4.1 Final publishable summary report

4.1.1 Executive summary

The overall health of the European Union (EU) has improved over recent decades. Yet this improvement has not been experienced equally everywhere or equally across all populations. Biological differences between women and men – sex - as well as sociocultural processes – gender - contribute to generate and to maintain inequalities. The EUGenMed project was started in 2013 in order to introduce sex and gender aspects into medicine as an innovative way to improve biomedical and health research and thereby the health of European citizens. For this purpose, we developed a European roadmap to implement sex and gender (S&G) into biomedical and health research.

We started by assembling European stakeholders in gender medicine and defining our intended outputs: publications, policy briefs, recommendations, information materials, contribution to congresses and flyers. As main working fields, we selected clinical medicine and pharmacology, public health and prevention, basic biomedical research, medicines regulations and medical education, and we selected foci of work where a body of knowledge already existed and recommendations for further research and implementation could be given on a solid basis of evidence.

In **clinical medicine and pharmacology,** we identified cardiovascular diseases, as an example for many others, where well-described differences in aetiology and clinical presentation between women and men exist. We provided evidence that a more stringent consideration of S&G differences in cardiovascular diseases will lead to better understanding of pathophysiology and more personalized therapeutic approaches. S&G differences in diabetes, stroke, asthma, lung cancer also need attention and we drafted policy briefs **(*Annex 1*)** and recommendations for funding agencies and scientific communities on these topics. **Public health** focused on modifiable risk factors contributing to the major Non-Communicable Diseases, such as tobacco smoking, physical inactivity and alcohol use, obesity mental and occupational health. To understand how sex differences may contribute to improvements in therapy, we included basic research in the project. Sex and gender must be included in medicines regulation and medical education at multiple levels to provide the best treatment for and care of patients. Regulatory agencies, such as the European Medicines Agency (EMA), will have to implement the new Clinical Trials Regulation by May 2016, which stipulates that women and older people have to be included in clinical trials and any exclusion has to be justified. This will make more information available on how a medicine works in women and older people.

We expect a major impact on medical societies, academia, regulatory bodies, funding agencies, industry, non-governmental organisations and government, in summary on the whole scientific and broader regulatory communities through the materials provided by the project, most important publications, policy and slide sets. Gathering together of representatives of the broader societal stakeholders and influencers was the catalyst for awareness and advocating for acceptance of the importance of sex and gender.

In order to assure **sustainability** of EUGenMed after project lifetime the **EUGenNet** was developed as an open structure for collaboration of stakeholders in the future.

In conclusion, in order to **implement** S&G into biomedical and health research, we suggest to strengthen the developing field of gender medicine and the **EUGenNet.** To assure research and clinical and teaching quality as well as recognition of overarching S&G viewpoints and concepts, gender medicine must be developed as an independent discipline with its own institutes and resources and must be able to build a scientific community.

4.1.2 Summary description of project context and objectives

The overall health of the EU has improved over recent decades. Yet, this improvement has not been experienced equally everywhere or equally across all populations. One source of health inequalities arises from different yet unsatisfied needs of women and men for specific treatments as well as from the different attitudes of the health care systems and biomedical research systems towards the needs of women and men. Biological differences between women and men – sex specific aspects – as well as sociocultural processes – gender aspects – do play a role to generate and to maintain inequalities.

The EUGenMed project was started in 2013 in order to introduce *SEX AND GENDER ASPECTS INTO MEDICINE AS AN INNOVATIVE WAY* to improve biomedical and health research and thereby the health of European citizens. For this purpose it used approaches generated by the novel discipline gender medicine and teamed up with experts from this discipline to achieve sustainability.

Definition of gender medicine

Gender medicine is an emerging novel and highly promising field in health research and biomedicine. It considers the target groups of women and men for disease manifestation and treatment options in gender specific approaches, following the conviction that targeted approaches will help to optimize treatment strategies for both. It should not be mistaken for women's health. Gender medicine provides increasing evidence on differences between women and men in pathophysiology and in the manifestation and response to treatment of many frequent diseases and offers solutions to improve the health of both.

Both, sex and gender, affect the health of women and men. Sex refers to biological differences between women and men: genetic predisposition to diseases, body size and composition, hormones, drug metabolism. Gender refers to cultural and social attitudes that together shape "feminine" and "masculine" behaviour. Humans function in large and complex societies through learned behaviours. Gender is one aspect of these behaviours and gender-based attitudes influence health and health care and interact with biological processes. In human diseases, sex and gender heavily interact and therefore, gender medicine includes sex as well as gender aspects.

The need for gender medicine throughout the world and in Europe

Despite the fact that all described advantages of considering sex and gender are agreed among most medical experts, implementation of sex and gender into European medicine is still lacking. This may be due partially to a lack of information, to a lack of clear recommendations, guidelines and teaching materials as well as a lack of structures to implement gender sensitive approaches.

The need for structures for sex and gender specific approaches has been recognised much earlier in the US than in Europe. Most recently, the relevance of cardiovascular disease in women has been recognized by industry and the American Heart Association (AHA) and the large action "Go red for women" has been installed leading to guidelines on cardiovascular prevention in women (http://www.goredforwomen.org/). Recently, NIH declared that consideration of sex is relevant to all research projects submitted to NIH (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html). The great relevance of gender medicine is agreed by the Canadian Institutes of Health Research (CIHR); in particular the Institute for Gender & Health (IGH) has invested much in developing awareness and training in sex and gender aspects of health research.

Whereas the American activities in gender medicine started from the idea of women's health, the idea that sex and gender specific approaches, i.e. unbiased comparisons between women and men, are more suitable to advance medicine has been developed in Europe, in particular in Berlin, Maastricht and at Karolinska Institute and at the European Institute of Women's Health from a policy and citizens health perspective. The mandate of the Advisory Group on Gender in Horizon2020 reflects the European approach.

Sex and gender aspects are frequently not covered in research calls, in policies, in guidelines or disease management programmes even when they are obvious. To implement sex and gender in European medicine, a diversified approach is needed targeting all potential stakeholders and fields where sex and gender are important. This includes discussions with representatives from all Member States, or as many as possible, throughout sectors and disciplines; i.e. politicians, policy makers,

research funding agencies, researchers, teachers, doctors, nurses, medical assistants, students, patients.

Main objectives of EUGenMed

The overall objective of EUGenMed is to improve the health of European citizens, women and men, by improving health research and biomedicine with a target group specific approach. For this purpose, we developed a European roadmap to implement sex and gender into Medicine.

The following steps were important objectives of EUGenMed:

- Assembly of stakeholders in gender medicine and generation of communication structure
- Agreement on strategy with definition of main working fields
- Definition of materials to be generated and target audiences
- Generation of a roadmap: materials for implementation of sex and gender aspects in biomedicine and health research for different target audiences in the following working fields:
    - Clinical medicine and pharmacology
    - Public Health and Prevention
    - Basic biomedical research
    - Medicines regulations; medical education
- Communication and dissemination of roadmap
- Creation of structures for sustainability

Working fields: Sex and Gender sensitive focal areas

As main working fields, we selected clinical medicine and pharmacology, public health and prevention, basic biomedical research, medicines regulations and medical education. These areas were, however, too large to be completely covered in every detail in the project. To make fast progress in a short time, we selected topics for our work where a body of knowledge already existed and recommendations for further research and implementation could be given on a solid basis of evidence. Final decisions on the topics were made in the workshops.

Clinical medicine and pharmacology

Sex and Gender sensitive approaches help to understand the clinical outcomes, death and disability, in frequent diseases. In some medical disciplines, a large body of knowledge how sex and gender affect the clinical course already exists, but it is not yet assembled and communicated in a systematic manner and not yet implemented in health research and clinical practice. A lot is known about the different presentation of women and men cardiovascular diseases, neuropsychiatric diseases, endocrinology, autoimmune and rheumatic or inflammatory diseases, nephrology and cancer but there are no consequences for medical practice. Thus, sex and gender knowledge must be assembled and communicated and research projects building on this knowledge should be outlined. Knowledge gaps must also be identified.

In pharmacology, during the last 20 years, the “one size fits all approach” was favoured. The development costs of a new drug has steadily increased, taking 10-15 years and costing up to 1 billion (€ 10^9) at present. This approach has now come to its limits. Ever since the human genome has been deciphered, there has been a growing recognition that better targeted approaches are needed for improving drug treatment. ~~O~~ur understanding of genomics is paving the way towards personalized medicine, but it will take years to be available in all disciplines. Alternative strategies are needed and targeting drugs for both sex and age may be an appropriate intermediate step. This requires drug development in women and men and testing for efficacy and adverse effects in both sexes.

Public health and prevention

Non-Communicable Diseases (NCDs) such as cardiovascular diseases, cancers, chronic respiratory diseases and diabetes, are a major global health concern and the leading cause of premature death (more than 40% of them occurring before the age of 70 years), and disease burden, both worldwide and in Europe. Modifiable risk factors, such as tobacco smoking, unhealthy diet, physical inactivity

and alcohol use contribute to the majority of NCDs. Addressing highly prevalent and relevant NCD risk factors is a significant public health and primary prevention topic, relevant for a large range of conditions. Gender-sensitive interventions are likely to contribute to an increased efficiency of interventions.

For women and men, most NCD risk factors show distinct associations with many NCDs, such as with cardiovascular diseases, and population attributable risks differ considerably for men and women. Furthermore, from a life course perspective, first manifestations of cardiovascular diseases differ in men and women, with men being more likely to develop coronary heart disease as a first event, while women are more likely to have cerebrovascular disease or heart failure as their first event, which may be explained partly by a different lifetime pattern of risk factors.

Risk factors have to be conceptualised as influenced by factors intersecting with sex and gender, relating them to culturally driven gender norms, socio-economic position, behavioural factors, genetic make-up, levels of susceptibility, exposure time to risk factors, differences in knowledge and risk perceptions, access to health care, health care seeking patterns and health systems responses.

Major publications, even when displaying detailed sex-specific data, do not address sex and gender aspects, and there is a paucity of sex- and gender-specific recommendations for prevention. Likewise, although a number of gender sensitive Public Health Policies have been developed and implemented in the last two decades, research on impact and efficiency of such approaches and on risk factor control and management is very scarce, and there is a lack of critical discussion on methodology of gender-sensitised interventions.

Sex differences in basic biomedical research

Sex differences in animal studies or cell culture systems are largely neglected at present. This is unfortunate since these studies constitute the breeding ground for understanding of pathophysiology of human diseases and for drug development. Animal researchers frequently avoid studies of females in the false belief that they introduce greater variability into their results because of their hormonal cycle than males. They often neglect sex of their animals since they do not consider it important. However, in the majority of mouse strains with cardiovascular or immunological phenotypes for diseases significant sex differences exist. Neglecting of sex may contribute to the poor reproducibility of experimental data that has recently been described – 70% of animal studies could not be reproduced in a second laboratory! Knowledge on sex specificity in animal models, on different metabolic pathways and physiology in male and female animals is needed to understand disease development in women and men and to use the animal or cell culture models for interpretation of human disease. Understanding these mechanisms and deciphering why preferentially one sex is protected or affected shall lead to chances to develop novel therapies in both.

