (PRP). Primitive Raynaud phenomenon is present in 5% to 20% of women and 4% to 14% of men, and due to its clear prevalence in women it is traditionally considered a gender pathology. The nailfold videocapillaroscopy (NVC) is an in vivo noninvasive instrumental technique easily repeatable, which allows to study in real time the morphological and functional characteristics of microcirculation. The purpose of our study is to verify whether there are gender specific capillaroscopic alterations in patients having PRP. We evaluated 434 subjects affected by PRP, observed in the last year at the outpatient NVC service of our Allergology and Clinical Immunology division. Three hundred-thirty were females (mean age 45 years  $\pm$  6,1 DS) and 96 were males (48  $\pm$  4,3 years DS). Patients affected by autoimmune pathologies, as well as smokers or those with a history of exposure to ionizing radiation or chemicals capable of inducing a secondary RP, were excluded from the study. No significant gender differences were found in the NVC patterns observed: 148 (43.7%) females and 46 (47.91%) males had a normal NVC pattern (high skin transparency, absence of morphological abnormalities, uniformity of diameter and distribution of the capillaries, hairpin capillaries arranged in a parallel fashion to each other), whereas 190 (56.21%) females and 50 (52.08%) males exhibited an abnormal nonspecific NVC pattern (microvascular abnormalities without findings suggestive of scleroderma, and characterized by lack of morphological homogeneity of capillaries, presence of tortuous capillaries, ectasia of the efferent tract of the loops). The PRP, even though it is a pathology that affects the females more than men, doesn't exhibit gender-related differences in the characteristics and distribution of capillaroscopic patterns.

### Human Induced Pluripotent Stem Cells as Alternatives to Animal Models For Studying Sex Differences

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Sex and sex hormones affect all the cells in the body resulting in different susceptibility to cellular stressors and disease development. Researchers engaged in basic research and pre-clinical studies are increasingly challenged by regulatory bodies, major funding agencies, and highly ranked journals to also include sex as a biological variable into their study designs. At present, these requirements are mostly met—if at all—through animal experimentation. Besides concerns about how well the human system is represented by animals, there is also an ethical problem. This is addressed by regulations to promote the principles of refinement, reduction, and replacement (3Rs) of animal experimentations (eg, Directive 2010/63/EU). Great efforts are addressed worldwide to the development of alternative methods to animal testing. However, in vitro models for researching and testing of sex differences are not in the focus. Human induced pluripotent stem cells (hiPSC) generated from human somatic cells present a new trajectory to develop novel and ethically acceptable in vitro model systems for studying sex differences. The cells can be differentiated into any cell type of the body. Cell culture conditions during reprogramming, stem cell propagation and differentiation need to be adapted in order to establish valid models for researching sex as a biological variable in vitro using hiPSC. We have developed a differentiation protocol for renal proximal tubular like cells from hiPSC. Currently, we work on refining the model to allow studying sex differences. For this purpose, hiPSCs derived from males and females are treated with different combinations of sex hormones during the differentiation process. Human induced pluripotent stem cells-derived models are expected to provide improved preclinical data avoiding problems arising from species differences between animals and humans and allowing to account for the genetic variability among the human population and sex differences.

### “Effect of Gender on Hypoglycemia’s Risk and Worse Clinical Outcome Among Diabetic Patients Admitted to Internal Medicine Departments.”

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**Background:** The incidence of hypoglycemia is high in type 2 diabetes mellitus (T2DM) patients who use insulin or hypoglycemic agents. Documented hypoglycemia is associated with poor prognosis among patients admitted to internal medicine departments. Marked gender differences in glucose control have been observed in several studies, however, the influence of gender on the frequency and impact of hypoglycemia in hospitalized patients with diabetes is not completely known. Previous studies have suggested that females with T2D are less likely to reach glycemic targets and have a higher risk of hypoglycemia with insulin therapy compared to males, suggesting that gender may play a role. **Aims:** We will conduct a not profit multicentric retrospective protocol study of a pilot trial. To investigate the effect of gender on hypoglycemia's risk among patients with T2DM in antihyperglycemic therapy admitted to Internal Medicine Units and to evaluate the association of hypoglycemia with worse clinical outcome. **Methods:** We will collect the electronic medical records of 500 patients with T2DM from 12 Internal Medicine Departments across Italy between January 2019 and April 2019. Data extracted will include all glucose measurements, glycated haemoglobin A<sub>1c</sub> values, estimated glomerular filtration rate values, clinical and demographic data, Charlson comorbidity index, insulin regimen or hypoglycemic agents, and incidence of complications during admission will also be collected. Regression analysis will be used to assess the association between documented hypoglycemia and age, sex, length of hospital stay, in-hospital mortality. **Conclusions:** Women with T2DM have poorer glycemic control than men, probably because of differences in glucose homeostasis, treatment response, and hypoglycemia's risk. Development and implementation of more gender-sensitive clinical approach and sex-specific treatment guidelines may help to reduce development of complications, such as hypoglycemia, may improve quality of life and increase health and life expectancy in men and women with type 2 diabetes.

## Sex and Gender in Complex Systems

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With the accumulation of large amounts of data, a new predictive, personalized and data-driven approach to medicine has emerged. It has become clear that most chronic disorders emerge from concerted interactions of multiple genetic, metabolic, social, or lifestyle-related risk factors. In this talk, we

will demonstrate how the theory of Complex Systems offers a novel methodological toolkit to understand how these different factors and their interactions impact patient health in a sex- and gender-specific way. Heterogeneous health-related data sets can often be quantified by means of networks that record individual risk factors (from molecular to societal levels) and their interactions in different diseases. For instance, we will show how males and female build their social networks in different ways and how the structure of these networks determines their susceptibility to disorders such as obesity or depression. Using administrative data from an entire country over several years, we find that males and females show highly distinctive patterns in the way in which their health typically changes over the course of their life which allows the identification of "typical male or female"-associated longitudinal disease trajectories. Furthermore, we show how network approaches can be used to gain insight into sex-specific adverse drug events and the extent to which males and females differ in their health-care utilization. In conclusion, sex and gender shows highly complex interactions with other disease risk factors across multiple domains, ranging from the very small (molecular level) to the very big (institutional configuration of the healthcare system). Novel methodological approaches are needed for a more stringent consideration of gender differences in (chronic) diseases and to contribute to better targeted prevention, more patient-oriented and more efficient therapeutic approaches.

## Sex and Gender Differences in Antihyperglycemic Treatment

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Type 2 diabetes mellitus and associated complications are an increasing problem worldwide in both sexes and go along with reduced quality of life and life expectancy. Therefore, optimal therapy is essential and should consider biological factors including age and sex as well as psychosocial factors and gender issues. However up to now sex and gender have no impact in most clinical guidelines and decisions. Nevertheless side effects of drugs as well as choices and preferences of and adherence to therapies differ between men and women. Gender sensitive programs to promote healthy lifestyle should be accompanied by personalized pharmacological therapy considering complications, sexual function, individual expectations and fears, and social environment. Antihyperglycemic drugs differ in regard to their risk of cardiorenal complications, hypoglycemia, effects on weight and possibly associations to risk of fractures and certain cancers. Metformin is the first choice for both men and women and appears to be particularly effective in women with previous gestational diabetes and obese men and women. Overall women have higher risk of hypoglycemia on

insulin therapy. However, normal weight appears to relate to higher risk of hypoglycemia in both sexes on basal insulin therapies. Due to higher risk of stigmatization of obese women, weight loss is even more important for women, favouring SGLT2 inhibitors or GLP-1 analogues; thus GLP-1 analogues were more often prescribed to obese women than men. SGLT2 inhibitors reduce cardiovascular events and hospitalizations due to heart failure and progression of renal disease in both sexes. However they are associated with a higher risk of urogenital infections and ketoacidosis in women compared to men. Pioglitazone associates with increased risk of bone fractures, particularly in postmenopausal women. During pregnancy, insulin is still the first choice therapy. Overall women seem to have lower success of antihyperglycemic therapies despite having more from drug side effects. Most clinical studies still include more men than women and do not stratify data analysis by sex. Taking into account sex and gender in diabetes management could contribute to more personalized better care in the future.

### Sex Differences in the Cardiovascular Consequences of Type 2 Diabetes

Judith G. Regensteiner, PhD<sup>1</sup>

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By 2017 estimates, diabetes mellitus affects 425 million people—approximately 90% to 95% have type 2 diabetes and the number is rising. The cardiovascular (CV) consequences of type 2 diabetes are overall worse in women than men across the life span. These disparities include: (1) increased CV mortality, (2) increased CV morbidity, and (3) lower rates of CV risk factor control. These sex differences appear partly related to biological factors, though there are also disparities in provider level prescribing patterns and patient-level adherence patterns. This talk will take a life span approach to describing these sex differences in CV outcomes, starting with children exposed to gestational diabetes in utero, and including those diagnosed with type 2 diabetes during youth, in midlife, and in later life, respectively. The major goal of this talk is to highlight research gaps that must be addressed to better understand how to potentially redress these sex differences. I also will summarize clinical opportunities to improve these disparities.

### Stroke and Dementia (Invited Speech)

Mia von Euler, MD, PhD<sup>1</sup>, Zupanic E<sup>1</sup>, Garcia-Ptacek S Kåreholt I<sup>1</sup>, Religa D<sup>1</sup>, Kramberger MG<sup>1</sup>, Norrving B<sup>1</sup>, Winblad B<sup>1</sup>, Eriksdotter M<sup>1</sup>, and Von Euler M<sup>1</sup>

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Stroke and dementia are common causes of death and acquired functional disability for both men and women. For ischemic

stroke and intracerebral hemorrhages, the incidence is higher in men up to the age of 85 years when it becomes more common in women. For subarachnoidal bleeding the incidence is higher in women. Stroke can lead to cognitive impairment and dementia itself is associated with a 3 to 7 fold higher risk of stroke. Although the risk factors for stroke and dementia are similar in men and women, the impact may vary. Effect of acute reperfusion treatment and pharmacological prevention seems similar between men and women but access to treatment has shown varied results. In a registry-based longitudinal cohort study on differences between men and women with ischemic stroke with and without prestroke dementia, we compared reperfusion treatment and outcomes. Using data from the Swedish Dementia and Stroke Registries 2010 to 2014, we identified patients with dementia and acute ischemic stroke (765 women, 592 men) and compared them with matched nondementia subjects (3838 women, 2917 men) regarding reperfusion treatment and outcomes at 3 months (death, residency and modified Rankin Scale score [mRS]). Of those surviving hospitalization, more women than men with dementia had a poor outcome, had institutional care or home help ( $P < .001$ ). When adjusting for age, dementia, and stroke severity (determined by level of consciousness) odds ratio was higher for women for a poor outcome, mRS 3-6, at 3 months (odds ratio [OR]: 1.60, 95% confidence interval [CI]: 1.42-1.81), lower for death 1 year after stroke (OR: 0.876, 95% CI: 0.78-0.98), and higher for higher level of assisted living (OR: 1.30, 95% CI: 1.15-1.47). For death 1 year after stroke, there was no difference between men and women if dementia was not included in the analysis while worse living conditions and poor functional level remained in women.

### Carotid Surgery in Men and Women

Rebecka Hultgren<sup>1</sup>

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Strong evidence based on multicenter RCTs support the benefit of vascular interventions in selected patients with significant stenosis of their internal carotid artery in order to decrease the risk of a subsequent fatal neurological event. The indication of surgical treatment should be correlated to the degree of stenosis, which have rendered debate, but consensus is that intervention should not be performed in men or women below 50%. However, as for all surgical procedures other factors strongly contribute in the preoperative work-up evaluation, and influences eligibility, such as age, ongoing medication, morphology of arteries. The selection for patients actually subjected to be evaluated for a vascular intervention does influence the possibility to in-depth analyze relevant sex-and gender differences. The presentation will cover the most recent reported findings in the field in vascular treatment for carotid stenosis, endovascular and open, and also present contemporary outcome data.

## Arrhythmias in Women and Men

Karin Schenck-Gustafsson<sup>1</sup>

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Recent research has revealed sex-difference in the appearance of rhythm disturbances as well as differences in the pathophysiology, symptoms, and treatment. Atrial fibrillation especially in elderly women, increases the risk of stroke as well as death and cardiovascular outcomes more in women than in men. Women have also been undertreated both with invasive treatment like ablation as well as with drug treatment. Atrial fibrillation is the most common sustained arrhythmia in adults and carries a risk of significant morbidity and mortality, especially an increased risk of stroke. Many of these patients experience palpitations, however not all of them. Also other treatable arrhythmias like supraventricular tachycardias for example atrio-nodal reentry tachycardia might induce palpitations and are important to detect as well as malignant ventricular arrhythmias. Independent of etiology, heart palpitations can cause anxiety, worry, depression, reduced quality of life, and more so in women than in men. Atrial fibrillation is uncommon below the age of 50 years but the prevalence increases by age and in ages older than 85 years it could be as high as 25% to 30%. It is well-known that women have more symptoms than men of palpitations and also of anxiety disorders and poorer quality of life. Studies also indicate sex-difference in adverse drug reactions like antiarrhythmic drugs, for example, women being more sensitive to long QT prolonging drugs. The aim of the on-going Swedish study Red Heart is to evaluate if instant analysis and feed back of underlying heart rhythm during palpitations reduces symptoms, anxiety, depression, and increases the quality of life. We informed about the study in connection with our yearly women's heart campaign in 20 cities. Recruitment also took place via social websites. For the first time we used a new form of eAuthentication via BankID when getting the informed consent of the study from the participants. During the first weeks in May 2018, totally, 2387 women reported interest to participate. Of these, the first 1132 were invited and finally 913 were included. The women who completed the study were between 21 and 88 years. Coala Heart Monitor was used by the participants and thumb and chest electroencephalography were recorded twice a day and at symptoms during 60 days. The system uses a well-validated algorithm to analyze heart rhythm and is connected to the user's smartphone and provides immediate response to the user. Questionnaires addressing symptoms like anxiety, depression, HRQOL were analyzed before and after the study period. In the great majority of episodes causing symptomatic palpitation in women, the underlying arrhythmia was benign. However, in 5% previously undiagnosed atrial fibrillation or supraventricular tachycardia were found. These women were referred to a doctor. Among the

participating women, 75% had palpitations more than once a week, 66% had contacted a doctor because of the symptoms. Notably 40% of the women experienced that they were not taken seriously by the health-care system when they seek help. Much more information will come out from our study and in the follow-up we will also include men. In total over 280 000 registrations were monitored making this study probably the largest arrhythmia study in women in the world.

## Sexual Function, Gender Role, and Sexual Preference in Females with Classical Versus Nonclassical Congenital Adrenal Hyperplasia

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Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is an autosomal recessive disease caused by mutations in the *CYP21A2*-gene. The severity of the mutations is mirrored by a wide spectrum of different biochemical (hyperandrogenism, hypocortisolism) and phenotypic (virilization, hirsutism) symptoms. The present cross-sectional cohort analysis aimed to evaluate sexual function, gender identification, and partner preference in classic (C-CAH) versus nonclassic CAH (NC-CAH). Depending on their pheno- and genotype (determined by Sanger sequencing and MLPA), 35 female patients with CAH were divided into 2 groups: classic CAH (severe deficiency, salt-wasting or simple virilizing, n = 17) and NC-CAH (n = 18). Sexual function and sexual distress, gender role and sexual satisfaction were assessed using established questionnaires (FSFI, FSDS, BSRI) and visual analogue scales. Phenotype (as defined by signs of hyperandrogenism) was assessed clinically (Ferriman-Gallwey score) as well as with the ovulatory function index. Moreover, sexual function was separately analyzed in the context of clinical signs of androgenization in women with (n = 13) and without acne (n = 22). Women with NC-CAH had significantly lower orgasm scores, a trend toward lower sexual function with higher sexual distress and biochemical evidence of hyperandrogenism (higher DHEA-S, lower SHBG). Presence of acne in all patients was related to lower sexual function and higher sexual distress. These findings stress the importance of early diagnosis and therapy initiation particularly in patients with NC-CAH.