Medicines Regulations

Medicinal products are safer and more effective for everyone when clinical research includes diverse population groups. Over the years, scientific knowledge has increasingly demonstrated that some treatments affect men and women differently. However, the proportion of treatments for which men and women respond differently is yet unknown. These sex and gender (S&G) differences have important implications for health and healthcare.

Yet, women are still under-represented in clinical trials. Since the Thalidomide tragedy in the early 1960s, there has been a reluctance to include women of childbearing age in clinical trials. "*The general assumption prevailed that women did not differ from men except where their reproductive organs were concerned and data obtained from clinical research involving men could simply be extrapolated to women*"(1). An article in the *Nature* journal argues that gender inequalities in biomedical research are undermining patient care and the article calls for the "*sex bias in basic research and clinical medicine to end*" (2). Moreover, there is a particular lack of information on the safe use of mediation during pregnancy and lactation.

Translating the evidence from S&G research into regulatory practice will lead to more targeted, effective opportunities for prevention, treatment and care. Currently, some S&G consideration are integrated into medicines regulation and information. However, many gaps continue to persist, so steps must be taken to make improvement in Europe in the future.

Sex and Gender in Medical Education

S&G influence access to health services and how health systems respond to their different needs. S&G affect all aspects of disease prevention: development, incidence, prevalence, symptoms, diagnosis and progression of both infectious and chronic diseases. Apart from reproductive health, it is rare that sex and gender are considered in medical education curricula. Over the last ten years, the importance of sex and gender in medical research and treatment of medical conditions has been increasingly recognised. However, the need for integration of this knowledge into medical education curriculum still remains a challenge.

High quality education and training is fundamental to achieving high quality healthcare. Historically, there has been a male-bias in medical education and training, which must be corrected. Medical knowledge and science have developed largely in the absence of diversity. Gender sensitive and diversity responsive healthcare in the future requires education and training of all health professionals involved in the delivery of care. A patient-centred evidence-based sex and gender perspective is required throughout medical curricula including graduate programs, medical programs, nursing, rehabilitation, and pharmacy, continuing medical education and continuing nursing education across Europe. The failure to acknowledge the impact of S&G differences affects the quality of health care provision, precisely what good medical education seeks to prevent. There must be a commitment to mainstream an evidence-based gender perspective throughout medical curricula.

Overall objective: The Roadmap

The aim of EUGenMed was to generate a comprehensive roadmap - i.e. materials, timelines, target groups and recommendations - for implementing of sex and gender into biomedical and public health research and improve prevention, treatment, healthcare strategies, medical education to achieve better outcomes and patient care. Materials have been tailored to different target audiences to convince them of the relevance of sex and gender in their respective fields including policy briefs ***(Annex 1)*** publications in scientific journals, reviews in target audience journals, brochures or toolboxes how to apply sex and gender research principles. Stakeholders in gender medicine or target audiences for our measures include medical doctors and (bio) medical societies, researchers, teachers and students in academia, industry, drug companies, science funding organizations, regulatory bodies, health policy makers and last but not least the general population, laymen. We also planned to develop a strategy how to reach out to these stakeholders in different conferences and via other communication structures.
The sustainability of EUGenMed after project lifetime was also an important goal. We planned to develop a structure to enable collaboration of stakeholders in gender medicine in the future.

4.1.3 Description of the main S&T results/foregrounds

The Roadmap is the main output of the EUGenMed project. It offers information and recommendations for implementation of sex and gender in biomedicine and health research for different target audiences and depicts a number of suggested implementation steps that shall take place during and after finishing the project. It has been established in the kick off conference and four workshops (***Annexes 2, 3***) and summarizes the results of the project of in a precise and coherent manner.

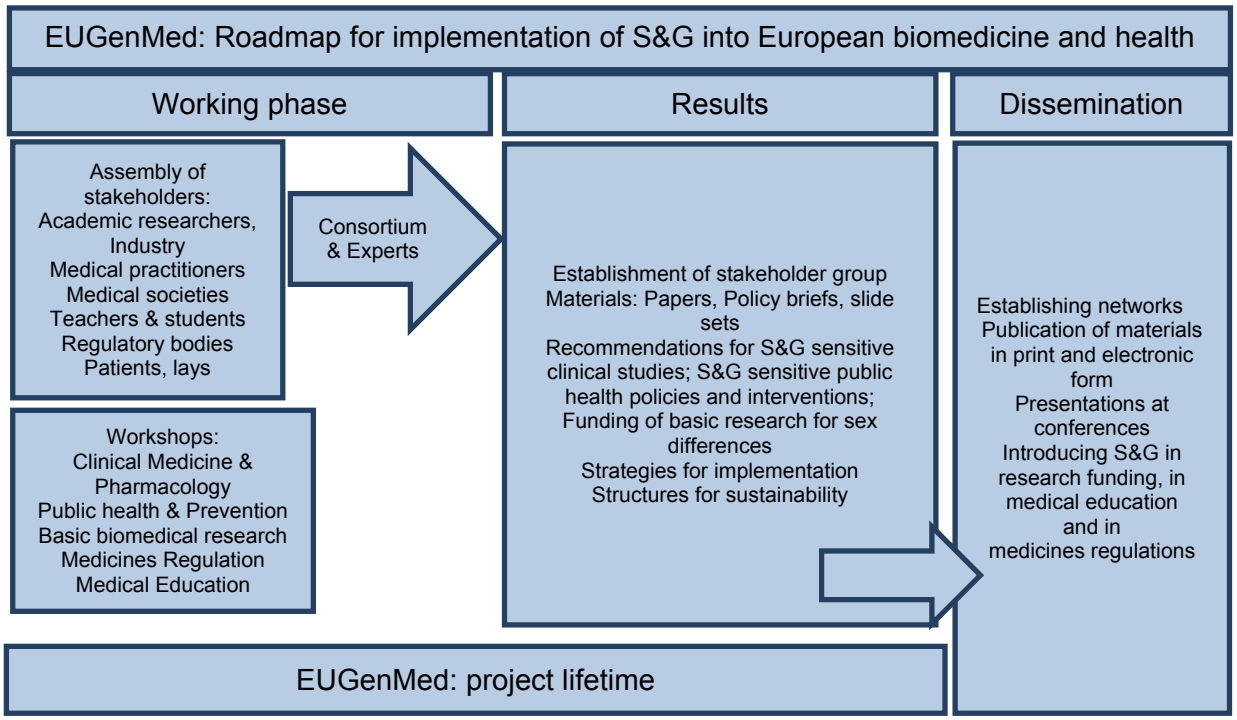

Fig 1: EUGenMed project roadmap

Methodology

Assembly of Stakeholders and Target audiences

The roadmap has been developed in a true spirit of openness, transparency and inclusiveness. Stakeholders in gender medicine or target audiences for our measures have been called and assembled by systematic searches and open calls on the Internet. We identified 503 stakeholders, from 25 EU and 10 non-EU countries ***(Annex 10: Stakeholder list).*** They were medical doctors and (bio) medical scientists, researchers, teachers and students in academia, industry, pharmaceutical companies, science funding organisations, regulatory bodies, health policy makers, patient organisations, representatives of civil society and lay people. Among them, there were 28 journalists and 28 partners working at different levels for the EU commission and related agencies. Of these about one third participated in our conferences and workshops, others followed via the Internet.

Developing the roadmap strategy

At the kick-off meeting we agreed on a strategy with definition of focal areas of work, materials to be generated and target audiences. We defined our main working fields:

- clinical medicine and pharmacology,
- public health and prevention,
- basic biomedical research,
- medicines regulations and medical education

and organised workshops in these fields.

Workshop methodology

Each one and a half day or single day workshop was organised by a different partner ***(Annex 3***). About 20 experts in the respective field were invited to each workshop with the ambition to cover a

wide range of geographical regions, countries, sectors and disciplines and their intended outputs, such as policy briefs(***Annex 1***), publications ***(Annex 6)***, slide sets (***Annex 7***), press releases ***(Annex 9),*** and experts made their contributions. In general, one or two experts introduced a topic to the group and this topic was then discussed and agreed by the whole group. The texts in the document reflect the content of the consented group discussion, not single expert's opinion.

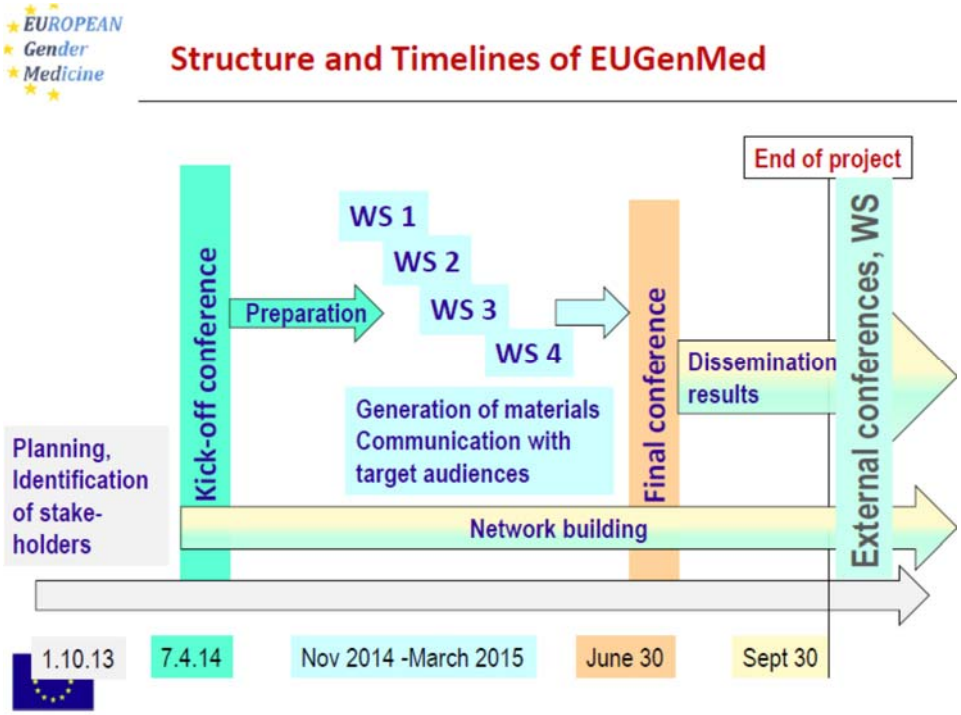

Fig 2: Organisation of work in the project.

We are summarising in the next sections the main results in our working fields as obtained in the different workshops***.*** Due to space limitations, some results are presented in rather condensed form. However, the findings are also submitted for publication and are also presented in more detailed form in our policy briefs (***Annexes 1, 6***).