## Cardiometabolic Effects of Cross Sex Hormone Therapy in Transgender Patients

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**Background:** Sex hormones are believed to play an important role in development and progression of cardiovascular disease. However, the gender gap in onset and mortality is not yet completely understood. Transsexuals undergoing hormone therapy are a promising collective for analysing the effects of sex hormones on cardiometabolic disease. **Methods:** Aim of this study is to identify gender specific cardiovascular changes attributed to high-dose hormone therapy in male-to-female (MtF) and female-to-male (FtM) transgender patients by performing an oral glucose tolerance test and 3T magnet resonance spectroscopy for hepatic (HCL) and myocardial lipid content analysis. **Results:** Until now we included 15 MtF and 10 FtM patients. The mean age was comparable in both populations (MtF  $31.12 \pm 2.31$  vs  $29.72 \pm 1.91$  as well as body mass index [ $23.59 \pm 3.81$  vs  $21.62 \pm 2.53$  kg/m<sup>2</sup>). The mean hormone therapy duration was similar in both groups (MtF  $4.58 \pm 1.20$  vs FtM  $2.35 \pm 0.95$ ,  $P = 0.29$ ). HOMA index did not significantly differ between the groups (MtF  $1.78 \pm 0.92$  vs FtM  $1.96 \pm 1.22$ ). Hepatic lipid content was significantly higher in MtF than FtM ( $1.50\% \pm 0.41\%$  vs  $0.54\% \pm 0.33\%$ ,  $P = .022$ , respectively). We also found a significant correlation between ejection fraction and testosterone levels in FtM only (Spearman's Rho 0.80,  $P = .002$ ). **Conclusion:** These preliminary data could indicate a positive effect of testosterone therapy in FtM on heart function. Contradictory to current data, we found a higher HCL in MtF than FtM suggesting a not so protective estrogen effect when looking at the liver. Long-term studies are warranted to assess whether cross sex HT results in different outcomes regarding cardiovascular disease.

## The Contribution of the Italian National Institute of Health on Transgender Health

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Transgender people are a medically underserved population in both primary and specialist care settings. Moreover, despite the growing interest of the scientific community in transgender health, this subject remains understudied. Unavailability of realistic estimates of transgender prevalence, limited data on general health status and the long-term effects of gender affirming hormone treatment and surgical interventions are among the main problems to be solved in terms of transgender health research. Nowadays, in Italy, as across much of the world, we do not know exactly how many transgender people there are, their health status and the services they need. This hinders a suitable health planning by policy makers and an appropriate activity by the Italian National Institute of Health (NIH). Additionally, given the probable size of transgender population (at least 500 000 people) and the large range of health-care needs, it is crucial that health-care providers could be trained in transgender health care. It is urgently warranted to fill all these gaps to provide an appropriate evidence-based prevention and care for people. To this aim, the Center of Gender Specific Medicine at the Italian NIH is creating a close network of collaborations among public health institutes, policy makers, health-care providers, and transgender communities. Different projects including research, medical training with specific courses, and communication campaigns directed to citizens have been performed and launched. Two studies aimed at evaluating the size of transgender people and their health status, respectively, are undergoing. We consider of great relevance the part of our project dealing with communication/information of the citizens with the creation of the first institutional web site on legal and health information dedicated to the transgender population. These activities could represent a first step toward a more inclusive health policy aimed at improving the interplay between transgender people and the health-care system.

## Making Sense of Sex Differences in the Brain; a Whole-Body Approach

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This presentation will play with three interrelated ideas. First, there are sex differences in all organs in the body; the brain is no exception. Second, sex differences in the body forge sex differences in the brain. Third, sex differences in the brain serve 2 roles: to prevent as well as to cause sex differences in behavior and physiology. The consequences of these ideas for the role of the brain in health and disease will be discussed using sex differences in vasopressin function as an example.



## Sex Differences in The Molecular Regulation of Memory: Implications for the Development of Sex-Specific Treatments for Memory Dysfunction

Karyn Morrione Frick, PhD<sup>1</sup>

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Estrogens play a key role in the etiology and symptomatology of psychiatric illnesses (eg, depression, anxiety) and neurodegenerative diseases (eg, Alzheimer disease). Thus, understanding exactly how estrogens regulate cognitive and emotional processes is essential to developing the next generation of therapeutics to treat conditions such as these for which women are at greater risk. However, estrogens modulate cognitive and brain function not only in females but also in males, so a thorough understanding of how estrogens mediate cognition requires knowledge of the mechanisms through which it acts in both sexes. Although we have learned much in recent years about the molecular mechanisms through which estradiol mediates memory consolidation in female rodents, considerably less is known about estrogenic regulation of memory processes in males. This talk will first summarize my laboratory's work in female mice identifying molecular mechanisms in the dorsal hippocampus necessary for estradiol to enhance memory consolidation and promote hippocampal and neocortical dendritic spine density. Next, our recent work examining how estradiol regulates memory consolidation in male mice will be described, including data suggesting significant sex differences in the cell-signaling mechanisms underlying estradiol-induced memory enhancement. Finally, the implications of these findings for developing sex-specific treatments for memory dysfunction will be considered.

## Women's Brain Health and Aging

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Growing evidence implicates ovarian hormones in maintaining brain health in women as they age. Following menopause, 17 $\beta$ -estradiol (E2) and progesterone levels decline, and this loss has an impact on women's cognition, and brain structure. Such effects are exacerbated following oophorectomy prior to spontaneous menopause, which is associated with accelerated cognitive decline and a 2-fold higher risk of dementia. Reduced sleep quality and increased sleep-disordered breathing is also associated with oophorectomy, which can worsen the cognitive effects of early hormone deprivation. Estradiol-based hormone therapy maintains cognitive function and in some instances, sleep quality in menopausal women. However, few studies have investigated benefits in women with an oophorectomy.

In this presentation, we present our recent work on cognition, brain structure, and sleep in middle-aged women with a BSO. Forty-six *BRCA 1/2* mutation carriers with a BSO prior to the age of 51 and 25 age-matched premenopausal controls were recruited. Participants with a BSO were stratified based on whether they were currently taking estradiol therapy (BSO+E2; n = 22) or had no history of hormone therapy use (BSO; n = 24). Participants completed a neuropsychological test battery, underwent a high-resolution T2-weighted structural magnetic resonance imaging scan (3T Siemens Prisma), and an at-home polysomnography recording for sleep staging and sleep-disordered breathing analysis. Results revealed that BSO is associated with lower memory performance, reduced hippocampal volume and increased sleep fragmentation, but only among those not taking E2. These findings demonstrate adverse effects of early hormone loss on sleep and brain health, which is prevented by E2 use. The importance of these results to understanding the role of ovarian hormones in promoting sleep, memory, and brain health as women age will be discussed.

## Cardiac Symptoms and Menstruation: A Risky period? The Cycle Study I

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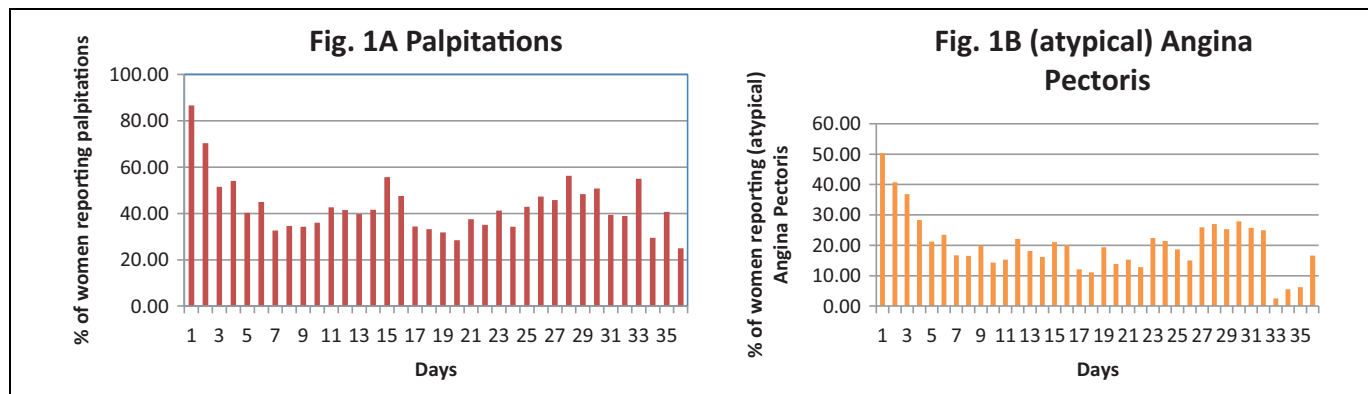
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**Background:** During the menstrual cycle endogenous female hormones fluctuate. However, the prevalence of menstrual cycle-related cardiac symptoms remains unclear. We hypothesize that premenopausal women show cyclic variation in cardiac symptoms with more symptoms during the (pre)menstrual phase when estrogen and progesterone levels are low, compared to other menstrual cycle phases. **Methods:** We performed a prospective cohort study in premenopausal women with self-reported cardiac complaints. Women with a regular menstrual cycle were asked to prospectively fill in an electronic diary for at least 10 weeks to record episodes of cardiac symptoms during 2 menstrual cycles. The prevalence of cardiac complaints was estimated as the mean of the reported cycles. **Results:** Until now, 172 (mean age 40.2  $\pm$  7.6 years) women participated in this ongoing study; 118 women reported on one menstrual cycle, 68 on 2 cycles. Most participants did not use any contraception (70%), the oral contraceptive pill (1 week hormone free interval per 3 weeks) was used by 8.5% and the