Final Conference in June 2015 in Brussels

Results of the workshops were integrated in our Final Conference in June 2015 in Brussels (***Annex 4).*** There, most of the Workshop participants and stakeholders met and discussed the results of the project. The conference ended with a roundtable discussion on the sustainability of a gender sensitive roadmap for improving health for all in Europe. Project partners and experts stressed the need to effectively disseminate the results in order to ensure the incorporation of sex and gender into future biomedical science and health research. They agreed that project findings will be disseminated in a targeted and customised fashion to key stakeholders at local, national and European level. The introduction of sex and gender into research and medical practice and medical and health professional edcuation and training will lead to significant innovations and has the potential to improve European citizens' health."

Working field 1: Sex and gender in clinical medicine and pharmacology

In order to discuss S&G aspects in clinical medicine and pharmacology, we invited 20 international experts to EUGenMed workshop 1 (***Annex 3a*****).** The group acknowledged in intense discussions that in many diseases well-described differences in etiologies and clinical presentation exist between women and men. It agreed that this knowledge is dispersed and incompletely translated into clinical practice and research programs. The highest density of evidence-based knowledge was found available for cardiovascular diseases. The EUGenMed workshop 1 groups therefore decided to focus first on cardiovascular diseases and to summarize the sex and gender related findings from the other disciplines under a different aspect. Nevertheless, S&G differences in diabetes, stroke, lung cancer and asthma were also discussed in detail and are presented in policy briefs ***(Annex 1).***

Ischemic heart disease

Ischemic heart disease now affects and kills almost as many women as men in Europe. However, there are significant differences between European countries. In general, men are affected 10 years earlier, but mortality of affected younger women is higher than in men. The number of the acute manifestations of ischemic heart disease, i.e. acute coronary syndromes in younger women has significantly increased. S&G differences in changing risk factors, including metabolic diseases, life style and stress may contribute. Whereas men are more frequently affected by the classical manifestations, i.e. narrowing of large coronary arteries, women are more frequently affected by small vessel or microcirculatory disease.

Unfortunately, small vessels are not visible by coronary angiography which is the best diagnostic technique for large coronary arteries. Therefore, coronary angiography is of limited value to establish Ischemic heart disease in middle-aged intermediate or low risk women since they have more frequently microvascular disease. Diagnostic modalities for assessment of coronary microvessel disease include measurement of coronary blood flow reserve by invasive and non-invasive approaches. These techniques are usually more demanding than simple coronary angiography.

Acute coronary syndromes can manifest differently in women and men. Typical female presentations include spontaneous coronary artery dissection (ruptures within the wall of a coronary artery). This is an underestimated cause of acute coronary syndromes that affects almost only women. Spontaneous coronary artery dissection is particularly frequent in younger women and particular in pregnant women or immediately postpartum. A second female typical syndrome is an acute life threating stress induced cardiac dysfunction that affects in Europe to 90 % women. Detailed pathophysiology is still not clear and worth to be studied in more detail.

Women do have increased 30 day and one year mortality after acute coronary syndromes and myocardial infarctions (MI). The outcomes are worse in women than in men, what may depend on age and comorbidities. Women have poorer quality of life after cardiac surgery than men. *(References:* ***Annex 6a)***

Heart failure

Heart failure is one of the biggest causes of morbidity and invalidity in western populations, particularly in the aging population. 10 % of the 70 years old are affected, significantly more women than men. We now distinguish heart failure with preserved ejection fraction that is due most frequently to a defect in diastolic filling of the heart and has a greater prevalence in women and heart failure with reduced ejection fraction which is more frequently found as a consequence of myocardial infarction in men. Prognosis is bad in both. However, there is no causal therapy for the female typic form of heart failure, whereas a large number of evidence based therapies have been developed for the typically male manifestation. A novel, expensive and invasive form of therapy (cardiac resynchronization therapy) is less often used in women than in men but offers greater benefit in women. Women with heart failure are referred to heart transplantation and ventricular assist device implantation in later stages than men. Some important heart failure drugs have S&G specific profiles of efficacy and adverse events. *(References:* ***Annex 6a)***

Valvular heart disease

In valvular heart disease, consideration of S&G differences is just starting. Women and men behave differently if they have a valvular aortic stenosis and the adaptation of the heart in this disease is different. Moreover, some important diagnostic tools have different cut-off levels. By computer tomography, women have less valve calcification than men for the same severity of aortic stenosis. By echocardiography, indexation to body surface is crucial for correct estimation of severity, particularly in women of small body size. Women with aortic stenosis have a more favourable myocardial adaptation, tolerate surgery less well and have greater benefit from the novel and less invasive transcatheter aortic valve implantation than men. Interestingly enough, women respond better than men to transcatheter aortic valve implantation. The reason for the better outcome of women is not clear yet and needs more research.

Women with severe mitral valve regurgitation are referred later to surgery than men and have worse outcomes. Indexation of ventricular dimensions to body size is of particular importance for correctly identifying the need for surgery in women. *(References:* ***Annex 6a)***

Cardiovascular disease - Policy brief

In the second policy brief, the sex differences in cardiovascular disease risk factors are outlined. The policy brief focuses on sex specific conditions/risk factors such as pregnancy and smoking and other gender specific risk factors and female specific syndromes in cardiovascular disease. The policy brief also explores the connection between cardiovascular disease, diabetes and depression as well as the underrepresentation of women in cardiovascular disease trials. Various issues pertaining to cardiovascular disease and S&G warrant further investigation. ***(Annex 1a)***

Sex and Gender in Asthma – Policy brief

In adulthood, more women suffer from asthma than men. Women in the age group twenty to fifty are especially affected. Severe complications from asthma are more common in women than in men, leading to more frequent or longer hospitalisation and higher rates of death. Women have a higher rate of non-allergic asthma. The reasons for these gender differences are not entirely understood, though researchers believe that the answer is strongly connected to hormones.

Female hormones have a large impact on asthma, affecting 40% of women with asthma, and can have almost as much of an impact as triggers such as allergens. Fluctuation in levels of estrogen can lead to airway inflammation. Thus women with asthma should monitor their menstrual cycles and avoid exposure to allergens during this time, as asthma attacks are more likely to occur right before a women's menstrual cycle when her estrogen is low. Most hospitalisations from asthma occur at the peri-menstrual state. In particular, girls during puberty can find that their asthma worsens before their cycle, though the frequency and severity may decrease with age. Scientists believe that genetic differences may impact the gender differences in asthma rates and severity. Certain specific genes are correlated with asthma in women but not in men. Researchers also speculate that there may be sex-specific differences in the regulation and expression of genes which impact on female prevalence and severity as regards asthma. In addition, women of the same age and height as men have smaller lungs and narrower bronchi than men.

Environmental exposures vary much between gender as women typically spend more time at home than men, which exposes them more to asthma triggers than men. Certain occupations in which the majority of workers are women, such as domestic cleaning, have elevated rates of asthma. With regard to healthcare, women may be more likely than men to identify their asthma symptoms, report them to a doctor and seek medical care during an asthmatic episode. ***(Annex 1b)***

Sex and Gender in Lung Cancer - Policy brief

Historically, lung cancer has mostly affected men and was considered rare in women. Overall, the smoking prevalence is lower among women than men. However, this gap has been narrowing due to a decrease in male smokers and increase in female smokers in some countries. Although more men are diagnosed with lung cancer, incidence is levelling off or decreasing in men, but is increasing among women over time.

In Europe, lung cancer causes 20% of all cancer-related deaths, the highest of any cancer. Smoking is the greatest risk factor. About 1/3 of EU citizens smoke; in some EU countries up to 50% of women smoke. Annually, 650,000 Europeans die prematurely. A high percentage of lung cancer in women is smoking-related. Despite lung cancer's strong association with tobacco use, one in five women who develops the disease has never smoked. Non-smoking women appear to be at two to three times greater risk for developing lung cancer, suggesting that other factors such as passive or environmental smoke play a role.

Researchers are just beginning to understand the differences in lung cancer between women and men. These differences affect lung cancer prevention, treatment and survival. Lung cancer results from the interactions between genetic, hormonal, behavioural and environmental factors.

Studies suggest that lung cancer in women is biologically different from that in men since their genes may make women more vulnerable to the harmful effects of smoking, women's bodies may metabolise the chemicals in tobacco differently, changes to genes that control cell growth may aid in cancer development, a lowered ability to repair DNA damage may aid in cancer development and women's hormones, such as estrogen, may directly or indirectly influence cancer progression.

More research into the gender and biological differences needs to be encouraged. ***(Annex 1c)***

Diabetes mellitus type 2 – Policy brief

Knowledge of S&G differences in Diabetes mellitus is large, but still did not make it to the guidelines. Diabetes mellitus type 2, characterized by insulin resistance, diabetic dyslipidaemia and a highly atherogenic proinflammatory state, is a stronger predictor for myocardial infarction in women than men. Diabetic women bear a 40% greater risk to develop coronary artery disease compared with men and also the risk of fatal coronary artery disease is greatly elevated in women and did not decrease over time. Although long-term survival after a first myocardial infarction has improved in diabetic patients, the effect of diabetes upon mortality has not diminished, and survival is markedly lower especially among women. More comorbidities including obesity contribute to greater cardio metabolic load in diabetic women than men. Therefore, it is important to detect women in the early phase of the disease and to treat or abolish all possible risk factors. This may require different testing than in men. In addition lower rates of lipid lowering treatment were reported in diabetic women and women are less often monitored for late diabetic complications.

A female specific condition is gestational diabetes, a frequent metabolic disorder detected during pregnancy in nearly 10% of pregnant women, which puts women at seven-fold higher risk to develop diabetes in later life and associates with two-to-threefold higher cardiovascular risk at follow-up compared to women without history of gestational diabetes.

Additionally diabetes is a strong risk factor for sudden cardiac death (threefold higher risk in the Nurses' Health Study), especially among women. Thus there is a need of sex-specific studies evaluating symptoms and outcomes in the subpopulation with diabetes compared to non-diabetics among coronary artery disease patients. ***(Annex 1d)***

Stroke – Policy brief

Cerebral stroke is a leading cause of death and the main cause of long-term functional deficits and disability in adults in industrialized countries. The annual incidence for first ever ischemic stroke within the European Union is 150 per 100,000 - although large regional variations exist with lower rates in countries in the south of Europe and higher incidence in Eastern Europe. Recent research has shown that differences between women and men exist in various aspects of ischemic stroke including incidence, risk, knowledge, effectiveness of treatments and outcomes.

Within most age strata, women have a lower ischemic stroke incidence than men, and as such, the overall age-adjusted incidence of ischemic stroke is lower for women than men. This holds true for most industrialized countries. Besides, men are significantly younger than women when suffering the first stroke (about 4 years younger). However, women appear to have a higher overall lifetime risk of stroke due to a higher life expectancy compared to men. Consequently, the absolute number of strokes is greater in women than in men. During the premenopausal years, women bear a lower risk for stroke than men. However, an increase in stroke incidence in women aged 45-54 years is suggested by recent data from the US.