**Figure 1.** Percent of Women reporting palpitations or (atypical) Angina Pectoris.

remaining used other (nonhormonal) contraception. 38% of women were currently treated by a cardiologist or GP for their cardiac complaints, whereas 41% were treated in the past. The majority of women (58%) were using cardiovascular drugs. During the first day of menstruation 87% of the women reported palpitations, which reduced to 32% at the end of the menstruation (day 6). An increase to 56% was seen during ovulation (day 14) and after a drop in the midluteal phase (day 19) to 28%, the number of complaints increased again in the late luteal phase (day 27) to 56% (Figure 1A). A similar time trend was seen with respect to angina pectoris (Figure 1B). **Conclusion:** Women most often report cardiac symptoms in the early follicular phase of the menstrual cycle when both estradiol and progesterone levels are lowest compared to the other phases.

### Gender Differences in The Risk Factors Associated With Atherosclerosis By Carotid Intima-Media Thickness, Plaque Score And Pulse Wave Velocity

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**Background:** Carotid intima-media thickness (IMT), carotid plaque score (PS), and brachial-ankle pulse wave velocity (baPWV) are useful atherosclerotic parameters, and these are evaluating the different aspect of atherosclerosis. The gender-specific impact on the risk factors for atherosclerosis by these parameters is unclear. **Hypothesis:** We hypothesized that there are gender differences in the risk factors for atherosclerosis evaluated by IMT, PS, or baPWV. **Methods:** We recruited 3888 participants (women 743 and men 3145 participants) who

underwent health checkups. Intima-media thickness and PS were evaluated by carotid ultrasonography, and baPWV was measured by an automatic device. We analyzed the association between IMT, PS, or baPWV and atherosclerotic risk factors such as age, obesity, smoking history (Smoking), hypertension (HT), dyslipidemia (DL) and impaired fasting glucose (IFG). Both women and men were divided into two groups using a median value of IMT, PS, or baPWV. **Results:** We defined high IMT, PS, or baPWV as >0.75 mm, >2.3 mm or >1530 cm/s, respectively, in women. Age and HT were common parameters in women which were significantly associated with IMT, PS, or baPWV in multivariate logistic regression analysis. Obesity, DL or IFG was an independent additional risk factor of IMT, PS, or baPWV, respectively. On the other hand, in men, we defined high IMT, PS or baPWV as >0.75 mm, >2.7 mm or >1484 cm/s, respectively. In multivariate logistic regression analysis, age, HT, DL, and IFG were significantly associated with IMT, PS or baPWV. Smoking is significantly associated with high IMT and PS, whereas obesity was correlated only with IMT. **Conclusion:** It is suggested that the risk factors associated with IMT, PS or baPWV differed by gender. In women, only HT is associated with all atherosclerotic parameters, and the management of blood pressure may lead to the prevention and progression of atherosclerosis.

### Sex Differences in Patients with Non-ST-Elevation Myocardial Infarction in Japan: A Report from the Miyagi AMI Registry

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**Background:** Acute myocardial infarction (AMI) is classified into ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) with different initial stratification of diagnosis and treatment. In the present study, we examined the sex difference in emergency care and outcomes of NSTEMI patients compared to those of STEMI.

**Methods and Results:** The Miyagi AMI Registry Study is a prospective and observational study where almost all AMI patients in the Miyagi prefecture (2.35 million populations) of Japan have been prospectively registered for 40 years since 1979. In the present study, we analyzed a total of 7145 AMI patients (STEMI/NSTEMI, 5511/1634) enrolled in the registry from 2011 to 2017. As compared to STEMI patients, NSTEMI patients were characterized by older age (NSTEMI  $70 \pm 13$  years vs STEMI  $68 \pm 13$  years,  $P < .001$ ), higher percentage of female (NSTEMI 25% vs STEMI 22%,  $P < .05$ ), and lower performance rate of percutaneous coronary intervention (PCI; NSTEMI 78% vs STEMI 90%,  $P < .001$ ). When dividing by age, NSTEMI patients had a higher percentage of women than STEMI patients in the younger age ( $\leq 64$  years), whereas no difference was noted between the two types of MI in the elderly patients ( $> 65$  years). In the NSTEMI patients, female patients were older, had a lower performance rate of PCI, and had a higher in-hospital mortality rate as compared to male patients. Especially in the very young NSTEMI patients aged  $\leq 49$  years, performance rate of PCI was extremely lower in female compared to male (female 52% vs male 80.5%,  $P < .05$ ) and the percentage of AMI with nonobstructive coronary arteries was also significantly higher (female 20.8% vs male 4.5%,  $P < .05$ ). **Conclusions:** These results indicate that NSTEMI develops more frequently in relatively young women and that its pathophysiology may be different between the sexes.

### Pulmonary Embolism and Gender: An Observational Study

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**Introduction:** Pulmonary embolism (PE) is a major cause of mortality, morbidity, and hospitalization in Europe, but few studies have highlighted sex differences in PE, in particular with regard to hospitalization, outcomes, treatment, complication and mortality. **Objective:** The aim of this study is to analyze the gender differences in-patient hospitalized with a principal diagnosis of PE. **Methods:** This is a retrospective population-based cohort study. Data for all patients discharged with a principal diagnosis of Pulmonary Embolism (ICD-9 415.1) by Apulian hospitals between 2010 and 2016 were retrieved from the National Hospital Discharge Register Database. **Result:** A total of 4795 patients were discharged with a principal diagnosis of PE during the inclusion period, the majority of which were females (F; 2762; 57.6%). Mean age was significantly higher in F versus male (M; 73.0 vs 67.9,  $P <$

.001). Females showed an higher prevalence of hypertensive heart disease (41.1% vs 32.9%,  $P < .001$ ), arrhythmia (16.3% vs 13.9%,  $P = .023$ ), diabetes mellitus (14.8% vs 11.7%,  $P = .002$ ) and obesity (6.6% vs 3.5%,  $P < .001$ ) and a lower prevalence of chronic obstructive pulmonary disease (10.0% vs 18.0,  $P < .001$ ), lung failure (11.1% vs 13.7%,  $P = .006$ ) and cancer (15.3% vs 22.9%,  $P < .001$ ) compared to M. The overall incidence rate (F: 17.4 vs M: 13.8; respectively; AR = +3.6;  $P < .001$ ) and the overall mortality rate (F:1.3 vs M:0.9; respectively; AR = +0.3;  $P < .001$ ) were higher in female compared to male. The overall case fatality rate was not different between gender (F: 6.4 vs M:6.4; AR = 0.0;  $P = 0.92$ ). **Conclusion:** Findings from our study showed significant sex disparities for age of hospitalization, comorbidities distribution, incidence and mortality, but no differences in the fatality of the disease. Further studies are needed to identify the determinants and consequences of the gender differences in PE.

### European Physicians' Awareness of the Difference Between Sex and Gender: the Imagine Survey

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Sex and gender shape health status through dynamic interaction, therefore the integration of sex and gender in research and clinical approach is mandatory and it drives toward a personalized medicine and equality in health care. On this basis, the European Federation of Internal Medicine built up the *Internal Medicine and Assessment of Gender differences in Europe* (IMAGINE) working group. The first phase of the IMAGINE framework was conceived to assess the awareness of the Internal Medicine community on sex and gender dimension in approaching clinical and research questions. Therefore, among December 2017 and March 2018, an online short survey was run among European internists clinicians. Briefly, the first 3 questions aim to assess the knowledge on terminology (sex vs gender) and the awareness of factors specifically related or not to sex and gender dimensions. The fourth question explores the

perceived knowledge on sex and gender differences in major diseases within the field of internal medicine. The fifth and sixth questions point out if physicians checked clinical guidelines for the presence of recommendations specifically tailored according to sex and whether they are aware of the low rate of women's enrolment in clinical trials. Finally, the seventh question is targeted to the identification the high-priority topics for internal medicine community in terms of knowledge in a sex- and gender-perspective. Preliminary results of IMAGINE survey (>1000 participants) will be presented.

### Gender Score Construction Based on Retrospective Data Analysis in the Berlin Aging Study II (BASE-II)

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Sex and gender are distinct constructs that require complex measurement. As intercultural differences may be an important factor in capturing the construct “gender,” we aimed to reconstruct a gender score (GS) comparable to the index published by L Pilote (APS 2015) in a retrospective analysis of the Berlin Aging Study BASE-II in 2009-2014 for 1869 participants aged above 60 years. From the psychosocial and gender-related (identity, roles, relations, institutionalized gender) variables we selected 13 with focused on data available in more than 65% of cases. Our approach was divided in 3 steps: GS development, GS calculation, and GS application. For step 1 all 1869 cases were used and 9 out of 13 selected variables were identified by PCA and LR that contributed to a GS that separated women and men. A correlation analysis of 13 selected variables was conducted and in any significantly correlated pair of variables, one of the variables was removed. However, we retained all the 13 variables. These 13 variables were loaded onto 6 components in PCA analysis. Any variable, loading equally high on 2 components was removed at this step. The 13 identified variables from the PCA were used to perform the

logistic regression analysis. Nonsignificant variables were removed one by one in a descending order of their *P* value (.05). The 9 most significant variables for the sex as an outcome variable were extracted. The coefficients of the final logistic regression were used to calculate the GS (0-100). The procedure enabled us to construct a gender score in a retrospective manner from available study variables. Gender score distribution was significantly different between women and men. In future analyses, we will examine the validity of the score by linking differences in gender with psychosocial, medical, and cognitive data and by comparison with a prospectively assessed gender score.

### How to Measure Gender? Developing a Context-Specific Gender Index to Improve Health Research in Switzerland

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**Introduction:** Differences in health outcomes by sex of patients and health practitioners have been repeatedly shown. Research has further brought attention on the role of social gendered position in explaining part of these differences. Nonetheless, health research mostly uses the binary sex variable when measuring the impact of gender on health issues. This approach is scientifically problematic at different levels. First social gender is not a mirror of biological sex, and the sex variable does not include the different dimensions of gender (identity, social role, relation). Secondly, gender is not a direct causal factor of health outcomes, and intermediate factors—economic inequalities for example—influence health, which are overseen by using biological sex. Thirdly, research often responds to the gender-analysis requirements by stratifying results by sex and interpreting observed results, and such *a posteriori* interpretation is subject to gender bias. In an attempt to address these issues, several scholars have worked on the development of a gender index and stressed on the importance of strengthening theoretical frameworks of health research in order to anticipate the effects of sex and/or gender in a priori hypotheses. **Project description:** Our project aims to develop a gender index for the Swiss context, and to test its quality (validity, reliability, pertinence and acceptability) in different research projects, such as population based cohorts. **Methodology:** First a literature review on Swiss context will support choosing gender discriminating items. Their number and pertinence will be reduced by primary component analysis. Pertinence will be confirmed by correlation to sex. The resulting gender index will then be used to distribute patients in (non-binary) categories according to masculine and feminine characteristics. The approach is multidisciplinary including social sciences, epidemiology, and clinical research experts. **Expected**

**results:** To develop, test and validate a context-specific gender index, to be used in health research and beyond.

## The Going-FWD (Gender Outcomes International Group: to Further Well-being Development) Project"

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**Background:** GOING-FWD, is a personalized medicine project recently funded by the Canadian Institutes of Health and Research, in addition to GENDER-NET *plus*, which is a part of the European EU H2020 initiative. Psycho-cultural-social factors, which are associated with the gender of individuals, are seldom assessed as determinants of health outcomes, despite their powerful contribution to overall well-being. Gender is a complex construct which is different from the “biological sex.” Gender-related factors including gender identity, gender role, gender relations and institutionalized gender are assumed to differ between sexes. **Objective:** To develop a standard methodology that can be applied in retrospective cohort studies for the integration of gender-related factors in assessing their impact for cost-sensitive outcomes. **Methods:** For the GOING-FWD project, we identified 32 accessible cohorts/databases that include noncommunicable chronic diseases (NCDs; ie, cardiovascular disease, chronic kidney disease, diabetes/metabolic disorders, and neurological disease) among a 5-country transatlantic network including Austria, Canada, Cyprus, Spain, and Sweden. A multistep process was applied. **Step 1 (Identification of Gender-related Variables):** each partner provided the data dictionary of the database/cohort they included in the GOING-FWD application. Based on the gender framework of the Women Health Research Network (ie, gender identity, gender role, gender relations and institutionalized gender), and available literature for certain disease, an optimal “wish list” of gender-related variables/factors was created. **Step 2 (Definition of Outcomes):** each of the cohort data dictionaries were screened for outcomes of interest outlined in the GOING FWD proposal, including clinical/survival and patient reported outcomes. **Step 3 (Building of Feasible Final List):** A cross-validation between gender-related variables and outcomes variables available per database was performed. In case of disagreement or discordant definitions of variables, a more inclusive approach was pursued for both gender-related variables and outcomes. Each variable was discussed at the inaugural meeting (April 2019) of the GOING-FWD investigators and consensus was reached on a final list of “gender-related” and “outcome variables.” Each country partner used the lists to apply to their respective research ethics boards. **Step 4 (Definition of Data Structure):** Depending on the type of database, each partner then provided the data management structure and the analysis plan based on the following options: (1) data are not transferable even if anonymized—study-specific data analyses will be done locally and followed by a meta-analysis

combining the study-level estimate (2) analyses will be done centrally, but the individual-level participant data will remain on local servers. (3) Data transferable: data will be pooled and analyzed at a central location. **Step 5 (Retrospective Data Harmonization):** Finally, a list of harmonized variables will be created using the Maelstrom Research guidelines for rigorous retrospective data harmonization and merging when possible.

In summary: Personalized medicine approach is increasingly appreciated in clinical research, where the need for analysis of already collected data requires a proper definition of variables and measures included. Therefore, when including gender, the existing lack of a standardized gender measure poses challenges which might be mitigated via application of a systematic multistep approach currently suggested and currently tested by our multidisciplinary team. Understanding of how sex and gender-related factors impact NCDs will help to improve clinical- and patient-related outcomes with potential to tailor future interventions with a sex- and gender-specific approach.

## Described Differences Between Men and Women Regarding Antiretroviral Drugs for Treatment of HIV

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In the data base Janusmed Sex and Gender ([janusinfo.se/genus/in-english](http://janusinfo.se/genus/in-english)) evidence-based medical knowledge on sex and gender aspects on drug treatment has been gathered into a searchable tool. In 25% of the included medical drugs included in the data base, information on sex and/or gender differences are lacking. Antiretroviral drugs for treatment of HIV is one of the therapeutic areas covered. These drugs are often used over a long period of time and in different phases of the reproductive life of both men and women. We hypothesized that sex/gender differences were studied and reported more compared to other drug classes. The following search string was used in PubMed: (“Sex Factors”[Mesh] OR “Sex Characteristics”[Mesh] OR sex[Title] OR gender[Title] OR “sex difference\*” OR “gender difference\*” OR “based on sex” OR “based on gender”) AND «antiretroviral substance» In all, 18 drugs were included. No information on sex or gender differences were found for one (5.5%) of the substances (cobicistat). For 13/18 (72%) of the included drugs the identified literature indicated no clinically

relevant sex differences while in 4 (22.5%) sex differences were identified. The most important being nevirapine where the increased risk of hepatotoxicity and skin reactions need to be considered particularly in women/girl as the risk is higher in female compared to male patients. For several of the nucleoside analogues the risk of adverse reactions such as lactic acidosis and severe hepatomegaly with steatosis are more common in women. More data on sex differences are published regarding antiretroviral drugs for treatment of HIV. The difference mainly concerns an increased risk of some specific adverse reactions more common in women.