In summary, sex and gender need to be considered in both experimental and clinical stroke studies, treatment choices and educational campaigns. They result from a combination of factors, including hormones, social and cultural factors. Many are unaware of the potential confounding factors of gender differences. To more accurately reflect the risk of stroke in women across the lifespan, as well as the clear gaps in current risk scores, we believe a women's-specific stroke risk score is warranted. ***(Annex 1e)***

Depression and stress

An array of psychosocial risk conditions covering the entire life span have been acknowledged as etiological and prognostic risk factors for cardiovascular diseases and a number of these are sensitive to S&G. Evidence exists for early life conditions like childhood adversity and low educational level, for living alone and loneliness, for sustained adverse marital and work stress but even more so for affective conditions like anger, anxiety and depressed mood. Among all factors under consideration, depression has gained most attention in recent years and is now regarded as an established risk factor for cardiovascular diseases. There is growing evidence that the prevalence of depression is substantially higher in female acute MI patients compared to male counterparts, particularly in younger age groups.

Despite the substantial malignant impact of depression on cardiovascular disease outcome measures, the first generation of large scale studies in depressed cardiovascular disease patients designed to study the effect of psychological or psychopharmacological interventions on hard cardiovascular disease endpoints did not provide evidence for beneficial effects on cardiovascular disease mortality and morbidity in gender mixed cohorts. For women, there was even a tendency for study results favouring usual care.

Recent trials with innovative collaborative care treatment approaches (primary care based, combining self-care support with pharmacotherapy and individualized goal setting) - all of them including more than 50% of female patients - show promising results. It seems that depression may need to be treated as chronic disease and too early withdrawal of anti-depressive treatment may compromise the treatment success.

Gender in pharmacotherapy and drug development

The effects of pharmacological interventions differ in women and men. Significant differences in pharmacokinetics, i.e. the handing of drugs in the body, have been established due to lower body surface in women but also to differences in kidney function, in drug reabsorption, metabolism, by hepatic enzymes and excretion. Many drugs require different doses in women and men for optimal effects. In addition, differences in pharmacodynamics, the mechanisms of drug action, are also evident. Ion channels in kidney and heart differ between women and men and this may cause sex-specific effects of drugs that are used to modify kidney function or heart rhythm. Major sex and gender differences have been reported for the efficiency and adverse effects of frequently used drugs, used for the treatment of heart failure drugs, like digitalis, angiotensin-converting enzyme (ACE) inhibitors and anti-arrhythmics. They have also been found in analgesic and neuropsychiatric drugs, in anticancer drugs, cardiovascular drugs, in the effects antiviral drugs. These significant differences are related to different efficacy of the drugs but also to differences in administration and use of drugs in the population. Therefore, different therapeutic procedures may be effective in both genders, and different strategies are needed to optimise procedures. Developing and incorporating these aspects into guidelines will enhance efficiency of pharmaceutical therapies.
As a consequence, first drugs for the use in only one gender have been marketed and gender specific recommendations on preferred drug use or dosing are developed in the US, but not yet in Europe.

Drug testing

Major efforts have been made to increase the participation of women in all types of clinical trials. However, studies published in 2008 concluded that women were still not included in mixed sex cardiovascular trials in numbers that reflect the disease prevalence among the general population. A 2005 study of 300 new drug applications between 1995 and 2000 found that even those drugs that showed substantial differences in how they were absorbed, metabolised and excreted by men and women had no sex specific dosage recommendations on their labels. This may be the reason that women are 1.5-2 fold more likely to develop an adverse reaction to prescription drugs than men. In an assembly of 48 large studies for novel drugs in Great Britain women had a 1.6 fold higher risk for adverse reactions than men. Even based on the most recent investigations women are still not adequately represented in clinical trials. They are particularly underrepresented in the area of cardiovascular diseases and in early studies. *(*References: ***Annex 6a)***

Workshop 1 outcomes

The participants agreed that in cardiovascular diseases, as an example for many others, well-described differences in etiologies and clinical presentation exist between women and men. The EUGenMed writing group decided to summarise S&G specific data that are relevant for patient treatment in cardiovascular disease that are incompletely covered in present guidelines and bring these differences to the attention of the scientific community.

Five policy brief have been written in English on S&G differences in Asthma, Cardiovascular disease, Diabetes, Lung cancer and Stroke. The policy briefs are concise in laymen's English (12-year-old reading level) to ensure that all information is easily understandable and accessible by relevant groups. The policy briefs explore both the biological and social factors that impact the development, diagnosis, progression, treatment and prevention of the five disease areas. All policy briefs are of similar length and structure to ensure consistency across the Project deliverables without compromising the information necessary to inform the different groups. The policy briefs were

reviewed by experts in each of the disease areas as well as by participants in the workshops. Reaching out to the patient groups, health NGOs and civil society by distributing the PBs to them will be of pivotal importance for the Project in order to create a 'sense of urgency' for action for other actors, such as policymakers, industry and medical professionals.

The participants recognized the necessity to communicate their knowledge to a broader scientific community, to present findings at congresses, to publish summaries, to present knowledge to medical societies and be included in their guidelines and to include knowledge to medical students and health care professionals in a structured manner. As a consequence, they decided to publish 2 papers and to contribute to the eGender learning programme that is built for medical students and HC professionals. The first paper has recently been published in the European Heart Journal ***(Annex 6a: Ref. 1).*** This publication will have major impact on guideline committees and clinical work in Europe. A next publication: Transdisciplinary criteria for the inclusion of sex and gender into diagnostic algorithms, (Oertelt Prigione et al, in preparation) will also impact on these societies.

Sessions were submitted and accepted for the ESC congress London 2015. Eight sessions were accepted, 2 with a presentation of the EUGenMed coordinator.

Furthermore, S&G differences in clinical medicine and pharmacology, in public health and basic research was integrated into the IGM congress September 2015 in Berlin. A whole session with FDA participation was devoted to S&G differences in drugs. The program of the congress that was visited by more than 200 scientists is attached ***(Annex 5: EUGenMed sessions at IGM Congress 2015, Berlin).*** Next steps are submission of sessions to OSSD congress 2016 and ESC 2016.

In conclusion, the workshop provided evidence that a more stringent consideration of S&G differences will lead to better understanding of pathophysiology and more personalized therapeutic approaches. We recommend to fund studies on these topics.

Recommendations for the future for funding agencies and scientific communities:

Expert discussions in the workshop and the final Roadmap conference agreed on the following recommendations for improving gender aspect in clinical studies and pharmacology in Europe:

- We recommend for funding agencies to support gender aspects in clinical studies. We identified relevant topics in the cardiovascular field and in stroke research, in diabetes research, and in lung diseases. For example, in studies in ischemic heart disease should clarify why ischemia in the presence of non-obstructed large coronary arteries is more common in women than in men, why diagnostic algorithms that perform well in men are less suitable for women. Furthermore, gender differences in stress induced heart diseases should be studied. Spontaneous coronary artery dissection occurs most frequently in younger or pregnant women and is also poorly understood. Remodelling in myocardial hypertrophy and heart failure is important in all valvular heart diseases. It differs in women and men, with more concentric hypertrophy and less fibrosis in women. Mechanistic studies in these areas should be financed.
- In pharmacology, we propose to study sex differences in pharmacokinetics determine bioavailability of CV drugs. Sex differences in pharmacodynamics may be based, among other factors, on molecular differences between male and female cells and need further investigations.
- S&G experts groups should be installed by all funding agencies to assure that S&G topics are adequately considered. Qualification of experts should be evaluated by their publications in the field, by participation in conferences.
- Medical societies should include gender sensitive topics in their guidelines. We have published a position paper in the cardiovascular field that summarizes the guideline relevant topic in this area. Other medical societies should stimulate the publication of similar papers from their members. The policy briefs offer starting points.
- Medical journals should ask for the consideration of S&G aspects in papers and reviews. Editors should take care that S&G are always discussed in paper that have human diseases as a topic.

Working field 2: Sex and Gender in Public Health and Prevention

In accordance with the general structure of the project, our work in public health and prevention was designed to include the largest possible number of stakeholders in the field. This appears most significant for the field of public health, which includes professionals from diverse backgrounds and fields of activity. Hence, a significant additional effort was made to identify and invite experts beyond the participants of the kick-off conference. Thematically, we focused on modifiable risk factors contributing to the majority of Non-Communicable Diseases (NCDs) such as tobacco smoking, physical inactivity and alcohol use, acknowledging their Public Health relevance. We chose to not only focus on these modifiable risk factors, but also on obesity insofar as it is both a condition and a risk factor, on mental health due to its strong relations with NCDs**,** and on work being both a protective and a risk factor ***(****References:* ***Annex 6b).***

The workshop held in Maastricht, included 22 participants covering all stakeholder areas (researchers, policy-makers, politicians, advocacy groups, funding bodies, WHO and European Commission representatives, media and communication actors). The workshop brought together the best evidence concerning sex and gender aspects of NCD risk factors taking account of intersecting factors, identified examples of effective interventions, pointed out current research gaps and formulated steps for implementation in public health practice based upon stakeholders' input. It was structured into two main blocks, (1) on sex- and gender-related evidence and (2) on implementation, where diverse experiences and expectations were summarized and analysed to produce a systematic catalogue of practical steps for the use in different public health domains. Furthermore, the process of generating this knowledge and 'doing gender medicine' was also analysed, paying particular attention to the ways in which sex and gender are redefined in this process.

Sex- and gender-related aspects of tobacco smoking, obesity, physical activity, and alcohol abuse

Reported here are key data on the sex and gender aspects of the above risk factors. Full data on epidemiology, gender sensitive interventions, remaining gaps in knowledge, data on mental health and work-related health as well as full references are reported in a position paper to be submitted to the International Journal of Public Health.

Tobacco smoking

Tobacco consumption is the single largest avoidable health risk in the European Union where, overall, 28% of the population is smoking ***(Annex 6b)***. It is the most significant cause of premature death in the EU, responsible for nearly 700,000 deaths of smokers every year and an estimated number of 19,000 non-smokers dying due to the impact of second-hand smoke. Death costs will persist for decades unless more rapid progress is made in tobacco control. Many forms of cancer, cardiovascular and respiratory diseases are associated with to tobacco use. While the EU and its member states have taken various tobacco control measures in the form of legislation, taxing and information campaigns, most initiatives miss the significance of the sex differences and gendered nature of this problem http://ec.europa.eu/health/tobacco/policy/index.en. htm).

Sex- and gender-related aspects of smoking: Key points

- More men than women smoke in all European countries except in Sweden, and there are great variations between countries and regions, with highest rates in Eastern Europe.
- There are gendered meanings and functions of smoking: Social pressure and the smoking of a significant other or a favourite movie star is a stronger predictor of smoking initiation in girls compared to boys; smoking as a symbol of masculinities for men and emancipation for women has been promoted by the tobacco industry; women are more likely to use cigarettes as a strategy to manage their weight and cope with stress and negative feelings, whereas men smoke more from habit or to enhance positive sensations.
- The intersectionality of gender-related factors, and how masculinity and femininity are layered and connected to social class, ethnicity, occupation and age factors, is an important factor to take into account. Particularly, poverty is increasingly associated with smoking, widening gaps in health inequalities across Europe.

- While overall more men are affected by health hazards of smoking, women are at significantly greater risk from the health effects of smoking than men: as compared to smoking men, smoking women have a higher risk for developing small and squamous cell lung cancer, an increased risk for cardiovascular heart disease, a more pronounced lung function reduction and more severe Chronic Obstructive Pulmonary Disease (COPD), and women have a higher overall mortality risk from light smoking.
- The coexistence of smoking and use of oral contraceptives is associated with a ten-fold increased risk of coronary heart disease and tobacco use among pregnant women is associated with pregnancy complications and decreased birth weight and infant stature.
- The benefits of smoking cessation on survival do not seem to differ between men and women although studies with the longest follow-up have mostly included men. Women are more likely to fear gain weight and to gain weight compared to men, especially young women who smoke heavily. Women may be more vulnerable for depressive symptoms at smoking cessation.
- Evidence from gender-sensitive interventions is still scarce and often inconclusive, and sex and gender have been insufficiently considered in smoking cessation research. Women seem to be less successful in quitting smoking than men interventions addressing weight gain and weight concerns show the most promising results in women; for girls, there is no evidence that school-based interventions are successful in preventing smoking. Women-specific programmes may particularly attract women who may otherwise not seek any treatment. Men are less likely to seek help for smoking cessation. There is a lack of initiatives and strategies to reach men for reducing their high smoking rates.

Obesity

The European Community recognises the increase in obesity over the last 3 decades and the threat that having over half the population and one in five children either overweight or obese may pose to its economic and social wellbeing. Obesity promotes the development and exacerbates the progression of diseases that are responsible for the largest proportion of deaths in the world, such as cardiovascular disease, diabetes and cancer. A broad spectrum of policy initiatives has been set in place to tackle the problem, acknowledging the complexity of this condition (e.g.***)***. However, most policies do not take into account sex-related differences and the gendered nature of this problem. The EU Action 2014-2020 on Childhood Obesity plan, e.g. only mentions pregnancy-related aspects and asks for attractive physical education for adolescent girls, especially those from lower socio-economic and ethnic minority backgrounds.

Sex- and gender-related aspects of obesity: Key points

- In the EU, the proportion of adults considered to be overweight or obese varied between 37.0 % and 56.7 % for women and between 51.0 % and 69.3 % for men in 2008.
- Gendered differences in body image, satisfaction and related weight control behaviours emerge around the age of 8-10, increase through adolescence, and extend into adulthood. Also, diet and food management are influenced by social processes related to men and women's perceived roles in society. These result in less weight concerns in boys and men than in girls and women; normal weight boys wanting to raise their weight and normal weight girls to diminish it; overweight boys being more likely to exercise and diet at higher BMI than girls; girls being more likely to attempt unhealthy quick-fix dieting practices.
- Diagnosis of obesity by BMI cut-off values does not directly reflect the amount of body fat, which may obliterate pathologically relevant differences between obese men and women such as predominant body fat storage regions (visceral intra-abdominal region in men, subcutaneous gluteal/femoral region in women).
- Intersectionality of gender-related factors are important: Lower socio-economic status and low educational attainment are associated with obesity, more pronounced in girls and women, and related to ethnic backgrounds. While 26% of obesity in men in the European Union (EU) can be attributed to inequalities in education status, the respective percentage for women is 50%. Social stigma with obesity is more pronounced in women.

- Weight loss services are aiming mostly at women on the background of strong societal assumptions that overweight and obesity is a female issue. Men and women show differences in the likelihood to discuss their weight at consultations with family doctors.
- Evidence from gender-sensitive interventions for weight loss and weight maintenance are still largely lacking, with key interventions studies adjusting for age and sex, reducing the ability to identify sex- and gender-related factors. A systematic review on weight loss trials point to a more pronounced weight loss in men than in women whereas a systematic review on healthy weight loss and weight maintenance found small or no differences between men and women **.** Promising results arise from a recent gender-sensitive men-only initiative targeting obese men and having a strong tie-in with physical activity ***(Annex 6b: Ref. 16-21)***.

Physical activity

Linked to obesity, physical inactivity is a further risk factor for NCDs, with prevalence rates ranging from 15 to 45% across countries of Europe ***(Annex 6b: Ref. 3, WHO database***: http://www.euro.who.int/en/search?q=nopa). Around 6-10% of all deaths from NCDs diseases worldwide are attributed to physical inactivity, being as high as 30% for ischaemic heart diseases ***(Annex 6b: Ref. 22)***. An inadequate level of physical activity (PA) and decreasing sedentary behaviour impacts negatively on physical and emotional health, while increasing activity and decreasing sedentary behaviours have positive benefits ***(Annex 6b: Ref. 23)***. Policies calling for increasing PA/reducing sedentary living have increased in recent years, and are mostly coupled with policies aiming at reducing obesity ***(Annex 6b: Ref. 3, 16, 18)***. PA is promoted particularly within disadvantaged communities. There exists quite a body of research on gender-and age-related aspects of PA, and the European Action Plan on Childhood Obesity 2014-2020 states that the needs of different target groups must be considered, giving as an example that school policies should strive to make PA more attractive to girls, especially from lower socio-economic and ethnic minority backgrounds ***(Annex 6b: Ref. 18)***. However, policies are not explicitly taking these findings into account.

Sex- and gender-related aspects of physical activity: Key points

- There is evidence of greater PA levels in males, starting at adolescence and increasing differences in adulthood and in older ages; in post-puberty, men perform better than women at physical activities requiring strength or speed; psychosocial factors contribute heavily to the explanations of gender differences in PA; gender differences have changed over time, with increasing female sports participation, although depending on type of sport.
- The social divide in sports participation is stronger among women, with those from deprived backgrounds less likely to engage.
- Perceptions and representations of PA tend to be stereotypically gendered, constructing sport and athleticism as typically male and masculine whereas girls' and women's participation is constrained by traditional notions of femininity. Women's PA is more likely to occur in a household and caregiving than in recreational and sporting contexts, having implications for the choice of measures.
- In adolescence, barriers to PA include negative school experiences, lack of role models, traditional notions of femininity and unwillingness to compromise appearance. Factors associated with post-school female drop out from PA include lack of access, safety and transportation issues, social stigma, and cost. In adults, time-pressures of work and home, competing with the desire to undertake sport are moderated by gender. Among older adults, additional barriers to PA include illness and injury, with some evidence of gender differences, e.g. fear of falling in community-living older adults is higher among women.
- Among girls, excessive PA is associated with a triad of anorexia, amenorrhea, and low bone density, leading to significant health hazards in later life, including premature osteoporosis and higher incidence of cancer risk.
- Evidence from gender-sensitive interventions: The considerable body of research on gender-related barriers of PA in males and females of different ages yielded information on which groups are hard to reach (such as those with early disengagement, teenage girls, non-sporty males at

and post-school, elderly men and women). This knowledge has been taken up for suggesting gender-tailored PA interventions. However, available effectiveness studies mostly did not address gender in a sufficient manner ***(Annex 6b: Ref. 18-32)***.

Alcohol abuse

The European Region is the world area with the highest levels of alcohol consumption and alcohol-related harm, and there are pronounced alcohol-related health inequalities between eastern and western Europe, in particular for deaths from alcohol-related injuries***)*** Alcohol abuse has a broad range of adverse health and social consequences through intoxication (drunkenness), chronic heavy consumption and alcohol dependence, including (worsening of) chronic diseases, increased risk of certain cancers, traumatic outcomes, disability, teratogenic effects, and death. Alcohol has consequences that go beyond the individual, affecting his/her family, the community and the larger social environment. The reduction of consumption and burden of disease and other social harms caused by alcohol has been set as a public health goal, acknowledging gendered aspects. However, in the objectives and action points of the European action plan to reduce the harmful use of alcohol 2012-2020, gender is not taken into account beyond the call that gynaecological services and midwifery should inform and advice pregnant women. In the extended list of evaluation indicators, a disaggregation by sex is only asked for a few (alcohol-related death rates, alcoholic use disorders, heavy episodic drinkers and underage alcohol users), and only counselling and prenatal care for pregnant women with alcohol problems is defined as an evaluation indicator ***(Annex 6b: Ref. 33-36)***.

Sex- and gender-related aspects of alcohol abuse: Key points

- There are gender differences in drinking rates: worldwide, more men are current drinkers of alcohol while fewer men are lifetime abstainers than women; men are diagnosed with alcohol use disorder five times more often than women and have a far greater rate of total burden of disease attributable to alcohol than women; harmful alcohol use is the leading factor for death in males aged 15-49 years; heavy drinking is more prevalent among more socio-economically *disadvantaged* men, and among more *advantaged* women.
- Biological differences lead to higher alcohol vulnerability in women (due to lower alcohol dehydrogenase and a higher fluid-fat ratio). More elevated alcohol concentrations may be found in women than in men following an equivalent drink, and these concentrations vary with menstrual cycle and fertility status. Women experience a more pronounced degree of non-reversible liver fibrosis if exposed to alcohol and are affected by an increased incidence of breast and ovarian cancer. There appears to be more neural-cognitive damage of binge drinking in girls compared to boys.
- Drinking is both gendered and related to age and life stage, and sex differences in drinking are mediated by gender-stereotyped beliefs: men in general drink larger quantities, more often in public and with friends, and have more irregular drinking patterns; women more often maintain a certain minimum level of inebriation most of the time, hiding the problem for many years, also because they drink more at home and are ashamed about drinking; drinking seems a means of 'performing' gender, not only in young men, but also in young women, and in adulthood; many societies hold more negative attitudes towards women's drinking than men's drinking alcohol.
- There is evidence that alcohol dependence and depression are associated in men while depression can also be a consequence of alcohol abuse.
- Alcohol abuse has been associated with increased risk of experiencing domestic violence, more frequently among women.
- Drinking alcohol during pregnancy affects the health of the foetus, increasing the risk of congenital disorders, growth retardation, and spontaneous abortions.
- Evidence from gender-sensitive interventions: There is a substantial body of knowledge on effectiveness and cost-effectiveness of interventions to reduce alcohol-related harm ***(Annex 6b: Ref. 3, 33, 37-44)***. While there is very strong evidence for the effectiveness of policies that regulate the alcohol market (e.g. taxation and managing the physical availability of alcohol, limiting hours and days of sale and raising the minimum drinking age), there is no study on their impact on men and women respectively or the evidence is displayed for different ages, but not by gender and no conclusions relate to gender aspects. Literature on interventions which is explicit on sex-and

gender-related aspects yielded some differential findings in women and men: The effect of brief alcohol interventions in primary care was only clear in men but not in women**.** Addressing male norms about masculinity helped reduce heavy drinking episodes and negative consequences from drinking in men**)** Alcohol screening, secondary prevention and low-intervention activities appeared to be effective for alcohol work place interventions in male-dominated industries**)** Recognition of different treatment needs of women had led to increased provision of gender-sensitive treatment services for women since the 1990ies and there is some evidence that gender sensitive treatment is more effective**,** but most research in this field is done in the US.