## Utilization of Antiepileptic Drugs in Men and Women with Stroke

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Stroke is a common cause of epileptic seizures in adults. However, treatment of patients with poststroke epilepsy is challenging since high-level evidence-based guidelines are lacking. Whether or not antiepileptic drugs (AEDs) should be used is therefore controversial. The aim of the present study was to investigate which AEDs are used in men and women with stroke in a nationwide population. All adults (>18 years) with a first dispensation of an AED (ATC-code N03A) in 2007 to 2014 were identified in the Swedish Prescribed Drug Register and cross-sectional data on history of a diagnosis of ischemic or hemorrhagic stroke in the five years preceding the first AED dispensation were collected from the National Patient Register. Patients with an AED dispensation preceding their stroke diagnosis were excluded. We calculated proportions of patients initiated on each AED, stratified by patient's sex. A total of 11 107 first dispensations of AEDs in 10 645 patients (52% women) were included. First AED after ischemic stroke was gabapentin in both men and women (32% respectively). First AED after hemorrhagic stroke was gabapentin in women (25%), and carbamazepine in men (31%). After excluding AEDs frequently used for other indications (gabapentin, pregabalin), carbamazepine was most common, followed by levetiracetam, in both men and women and in both stroke subtypes. During the study period, the proportion of patients initiated on gabapentin and levetiracetam increased while the proportion initiated on carbamazepine and pregabalin decreased. The use of gabapentin is in agreement with guidelines for treatment of focal seizures in the elderly. However, the high use of gabapentin, as well as pregabalin, could also reflect high prevalence of neuropathic pain, particularly in women. Carbamazepine has traditionally been recommended for use in adults with focal seizures, but its tolerability has been discussed.

## The Diagnosis of Osteoporosis in Statin-Treated Women and Men is Dose-Dependent

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**Objective:** Postmenopausal women are at exaggerated risk of developing osteoporosis. Statins lower cholesterol levels by inhibiting the HMG-CoA-reductase inhibition, which is the main substrate for the synthesis of sex hormones. Consequently, this study was set out to investigate the sex-specific relationship of different kinds and dosages of statins with osteoporosis. **Methods:** Medical claims data of all Austrians from 2006 to 2007 was used to identify all patients treated with statins to compute their daily defined dose averages of six different types of statins. We applied multiple logistic regression to analyse the dose-dependent risks of being diagnosed with osteoporosis for each statin individually. **Results:** We identified 353 502 statin-treated patients (175 506 males, 177 996 females) out of which 11 701 patients (1765 males, 9936 females) were diagnosed with osteoporosis. The control group (no statin exposure) consisted of 7 543 947 patients (3 527 066 males, 4 016 881 females), including 68 699 patients (10 410 males, 58 289 females) diagnosed with osteoporosis. Within the whole study population, our results show that women are at a higher risk of being diagnosed with osteoporosis when compared to men (odds ratio [OR]: 5.08, 95% confidence interval [CI]:4.98-5.18,  $P < .01$ ). In a sex-specific analysis, only a low dose simvastatin ( $\leq 10$  mg) treatment was related to an underrepresentation of diagnosed osteoporosis in males and a low dose lovastatin ( $\leq 10$  mg), fluvastatin ( $> 10$ -20 mg), pravastatin ( $\leq 10$  mg), and simvastatin ( $\leq 10$  mg) treatment in females. In both females and males, the increase in the dosage of simvastatin ( $> 40$  mg) and atorvastatin ( $> 10$  mg) was related to a higher occurrence of a diagnosed osteoporosis. However, females with a rosuvastatin dosage of  $> 20$  to 40 mg had an exaggerated risk of being diagnosed with osteoporosis (OR: 3.01, CI: 1.73-5.21,  $P < .01$ ) when compared to controls. **Conclusion:** Our results show that the diagnosis of osteoporosis in statin-treated patients is dose-dependent in both, women and men. Thus, osteoporosis is underrepresented in low-dose and overrepresented in high-dose statin treatment.

## Differences in Discontinuation of Statin Treatment in Women and Men With Advanced Cancer Disease

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Statins are often discontinued in patients with advanced cancer since the net effect of treatment is considered negative. However, guidelines concerning discontinuation of statin treatment are lacking. The aim of this study was to investigate any differences in time of discontinuation of statin treatment between men and women with advanced cancer disease. Medical records from 195 deceased patients with palliative cancer from a previous study cohort were reviewed. Patients treated with statins 2 years before death were identified as “statin users.” The time of discontinuation of statin therapy was identified and correlated to time of death. Only patients with incurable cancer disease at time of statin discontinuation were included in the analysis. Fifty-four patients were identified as statin users, 29 women and 25 men. The average time span between discontinuation of statin treatment and time of death was significantly longer in women than in men, 10 months compared to 4 months ( $P < .01$ ), with a range of 1 to 24 months among women and 1 to 12 months for men. All patients died due to cancer disease. More men than women had a history of stroke or cardiac infarction ( $P = .02$ ). There were no differences in age, socioeconomic factors, or survival time from study inclusion between men and women. There was no difference in self-assessed quality of life (QoL) between statin users who had discontinued statin treatment and those who are still on treatment. Men generally assessed their QoL lower than women in this study ( $P = 0.03$ ). Statin treatment was discontinued earlier in women than in men with advanced cancer disease, and discontinuation was not associated with any negative effects. However, the results need to be confirmed in larger studies before any firm conclusions can be drawn. Future studies will elucidate if early statin discontinuation is safe in both men and women with advanced cancer disease.

## Gender Violence: A Study of Awareness Implementation at the University Hospital of Ferrara, Italy

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Gender violence represents international public health burden. However, there is limited knowledge of epidemiological data in Italy. Thus, we decided to perform a study with the following aims: (1) collecting epidemiological data aimed at assessing implementation of the guideline protocol “Care and treatment for women victims of gender violence” developed by the University Hospital of Ferrara (year 2013) according to the Istanbul Convention on Violence against Women, (2) developing an integrated approach between health-care professionals and police officers in case of gender violence. Data were extracted from the reports of women referring to the emergency room (ER) for gender violence, University Hospital of Ferrara, Italy, years 2008 to 2016. The final total sample included 1955 women, average: 217 cases/year. Women were predominantly Italian, aged between 26 and 60 years. In details, 94% of cases involved assault and battery as gender violence; 3.1% involved sexual assault, 2.9% had no precise data, since women omitted any description of the violence. In 2.6% of cases, women victims of gender violence were pregnant. The abuser was more often the victim’s partner, followed by former-partner/relative, and identity remained unknown in 1.7% of cases. Repeated violence occurred in 318 (16.3%) cases. The introduction of the above quoted Guideline Protocol led to improvements in the regional network of services for women victims of gender violence. Furthermore, the training for health professionals improved awareness and quality of delivered care. The ER clinical notes were more accurate in reporting details about type and frequency of violence episodes, allowing considerable improvement in the clinical practice. Finally, in cases of gender violence, the number of yellow tags, according to the triage codifying system, increased, and information exchange between hospital health-care professionals and police officers significantly improved.

## Gender Related Violence: An Observational Study

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**Introduction:** The Istanbul Convention (2011) is the first binding instrument on preventing and combating violence against women and domestic violence. **Objective:** It is to put in place the actions in favor of women victims of male violence through

a multifactorial approach and followed actually. **Materials and Methods:** We enrolled 28 women with an average age of  $52 \pm 4$  years, who arrived at the Sessa Aurunca ASL Caserta, Italy, in the period 2017 to 2018 for gender-related violence. **Results:** The study population consisted of 25 women of Italian origin and 3 of non-EU origin. Of these, 70% were married, 10% separated, 10% unmarried, and 10% widowed. Over 50% of cases were victims of family violence. In over 50% of cases, the perpetrator of violence was a husband or a former husband. In particular, in 20% of cases, it was psychological violence, in 30% of cases of stalking, in 25% of cases of relational conflicts, in 25% of cases legal problems. The interventions carried out by the multidisciplinary team contributed to send 4% of cases in a hospitalization, 4% of cases in shelters, and 92% of cases to support victims of violence with specialist advice from internists, gynecologists, lawyer, and psychologists. Among these 65% were integrated into the world of work. All were supported psychologically and legally. The perpetrators of the violence in 95% of the cases were removed from the home and in 5% of the cases were arrested. **Conclusion:** It is therefore essential to prevent the phenomenon of violence against women using as primary tools information and awareness of the community, strengthening the awareness and culture of men and young people.