Workshop 2 outcomes:

A thorough review of available literature provided evidence that sex and gender are crucial aspects of risk factors for NCDs. The prevalence, manifestation, and association with NCDs of modifiable risk factors are mediated by sex and gender. Women and men are differently vulnerable to tobacco smoking, alcohol drinking, obesity and physical in/activity, while patterns of drinking and obesity as well as reasons for smoking and being physically inactive are gendered.

Moreover differences among women and among men are important. Risk factors for NCDs are influenced by factors intersecting with sex and gender. Gender norms are not only culturally situated, they also intersect with e.g. socio-economic positions, ethnicity, migration background, and sexuality. This intersectionality contributes to subgroups' different behavioural factors, exposure time to risk factors, levels of susceptibility, knowledge and risk perceptions, access to health care and health care seeking patterns and health systems responses (control and management).

Next to the 'classical' risk factors (tobacco smoking, alcohol ab/use, physical in/activity and obesity), the workshop2 working group addressed mental health and work related health pointing to more structural dimensions and having strong relations with NCDs. Mental disorders distribute uneven between women and men in Europe, with women being more often affected by depression- and anxiety disorders (female versus male ratio ≥ 2:1) as well as eating disorders (9:1), and men being more often affected by substance use disorders (male versus female ratio ≥ 2). Working environments and conditions too are determinants of NCDs with differences between men and women in employment status, type of occupation, assigned tasks and responsibilities, leading to different work environments that differentially affect health.

The workshop 2 working group decided to produce an evidence based position paper on sex and gender aspects of risk factors for NCDs. This manuscript is in preparation and will be submitted to the Int. J. of Public Health. Other products to inform the scientific community and policy makers are 1) an article describing defined implementation steps for gender-sensitive public health practice and 2) an article reflecting on the practice of 'doing gender medicine', in this EUGenMed project. Workshop 2 has also been keen to disseminate their findings to relevant audiences among which the EC Programme Committee for Health (Sept 2014) and the Horizon 2020 Advisory Group for SC1 (May 2015). A Session on public health and prevention was integrated into the IGM congress (see workshop1). Results were further communicated to the ready for Dialogue conference (Nov. 2015) and the Gender Summit (Nov. 2015), both in Berlin and abstracts were submitted to EUPHA 2016 and EASST 2016. Finally, results were communicated and discussed in a workshop on measuring gender variables for health, held at Stanford (US) in October 2015. The collected evidence is ready for uptake in curriculum development and textbooks.

Recommendations for funding agencies, scientific communities and policy makers

- Funding bodies should develop guidelines to make the integration of methods for sex and gender analysis a condition for funding. Those methods are available, developed by the Gendered Innovations project. Researchers should be stimulated to apply these methods in their work; methods, checklists (both GI) and trainings (by IGH) are available. A financial 'innovation' bonus should be considered. Evaluators of research should be stimulated to use the same tools to facilitate the evaluation of sex and gender analysis in a proposal.
- Exploration of methods (quantitative, qualitative and mixed methods) to conduct an intersectional analysis need to be funded. This concerns data collection, measurement instruments, and statistical methods. This is an urgent issue given the cross cultural differences across Europe.

The development of a model for sex and gender relevant health determinants and connected measurement instruments a.o. for measurable gender variables needs to be prioritised and funded.

- Preventive interventions should take account of best practice examples of community-oriented implementation and be gender sensitive. Research on impact and efficiency of such approaches and on risk factor control and management needs to be stimulated.
- Gender specific policies (whether targeted to women or men) should aim to transform gender inequities instead of accommodating or exploiting gender.
- Special consideration should be given to the development of more effective channels of communication between public health researchers/practitioners and politicians and the media since many of the relevant topics are unknown beyond the community of peers.

Working field 3: Sex Differences in Basic Biomedical Research & Preclinical Drug Development

Basic research was included into the EUGenMed project to understand how sex differences may contribute to improvements in therapy and how the impact of sex should be studied in basic research. In February 2015 the third EUGenMed workshop took place in Berlin. 24 experts were invited based on their interest and previous work in the field, as well as with the goal to form a transnational ad trans-sectoral team, representing different fields of interest, different European regions and approaches. They convened to discuss five major topics:

1. Assemble knowledge about evidence that sex and gender (S&G) play a role in major cellular functions
2. Outline underlying mechanisms like interactions between sex chromosomes and hormones and the epigenetic control of gene regulation
3. Discuss present translational approaches in sex specific medicine
4. Discuss benchmarks for high quality in S&G research and sex differences in drug development
5. Write a position paper

It was agreed that it is important to study sex specific mechanisms in a very basic, disease-independent manner since a number of mechanisms like genetic and epigenetic mechanisms, regulation of gene transcription, protein synthesis and degradation, mitochondrial and membrane function, cell death, proliferation play a role in many diseases and must be studied with broad approaches with sufficient resources to avoid duplication of efforts and redundancy and to make optimal use of the complicated and costly animal models. We therefore structured the workshop along these lines.

Genetic mechanisms for sex differences

The first reason for sex differences is obviously the difference in sex chromosomes between women and men, i.e. the presence of an XX or XY genotype. In the last years, genome wide association studies (GWAS) have analysed genetic variants on all genes and led to the identification of new therapeutic targets. However, women are heavily underrepresented in these analysis since they are costly and investigators tried to keep their cohorts as small and homogenous as possible. Erdmann and König point to the need to include women in GWAS studies.

Furthermore, the role of the X chromosome was so far neglected in GWAS. An extremely large proportion of published GWAS has focused on the analysis of the 22 autosomal chromosomes only. As a consequence, although the X chromosome constitutes 5% of the nuclear genome and underlies almost 10% of Mendelian disorders, it harbours only 15 of the 2,800 (0.5%) significant associations reported by GWAS of nearly 300 traits. Workshop participants suggested strategies to include the X chromosome in future GWAS. The inclusion of X chromosomal data might partly explain the so-called missing heritability of complex diseases, especially those with sex-specific features. ***(Annex 6c: Ref. 1-3)***

Sex differences in epigenetic modifications

Sexual dimorphisms were described for various diseases in mammals and arise due to a combination of genetic determinants as well as environmental cues which are frequently transmitted by epigenetic regulations. However, involved epigenetic processes are poorly understood. Including DNA methylation, non-coding RNAs and histone modifications, epigenetic regulation is essentially involved in X-chromosome inactivation as well as imprinting in men and rat. Another epigenetic control of gene expression is the X-chromosome inactivation that appears in females and describes the random inactivation of one of the two X-chromosomes for dose compensation. ***(Annex 6c: Ref. 4-6)***

Sex differences in the transcriptome

The limited approaches for genome-wide expression profiling of the heart under physiological conditions indicate that there are relatively few differences between the male and female transcriptome. Primarily, the few sexually-dimorphic genes in the heart of humans and mice in physiology seem to be sex chromosome-linked. Collectively, in order to unravel transcriptome variability in the heart and the underlying mechanisms, genomic diversity caused by sex needs to be considered. ***(Annex 6c: Ref. 7-9)***

Role of sex chromosomes and sex hormones

To analyse the role of sex chromosomes in animal models and to separate it from the effects of sex hormones, very sophisticated mouse models have been established. One is the four core genotype (FCG) model, with the translocation of the sex determining Sry gene to an autosome,. This allows to study interactions between sex chromosomes and hormones. Examples were presented.

Some very recent evidence suggests the involvement of the epigenome in sexual differentiation. Epigenetic marks can be acquired in utero and during lifetime and lead to long lasting DNA changes. These marks can be highly sex specific, as documented in large population studies where exposure to famine in pregnancy led to sex specific DNA methylation and phenotypes in the offsprings. ***(Annex 6c: Ref. 10)***

Sex differences in cellular functions

The group focussed on the cytopathology and analysed the role of “cell sex” (isolated cells with XX or XY chromosomes) for the susceptibility to cell death induction. Under stress conditions, estrogen rescues female cells from death, whereas it shifts cell death to apoptosis in “male cells”.

It introduced sex differences in cardiac fibrosis in animals and humans and its association with the development of myocardial hypertrophy and progression to heart failure. Female mouse hearts show significant less cardiac fibrosis compared with males under pressure overload and in the DOCA-salt model. This is strongly correlated with less activation of pro-fibrotic genes in females compared with male hearts. These findings are similar to those in clinical settings.

Mitochondria, the power houses of the cell participate in sex-specific pathologies. ERs are localized in mitochondria of a number of cell types and suggesting an action on mitochondrial DNA transcription and replication. Estrogen increases the expression of mitochondrial proteins from both nuclear and mitochondrial genomes and favours mitochondrial biogenesis, while testosterone inhibits mitochondriogenesis. ***(Annex 6c: Ref. 11-14)***

Sex differences in lipoprotein and glucose metabolism

Menopause causes a loss of musculoskeletal tissue mass and quality, thereby aggravating disease-induced sarcopenia, an impairment of muscular function. This may well contribute to the elevation in cardiovascular disease risk documented in women with diabetes. The discoveries are highly relevant for the development of novel treatment options for sarcopenia. They are specifically relevant for women with diabetes since they have been consistently characterized by lower HDL and apoAI levels. ***(Annex 6c: Ref. 15-17)***

Structure-Function of Estrogen Receptor in vivo

The goal of a French team is to understand the protective effects of estrogens on the development of atherosclerosis and type 2 diabetes in animal models. It was demonstrated that the estrogen receptor alpha (ERa), but not ERb, is absolutely necessary for most of the arterial and metabolic actions of E2. New projects involve pre-clinical approaches based on transgenic mouse models and clinical studies

in an attempt to uncouple: i) the beneficial effects of E2 (arterial, metabolic, bone) from ii) its proliferative effects on reproductive targets (that are undesired after menopause) and/or its venous pro-thrombo-embolic effects. ***(Annex 6c: Ref. 14, 18-19)***

Sex differences in the anti-inflammatory response of cells stressed by cigarette smoke

Chronic exposure to tobacco smoke is known to be a major cause of respiratory and cardiovascular diseases, as well as different kinds of cancer. In addition, cigarette smoke affects cell responsiveness and exerts a deep impact on the immune system. Interestingly, the smoking-related increase in methylation was significantly higher in male infants, for whom about 20% of smoking-related low weight at birth was attributed to DNA methylation at *IGF2* (Murphy et al, 2012). The causal role of cigarette smoking in both heart and lung diseases is well established and tobacco has been shown to affect monocyte/macrophages responsiveness. By evaluating a larger cohort of coronary artery disease patients, it was documented that effects of tobacco smoke seems to be sex-related in some chronic inflammatory diseases and this may contribute to the pathogenesis of lung cancer. ***(Annex 6c: Ref. 20-21)***

Preeclampsia and later cardiovascular disease: focus on vascular function

Up to 5-10% of women in their first pregnancy will develop preeclampsia a severe hypertensive complication in the second half of pregnancy. Preeclampsia places young women at risk for kidney, liver and heart failure, seizures and/or stroke. The most well-established relationship of pregnancy related events to later life cardiovascular disease is indeed for preeclampsia. Former preeclampsia women have ≈4 fold higher incidence of hypertension and twice the risk of ischemic heart disease (IHD), stroke and venous thromboembolism. The future risk depends on the disease severity, as women with previous severe preeclampsia delivering preterm and low-birth-weight babies have 7 fold-increases (95%CI 3.3-14.5) in death or hospitalization from IHD at ≈15 years after. Therefore, in women who develop preeclampsia, the threshold for clinical cardiovascular disease is breached during pregnancy and subsequently again later in life, as increasing age is added to the already present and/or newly acquired cardiovascular disease risk factors. In this way, adverse pregnancy outcome may reveal women at increased risk of metabolic and vascular diseases in later life. ***(Annex 6c: Ref. 22)***

Sex differences in drug development

Drug development is characterized by the fact that most research is done in male animals. However, significant differences exist in the outcomes of male and female mice in models of myocardial infarction, pressure overload and genetic cardiovascular diseases that are often not considered by the researchers. Because of the more severe phenotype, therapeutic effects in males are likely to be greater and therefore these animals are preferred by investigators. However, in the extreme, a drug may have a major effect in males and not be effective in females at all.