### Connecting Midwives and Violence Prevention Institutions—One Step in Fighting Violence Against Women

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Violence against women (VAW) is an ongoing concern in health care. It encompasses domestic violence, but also other types of violence only or disproportionately often affecting women. Constant improvements are made to provide best possible support for women affected by VAW. Reducing barriers in accessing violence prevention institutions and knowledge about referral possibilities are important aspects when caring for women affected by VAW. Three qualitative studies with 15 midwives, 21 midwifery students, and 11 representatives of violence prevention institutions, respectively, were conducted by using either interviews or focus groups. These studies were conducted in one part of Austria. Findings showed that there is still a disconnection between these professionals in particular regarding pregnant women. It was also found that midwives who had received training in VAW and younger midwives and midwifery

students were more open to including VAW. Continuous care was an important concern in interviews. This is also reflected in the midwives' role as guided guides. Violence prevention institutions reported that only very few pregnant women contacted them. By combing the findings of all 3 studies, a disconnection between all actors in the field of VAW appeared. Therefore, the so-called meet and greets were developed and will be implemented in autumn/winter 2019. Thereby, midwives, professionals (psychologist and psychotherapists), and representatives of violence prevention institutions will constitute a support network for each other in fighting VAW. Setting up small networks in several areas in Tyrol, Austria, is expected to reduce barriers and increase access to support.

### Gender Differences in Dentists' Working Practices and Job Satisfaction in Germany

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There has been a steady increase in the proportion of women among dentists over the last 30 years. Female dentists have been shown to work fewer hours per week and take longer career breaks, raising concerns about maintaining community-based dental care in the future. This pilot study aimed to compare the working practices, family life, and job satisfaction of male and female dentists. The study was a web-based 50-item survey on sociodemographic data, working situation, work-life balance, family life, and income. Of this, 1500 dentists were contacted by mail using the database of the local state chamber of dentists. One hundred eighty-nine questionnaires (93 M, 96 F;  $44.5 \pm 12.0$  years) were eligible for analysis which included  $\chi^2$  and Mann-Whitney *U* test, Spearman-correlation, and linear-regression analysis. Of this, 71.0% of the men and 37.9% of the women owned their own practice, 4.3% of the men and 46.3% of the women worked as employees. The mean number of working hours per week was 51.1 for males and 42.1 for females; 26.7% of the men and 49.4% of the women were childless. The mean number of children was 1.2; males had more children than females; 66% of the women's partners worked full time, but only 24% of the men's; 30% of the women (men: 7.5%) reported that their income had decreased after a career break for child rearing. Women's average income before taxes was significantly lower than men's. Mean job satisfaction for males was 12.6 and 11.9 for females ( $P < .05$ ). Job satisfaction of males was determined by "burden" and "income," whereas "number of persons living in the household" determined job satisfaction of females. Male and female dentists differ in their working and family situations; this affects their job satisfaction. Such differences should be addressed in order to improve and maintain community-based dental care.



## Masculinity Is Associated With Male Medical Students' Discomfort With Regard to Asking Patients About Sexual Health Issues

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Factors contributing to physicians' or medical students' discomfort with addressing patients' sexual health have rarely been addressed. The current study analyzed whether masculine gender role conflict (GRC), next to the often cited factor of knowledge, was associated with male students' comfort with regard to asking future patients about sexual health issues. A cross-sectional questionnaire study was conducted at an Austrian medical university with 164 male medical students (mean age = 24.4 years, SD = 2.4). Students' self-perceived knowledge of sexual health, how prepared they felt about this topic and their comfort with regard to asking future patients about sexual health issues were assessed. The Gender Role Conflict Scale—Short Form was used to assess GRC. Male students reported being more comfortable about asking male patient groups than female patient groups ( $P_s < .040$ ). Male students who indicated difficulty with expressing affection towards men were more likely to report being uncomfortable about asking patients overall, male patient groups, and elderly female patients (ORs > 1.6,  $P_s < .020$ ). Furthermore, male students who felt distress when showing emotions were more likely to report being uncomfortable about asking adult female patients (OR = 1.6,  $P = .012$ ). Knowledge was positively associated with comfort about asking patients overall and female patient groups (ORs > 2.3,  $P_s < .037$ ). The current study shows that it is not enough to convey facts and skills in order to increase male medical students' comfort in dealing with patients' sexual health issues. Male students should be made aware of gender role norms that influence such conversations, and the discussion of strategies for overcoming the barriers set by these norms should be part of sexuality education.

## Mistreatment and Incivility at the Medical University of Innsbruck—Focusing on Muslim Students

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The study focuses on mistreatment and incivility in medical students at the Medical University of Innsbruck (MUI). Mistreatment and incivility includes subtle sexist and racist remarks and lack of regard and was found to affect more often marginalized and minority groups (eg, migrants, women,

sexual minorities, etc). In Austria, Europe, 8% of the population is estimated to be Muslim. The objectives of this study were to investigate whether women and minority groups experience more incivility and might compensate this experience with more persistence and ambition regarding their career compared to men and majority students. In a pilot study, Muslim medical students ( $n = 35$ ) filled in a questionnaire on resilience, incivility, and career orientation in the workplace. A non-Muslim control group of 42 medical students was recruited to compare findings on resilience, incivility, and career orientation. Findings show that Muslim students experience significantly more often incivility than the control group, but no gender differences were found regarding incivility. Muslim students also reported a significantly greater orientation toward careers, which was not connected to incivility. Contrary to our expectations, women at the MUI do not report incivility more often than do men, but Muslim students report more often incivility than non-Muslim students. This study elucidates the need to detect mechanisms of which aspects are intersecting and experienced as uncivil and mistreating and how this influences the career orientation. Long-term studies to see the impact of incivility and careers in minority and majority groups would be interesting and important.

## Sex and Gender Specific Aspects in the Development of Post Stroke Depression and ITS Effects on Neuro-Rehabilitation Success

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Worldwide stroke is one of the most common causes of death. Survivors are often dependent on assistance in their daily life activities. Beside the personal fates, the resulting economic burden to health-care systems is high. Effective rehabilitation programs increase the quality of life and reduce the economic burden by lowering the costs for continuing care. Considering the individual needs of every patient is a basic requirement for a successful rehabilitation process. The examination of sex- and gender-specific differences in rehabilitation shall contribute to the further improvement in the rehabilitation processes. This retrospective study included 1593 stroke patients who underwent neurorehabilitation from 2010 to 2015. The change in the Barthel Index during rehabilitation was chosen as marker for the rehabilitation effect. A linear regression model was used to examine the influence of sex and multiple confounders on the rehabilitation effect as well as on the occurrence of depression and pain. The age was comparable between sexes (male:  $68.2 \pm 11.9$  vs female:  $69.3 \pm 13.6$  years). At admission, women had lower Barthel Index ( $m = 84.7 \pm 23.8$ ;  $f = 79.9 \pm 25.9$ ;  $P < .001$ ). Parameters

affecting the change of Barthel index significantly were age, time since stroke and Barthel Index on admission. Pain level on admission, sex, and depression was not associated with the rehabilitation effect. However, female sex, high pain levels, and low Barthel Index on admission were significantly associated with depression. Women suffered more frequently (male = 226/34.6%; female = 205/44.3%;  $P < .001$ ) from pain and additionally were indicating higher pain levels (male =  $1.6 \pm 2.4$ ; female =  $2.0 \pm 2.6$ ;  $P = .002$ ), which was associated with depression. Men and women have beneficial effects of neurorehabilitation, but factors associated with female sex (low Barthel Index on admission, pain) impact the rehabilitation effect in a negative way. Women are at higher risk for depression, as well as indicate pain more frequently and in higher intensity.