In addition, adequate animal models for menopause transition are lacking. Mostly, ovarectomy in young female mice is used. This eliminates all ovarian tissues and ovarian hormones, including testosterone synthesizing stroma cells, and not only ovarian follicles as it is the case in natural menopause.

It is necessary to understand the sex-specific differences in the pathophysiology and pharmacology to provide optimal treatment, which includes drug discovery, development and application. The new technical possibilities to study the “omics” including metabolomics help to select sex specific targets. Pharmacodynamic aspects should be considered more intensely in sex specific drug design. ***(Annex 6c: Ref. 23)***

Workshop 3 outcomes

The participants recognized the necessity to communicate their knowledge to a broader scientific community, to present findings at congresses, to publish summaries and to enter knowledge into guidelines. The vision is to act together with the International Society of Gender Medicine (IGM), the Canadian Heart Research Centre (CHRC) and the American Organization for the Study of Sex Differences (OSSD). S&G should be integrated in basic research projects, as in RADOX (RADical reduction of OXidative stress in cardiovascular diseases, EU ITN, FP 7, Grant no: 316738). It is recommended to funding agencies to fund projects in the fields discussed above.

The group decided to publish a review paper S&G specific data and methods in basic research. In the preparatory phase, sessions were submitted to the European Society of Cardiology (ESC) congress and a session with gender specific basic research EUGenMed topics was held at ESC in London.

Furthermore, sex differences in basic research were integrated into the IGM congress September 2015 in Berlin (www.igmcongress.com, http://genderkongress.com/). 2 oral sessions and a poster session followed on the issues discussed in the workshop.

Next steps will be participation at the "2015 APS Conference: Cardiovascular, Renal and Metabolic Diseases: Physiology and Gender" (November 17-20, 2015 in Annapolis, Maryland, USA), submission of sessions to OSSD congress 2016 and the basic research congresses of ESC 2016 and AHA.

Recommendations for funding agencies, scientific communities and policy makers

Expert discussions in the workshop and the final Roadmap conference agreed on the following recommendations for improving gender aspect in basic research and drug development in Europe:

- We recommend for funding agencies to support studies on sex differences in basic research. We identified relevant but exemplary topics which are listed above. Other topics may arise with later discussions.
- In animal studies, sex differences should be studied in systematic manner.
- Not all molecular or cellular or animal studies should be required to include sex differences (see page 38, Fig 3). Single sex experiments must be possible, however, recognition of this fact and justification should be required. Most importantly, the systematic analysis of sex differences should be stimulated and funded.
- S&G experts groups should be installed by all funding agencies to assure that S&G topics are adequately considered and studies and projects are of high quality. Qualification of experts should be evaluated by their publications in the field and by active participation in conferences.
- Biomedical societies (physiology, pharmacology, biology etc) with strong basic research components should be stimulated to include sex differences in the topics of their congresses, in their lists of keywords. We are preparing a position paper in the basic research in cardiovascular disease field that summarizes the most important directions of research in this area. Other societies should stimulate the publication of similar papers from their members.
- Medical journals should ask for the consideration of S&G aspects in papers and reviews. Editors should take care that S&G are always discussed in all papers that are dealing with animals or cells. Justification why only one sex is studied is need if such studies are submitted.

Working field 4a) Sex and Gender in Medical Education

To help to integrate sex and gender into training of medical professionals**,** the European Institute of Women's Health (EIWH) organised a workshop on 4 March 2015 in Brussels, bringing together a multidisciplinary, multi-sectorial group of about fifty experts to examine existing evidence and future challenges. Peggy Maguire, Director General of the EIWH opened the workshop and Petra Verdonk (Amsterdam, NL) and Katrín Fjeldsted (Reykjavík, IS) co-chaired the workshop. Karen Ritchie (Montpellier, FR) chaired the first panel of speakers on the best practice for integrating S&G in medical education. The second panel explored how to move forward and the opportunities to integrate S&G in medical education. Sinead Hewson (NL) facilitated a discussion with participants on next steps and the delegates collaboratively agreed on recommendations*.*

Making a gender difference. Challenges of sex and gender mainstreaming in medical education

A Dutch national project worked to integrate gender-mainstreaming (GM) in all medical curricula from 2002 to 2005. GM is a long-term strategy that aims to eliminate gender bias in existing routines for which involvement of regular actors within the organisation is required. Steps taken included the

evaluation of a local project, establishing a digital knowledge centre with education material, involving stakeholders and building political support within the schools and national bodies, screening education material and negotiating recommendations with course organisers, and evaluating the project with education directors and change agents. Successful GM in medical education is both a matter of strategy as well as how such strategy is received in medical schools. Time-consuming strategy could overcome resistance as well as dilemmas inherent in GM. Also, more female teachers than male teachers were openly accepting. However, women were situated in less visible and less powerful positions. Hence, GM is accelerated by alliances between women aiming for change and senior faculty leadership.

Integrating sex and gender in different curricula at the Medical University Innsbruck

Gender Medicine is integrated as a compulsory course in the curricula for human, dental and molecular medicine at the Medical University of Austria, namely in the third semester (Fundamentals and Terminology of Gender Medicine) and the tenth semester (Clinical Relevance of Gender Medicine) and also in the compulsory examinations (SIP1 and SIP2). Moreover, Gender Medicine is a compulsory part of the Clinical PhD programme, three semesters and a final examination. After several years, Gender Medicine is fully integrated as a "regular" compulsory subject. The University currently has approximately 200 diploma theses and about 25 PhD posters on Gender Medicine. Furthermore, Gender Medicine is fully integrated in physicians' post-graduate training since 2014. The Medical Association has issued a diploma in Gender Medicine. Finally, Gender Medicine is included in the training for all allied healthcare professions at the university.

Extension of S&G knowledge in medical education - the concept of eGender

Although S&G has been integrated into medical education curricula in a few countries, systematic implementation remains a challenge throughout Europe. Steps must be taken to help implementation. Firstly, there should be systematic, organised communication between basic researchers and teachers, because evidence-based knowledge is essential to medical expertise and high quality medical education. Secondly, a European "Teacher-Pool" by performing a shared European teacher training should be established. Thirdly, research must be developed on how should to assess the S&G aspects/content for performance. The use and further development of the "e Gender" platform would help close these gaps. This web-based platform is easily to access from everywhere in Europe and is based on a blended learning concept S&G knowledge is provided in eight medical disciplines. This platform is well suited to promote communication between basic researchers and teachers.

Curricular integration of sex and gender aspects into the new modular medical curriculum at Charité Universitätsmedizin Berlin

A new modular outcome-based, interdisciplinary medical curriculum was introduced at Charité - Universitätsmedizin Berlin in 2010. The central declared goal was to systematically integrate sex and gender aspects into the new medical curriculum in order to guarantee that future doctors have adequate knowledge, practical and communicative skills on gender differences as far as the development, diagnosis and therapy of diseases is concerned to consider gender dimensions in their research. A systematic approach and the appointment of a gender change agent can be key to successful integration of gender and sex aspects into a new medical curriculum. The change agent played a dual role. First, it identified sex and gender issues relevant to the curriculum, place them in the appropriate module session and provide counselling to module planners. Secondly, it built a network of stakeholders involved in the curricular planning process.

How communication was successfully integrated into Medical Education - can we use the same strategy for integrating S&G?

Communication has been successfully implemented in many medical education curricula in Western Europe. Things can be learned from the communication experience given the barriers encountered to achieving the acceptance of gender issues. First, contextual or political factors are helpful. Lay pressure was extremely important. Secondly, if change is to be accepted, one must consider the motivation of the medical profession, particularly the importance of communication. Thirdly, there is an important need to develop a perfect presentation at the centre of the medical training. This involves attracting the best teachers and providing the best didactic, visual design. The success of communication training in medical education, thus, has quite abstract as well as very concrete roots and has to be approached from a top down as well as a bottom up approach.

How can we address the sex and gender gaps in medical students' knowledge?

S&G differences have been proven to impact medical outcomes, so they should be incorporated into the training of doctors. There are enhancers in integrating S&G into medical curricula: the general interest because of the topic appeal; the involvement of all stakeholders; and the use of tools, which would translate theory into practice. However, there are also barriers: the conservative nature of medicine; resistance from regulatory perspective; and financing. Medical students play a large role in medical curricula development, by identifying the gaps; evaluating medical curriculum; increasing awareness; advocacy for implementation; and involvement in policy making. It is important to involve medical students to address S&G gaps in education.

How can we address the sex and gender gaps in medical professional knowledge through continuing medical education?

It is at the core of CPME's mission to promote best possible quality healthcare for every patient according to his or her needs. High quality patient care must, therefore, consider sex and gender specific requirements. At the same time, CPME has a strong policy stance on equal opportunities, relating not only to the profession itself, but to health and healthcare as a whole. As set out in the 2001 CPME Policy on Equal Opportunities, gender differences are one of the dimensions in which discrimination cannot be tolerated. In order to achieve high quality equitable healthcare, it is necessary to reflect awareness for sex and gender based patient needs in medical education and training, research, health technologies, medical ethics and the everyday patient-doctor relationship. CPME looks forward to recommendations on how to improve patient care for a healthier Europe.