### Malnutrition Influence and Outcome in Cardiovascular Rehabilitation: Pilot Study

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Cardiovascular diseases are the leading cause of death worldwide. Modern medicine increases the number of elderly and old patients in stationary rehabilitation. Malnutrition, weight loss, sarcopenia, and low protein levels are associated frequent falls, which, in combination with high age, count as independent risk factor for cardiovascular diseases. The aim of this pilot study was to evaluate the efficiency of cardiovascular rehabilitation treatments in elderly and old patients and the influence of a purposeful screening and treatment for malnutrition on the outcome. All patients underwent AKE-screening, blood sampling, BIA, SPPB, and the 6MWT at start and at the end. To calculate the total energy demand of our patients, we used our gender-specific energy calculator. In stationary rehabilitation on ward a total of 31 people (19 female, 12 male) took part in the study. Thirteen patients had a risk of malnutrition, 18 already were malnourished. Patients with a risk of malnutrition were randomized 2 groups. The test group and all malnourished patients got daily a nutritional supplement with high protein levels. All participants of both study groups showed improvements in their physical ability like the 6MWT (A:  $233.11 \text{ m} \pm 81 \text{ m}$  to  $294.6 \text{ m} \pm 76.7 \text{ m}$ ;  $P = .002$ ) and the SPPB (A:  $6.25 \pm 2.26$  to  $10.9 \pm 1.66$ ;  $P = .002$ ). Results of 6MWT ( $211.7 \text{ m} \pm 56.9 \text{ m}$  to  $280 \text{ m} \pm 54.7 \text{ m}$ ;  $P = .001$ ) and SPPB ( $5.62 \pm 1.99$  to  $10.57 \pm 1.9$ ;  $P = .015$ ) in the test group increased significantly compared to the control group. Malnutrition is a primary issue in rehabilitation. Elderly and old people benefit from rehabilitation. Malnutrition significantly affects treatment outcome and aims of cardiovascular rehabilitation. Targeted interdisciplinary treatment of malnutrition goes along with

a significant improvement of muscle strength, walking speed and balance, important for fall prophylaxis, and cardiovascular outcome.

### Sex Related Differences in Major Depression in an Austrian Sample: Evidence for the Necessity of Gender Specific Treatment

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The preponderance of depression in women appears to be a universal and substantial finding. A woman is about 1.7 times more likely to have unipolar affective disorder than a man. Aim of this study was to investigate sex sex-related differences in unipolar affective disorders. Differences between men and women regarding sociodemographic variables, symptoms, medical treatment, and comorbidities were examined and multiple explanations for the differences were discussed. The data of 695 patients of a rehabilitation clinic in Austria were analyzed. Of the 695 patients, 465 were admitted with the diagnosis of major depression and therefore were included in the study. Different (neuro-) biological and psychological parameters were compared at the beginning and at the end of a 6-week rehabilitation period between women and men. Men and women showed no differences in depressive symptom severity; however, anxiety was significantly higher in women. Male individuals showed a significantly higher body mass index than women, and in line with that, cardiovascular diseases were more frequent in men. Women on the contrary displayed a significantly higher rate of thyroid dysfunctions. There was no significant difference in the number of psychotropic substances taken. Not only are women almost twice as often affected by depression than men, the chronic disease affects the male and female body and mind in a different way. Men have a stronger vulnerability of the cardiovascular system, women seem to have a hormonal imbalance (thyroid gland), which could explain the higher rate in anxiety, since thyroid dysfunction and anxiety have been found to be highly correlated. These gender-specific differences need to be taken in to account in the treatment of major depression to improve the psychological and physiological well being of the patients.

### Gender Gap in Diagnosis of Depression More Prevalent in Type 2 Diabetes Mellitus Patients than Non-Diabetics in Austria

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**Introduction:** In addition to type 2 diabetes patients being more prone to depression, gender differences such as a higher probability of females being diagnosed with depression have been established in the past. The exact causes are still unclear, but biological factors, hormonal differences, and gender stereotypes are likely contributing to males being under- and women overdiagnosed. For instance, cardiovascular diseases (CVD) are still commonly missed or mistaken for mental health problems in women despite the 2 to 3 times elevated risk for CVD in female type 2 diabetics. **Methods:** An analysis of a medical claims database of the Austrian Ministry of Health containing the entire Austrian population (N = 8 996 916) from 2003 until 2014 was conducted. Of these, 213 986 patients with diabetes mellitus type 2 were extracted and compared to nondiabetic controls. **Results:** In Austria, females with type 2 diabetes mellitus have 2.14-fold increased odds to be diagnosed with depression compared to nondiabetic females (OR = 2.14, 95% CI = 2.09-2.19) whereas diabetic males had significantly lower increased odds ( $P < 10^{-13}$ ) with 1.88-fold increased risks compared to nondiabetic males (OR = 1.88, 95% CI = 1.84-1.94). **Conclusion:** In comparison to the general population, the gender gap in the diagnosis of depression is greater in the diabetes cohort. Besides biological factors, this significant sex difference might stem from female diabetics being even more likely to be overdiagnosed with depression and underdiagnosed in other areas such as cardiovascular diseases when compared with nondiabetic women.

### Lack of Gender-Specific Knowledge on How Psychological Factors Contribute to Pre-Hospital Delay After Myocardial Infarction

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Women suffering from myocardial infarction (MI) wait longer to contact medical services than men, while quick treatment is crucial to reduce permanent cardiac damage. Traditional gender roles may affect health-care-seeking behaviour by defining gender-specific socially acceptable behavior. Faced with the same medical emergency, women and men may thus act

differently according to their internalized gender role. However, this has not yet been fully elucidated. We performed a systematic review of the literature to evaluate whether the effects of psychological factors on prehospital delay differ between women and men and validated our findings in a pilot study. Our search of PubMed and Embase returned 3634 unique articles, of which 92 were eligible for full-text screening and 11 (published between 1998 and 2018) were included. These articles included 2624 patients (30% women) and covered the psychological factors denial (n = 3), anxiety (n = 6), embarrassment (n = 3), and fear (n = 6), with some articles covering multiple factors. Half of the evaluations (9/18) only reported factor prevalence by gender. Some results suggested that denial increased delay (n = 1, 161/533 women), anxiety decreased delay (n = 2, 120/328 women), and embarrassment and fear had no effect on delay (n = 1, 96/194 women) in both genders. Others showed that anxiety decreased delay only in men (n = 1, 36/98 women) or only in women (n = 1, 162/619 women), while embarrassment and fear increased delay only in men (n = 1, 24/134 women). We screened the electronic health record (EHR) of 100 men and 104 women admitted to the University Medical Center Utrecht with an ST-elevation MI. With the exception of embarrassment as delay reason for one woman, psychological factors were not mentioned in the EHR. Psychological factors seem to affect prehospital delay after an MI similarly in both genders, but limited data question the validity. Large standardized studies with proportionate numbers of women are needed to draw final conclusions.

### Real Men Don't Cry—Gender Differences in Coping With Cancer

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“Real men don't cry,” “talking about fear and sorrows are only for women”—do these and similar prejudices still exist today? Men and women handle life challenges differently. They differ in the way they perceive challenges, communicate, in their social relationships, and in the way, they deal with major challenges, such as cancer and disease. Despite medical progress cancer is still a life-threatening disease and throws a person's views on life into disarray. Studies indicate that depression and anxiety are highly prevalent in patients with cancer and that gender plays an important role in the way patients cope and communicate with their oncologist, family, and friends. By providing patient-centered care, we would benefit from acknowledging and talking about gender issues and gender differences concerning how male and female patients cope with their cancer disease—what it means to them, how they deal with it in their daily life, and how it influences their personal life and relationships. Interviews with male and female patients with cancer show a clear tendency toward gender differences in coping with cancer. The results do not support any stereotypes of male and female behavior or

social structures—but it mirrors the real life of human beings!  
*And yes, real men do cry!*

### **Self-Harm and Suicidality—Are There Gender Specific Causes?**

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**Objective:** Self-harming and suicidal behavior are common in individuals with psychiatric disorders. The objective of this study is to examine whether there are gender-specific differences in risk factors for self-harming and suicidal behavior.

**Methods:** We analyzed self-report data of N = 677 inpatients (37.4% male) from a psychosomatic clinic in Austria using logistic regression analyses. Self-harm and suicide attempts were assessed by one question with a dichotomous answer format (yes/no). Assumed predictors were childhood trauma, anxiety, depression, type of mental disorder, family situation, education level, and general life satisfaction. **Results:** Separate analyses for each gender revealed an increased risk for self-harm and/or suicide attempt in females with a history of physical abuse during childhood. For males with history of emotional abuse or physical neglect during childhood or who are currently living alone the risk was also increased. **Discussion:** These results suggest a critical role of childhood trauma for self-harm and/or suicide attempts in adulthood, with gender-specific difference regarding the type of childhood trauma.