Association of Medical Schools in Europa (AMSE): Standard setting and quality assurance

AMSE´s major goal is to ensure and enhance the quality and quality standards of medical education in Europe by serving as the European forum for medical schools. AMSE closely works together with the World Federation for Medical Education (WFME) and the Association of Medical Educators in Europe (AMEE). Advancing equity and social justice are among the key values of AMSE. AMSE is committed to lead innovation in medical education and to contribute to the setting of standards in medical education for good practice in GM.

How can we integrate and co-ordinate sex and gender into medical education cross-nationally across Europe?

Integrating and coordinating S&G-related elements into medical education should embrace all domains of medical education. One of the key issues in implementing gender into medical education is a correct understanding of all intersecting factors. The differences between countries, cultures and local contexts include not only educational standards but first of all knowledge and perception of gender equality with the resulting varied readiness to accept change. Identifying appropriate national and institutional change leaders should promote the collective approach with the consecutive long-lasting results. AMEE, identifies diversity, and inclusiveness as the crucial factors in contemporary medical education. AMEE is currently working on the guide on Gender in Medical Education and is willing to develop co-operation with members forming the Special Interest Group in this area.

What European policies impact medical education?

Medical education remains the remit of each individual country. Each EU Member State has its own regulatory body that accredits, regulates and evaluates medical education. However, some steps have been taken at European level. Streamlining European educational systems began with the Bologna Process in 1999, which seeks to harmonise third level educational systems in Europe by adopting a system to easily compare university degrees (1). Legislation relevant to the European medical education systems is EU Directive 2005/36/EC, which involves the mutual recognition of professional qualifications across EU Member States (2). The Directive outlines the requirements for medical undergraduate and postgraduate education as well as medical professional development. The requirements are not geared specifically towards regulating or evaluating third-level education or the contents of individual curricula.

Workshop outcomes

The lack of one pan-European regulatory situation impedes regulatory development at a European level. However, Member States are bound by EU Directive 2005/36/EC to provide some form of regulation and most collaborate in the Bologna Process. Consequently, there might be an opening to raise awareness of the issue of sex and gender and encourage coordination across borders to share best practice. The inclusion of vocabulary such as "*socio-economic realities*" and the "*social surrounding of the human beings*" in EU Directive 2005/36/EC highlights an existing awareness to combine the clinical component of medical education with social and cultural questions.

Sex and gender and diversity awareness must be included in the dialogue. Medical education in Europe involves many bodies at multiple levels, such as governments, physician associations and local universities. Although the Bologna Declaration works towards greater harmonisation of both undergraduate and graduate programmes across countries in Europe, the aim of the Declaration is for workforce mobility and comparability of degrees, not universal uniformity of curricular content.

There are different approaches to integrate sex and gender into medical education: single courses (sometimes electives) or integrated (mainstreaming throughout the curriculum) or both. Sex, gender and diversity must be included in final objectives of programmes, as part of accreditation, in quality criteria and considered by visitation committees. A multilevel approach is needed and experts much work with each other, Ministries of Health, Ministries of Education, medical schools, universities, student organisations, patient organisations and NGOs and physicians associations to integrate sex and gender into medical education and training.

Recommendations for the future for funding agencies and scientific communities

There were five main, concrete recommendations for future activities to encourage the integration of sex and gender into medical education.

- First, materials and publications on sex and gender (S&G) in medical education should be generated and widely distributed in an accessible and inclusive manner. Materials - such as policy briefings, background documents, reports and other publications - should explain the importance of integrating S&G medical in education, including best practice, existing policy and effective steps for action. These documents should be written in clear language to ensure accessibility as well as diffusion.
- Integration of sex and gender in medical education should be done in collaboration with educators and students, thereby adjusting curricula to improve its content. Students and educators should be informed of the importance of integrating sex and gender into medical education. Best practice and lessons learned from the experiences should be promoted at institutional, local and national levels. Evidence should be used to improve patient outcomes. Interactive education should be encouraged when possible.
- The communication of the importance of sex and gender in medical education must be improved in order to expand to a wide audience. Education and dissemination efforts must include a broad audience of all the key stakeholders in the medical field from research to all medical professionals to policymakers.
- Medical professionals must be educated on the importance of sex and gender in the prevention, development, diagnosis and treatment of various conditions in medical training. Medical education continues after the completion of medical school. Medical training should include education for experienced practitioners through efforts such as symposiums on sex and gender in medical education in professional conferences.
- Support must be given to EU-wide collaborative efforts and programmes that promote the integration of sex and gender into medical education and training. There are examples of the integration of sex and gender into various curricula throughout Europe. There is no European mandate in medical education, but cross-national collaboration should be encouraged. The setting up a European stakeholder group on sex and gender in medical education was suggested.

Working field 4b) Sex and Gender in Medicines Regulation

To address the sex and gender based disparities in Medicines Regulation and the underrepresentation of women in clinical trials**,** the European Institute of Women's Health (EIWH) organised a workshop on 4 March 2015 in Brussels, bringing together a multidisciplinary, multi-sectorial group of about fifty experts to examine existing evidence of regulatory practice in Europe and make recommendations how future legislation, policies, guidelines of Ethics Committees could support Sex and Gender consideration in clinical trials to improve the evidence-base for women. Ingrid Klingmann, chair of the European Forum for Good Clinical Practice (EFGCP) and Hildrun Sundseth, EIWH (Brussels, BE) co-hosted the session. References are listed in ***Annex 6d***.

Regulating Medicines in Europe

The European Medicines Agency (EMA) reviews and approves innovative medicinal products, based on the clinical trial data supplied by the applicant organisation/pharmaceutical company. This approval process is strictly defined and guided by EU legislation. The recently adopted EU Clinical Trial Regulation No 536/2014 (1) sets out the legal conditions under which clinical trials will have to be conducted in Europe in the future and includes several new provisions that will improve the inclusion of S&G in medicines regulation.

Sex and Gender in EU Regulatory Practice

Traditionally, there has been an underrepresentation of women in clinical trials. Going forward, the numbers of participants should be such that subgroup analyses are adequately powered to allow for meaningful conclusions on gender that can then be reflected in the product information. The new Clinical Trials Regulation is a major step forward in improving the evidence-base on which a medicine has been approved for different population groups, such as women and making clinical trial data more transparent. In addition, the new pharmacovigilance legislation and the 2014 Delegated Regulation on post-authorisation efficacy studies provide a firm legal basis to gather new and additional evidence where well-reasoned scientific uncertainty on efficacy exists for population subgroups including gender. All this leads to generation of new data and information to improve knowledge, which should be reflected in the publically available information on medicines for safe and effective use.

The Case of Cardiovascular disease and Women

Cardiovascular diseases are the leading causes of death in both men and women. Gender differences in the clinical presentation of cardiovascular diseases have been demonstrated, and some therapeutic options may not be equally effective and safe in men and women. Furthermore, sex differences in pharmacokinetics, pharmacodynamics and physiology may contribute to a different response to cardiovascular drugs in women when compared with men. Accordingly, preventive and therapeutic interventions should be tested in populations that fairly represent the gender distribution for each specific clinical condition or group at risk. In a project funded by the Commission, the percentage of women enrolled in clinical trials is 33%. Women are under-represented in randomised clinical trials, and the majority of therapeutic interventions are tested for safety and efficacy in male populations. Scientific societies, patients' associations and medical product industries should cooperate with European institutions, national health care authorities and regulatory agencies to promote scientific research on gender issues in cardiovascular disease medicine and a larger representation of women in trials.

Ethics Committee Guidelines

The Ethics Committee of the Medical University of Vienna has drafted Guidelines in 2004 that both genders should be included in all biomedical and behavioural research projects involving human subjects in scientifically appropriate numbers. Women of childbearing potential should not be routinely excluded from participation in clinical research, but appropriate measures to exclude potential foetal damage must be taken. Patients of both genders should be included in the same trials, if possible in numbers adequate to allow detection of clinically significant sex-related differences in drug response. If one gender is excluded, the reason must be clearly stated in the study protocol. One gender can be excluded because one of the following applies: research question is relevant to only one gender; prior evidence strongly suggests no gender difference; data exists for excluded gender; or subject selection is constrained due to purpose of the research. Cost is not an acceptable reason for exclusion (***Annex 6c, ref 1***).

Moving Forward: The New Clinical Trials Regulation

In the new regulation on clinical trials regulation, a description of the group/subgroups participating in the trial has to be given together with a justification for the gender and age allocation of subjects. Furthermore, if a specific gender or age group is excluded from the trial, the reasons have to be given. The assessors of a clinical trial application will have to have a specific expertise if the trial is designed for a specific population group, such as the new provisions to facilitate the conduct of clinical trials and to collect data in pregnant and breastfeeding women. The main features of the future EU portal and EU database under preparation by the European Medicines Agency will greatly increase the transparency and information concerning clinical trials in Europe.

Safe Use of Medicines during Pregnancy and Lactation

Most of the 5 million babies born in Europe every year have been exposed to medication(s) taken by their mothers during the pregnancy. More accurate epidemiological estimates in Europe today do not exist. Ever since the thalidomide tragedy around 1960, the issue of medicines in pregnancy has been ignored in research and public health policy. Changing the visibility and language around the issue is a first and necessary step: informed decisions around medicines and pregnancy should be the common goal. We need to increase the reporting of real-life pregnancies and their outcomes. Many mothers already use health or pregnancy apps and these should be leveraged as data source. For prescribers and dispensers, a safe harbour legal setting will reduce the reluctance to report what today is still “off label” medication use, and a standard reporting template for pregnancy will allow us to gain more knowledge from these cases. Progress on an issue as complex as this requires collaboration between all stakeholders and official EU funding support for data collection.

The Research Evidence for Integrating Sex and Gender into Clinical Studies

- Ineke Klinge (Maastricht, NL) presented an overview of the full EUGenMed project.
- Ute Seeland (Berlin, DE) presented examples of basic research findings on cardiovascular diseases and gender, including its various clinical manifestations and summarised the evidence of sex and gender differences in cardiology that should be considered for future.

Patient Perspective

- Sophie Peresson (Brussels, BE): Women with Type 1 and 2 diabetes are more vulnerable to complications, including to cardiovascular disease. There is a unique burden of diabetes affecting both woman and the unborn child. The rates of diabetes in pregnancy have increased in recent years due to rising obesity rates among the general population and due to the increasing number of pregnancies among older women. Gestational diabetes only occurs in pregnancy, when the body cannot produce sufficient extra insulin to meet the demands of pregnancy. Gestational diabetes can occur at any stage of pregnancy, but is more common in the second half of pregnancy.
- Laurène Souchet (Brussels, BE): The gender perspective is important to EPF, as they are committed to health equity and tackling discrimination. EPF collaborates closely with EIWH. EPF have raised gender issues in some of their position papers, including the position paper on clinical trials. The implementation of the Revised Clinical Trials Regulation should be monitored closely to ensure a gender balance.

Health Professional Perspective

- CPME’s activities include Regulation No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use and Regulation (EC) No 1901/2006 on medicinal products for paediatric use. CPME supports the EIWH on its work in the field of gender equity in health and will prepare a position paper on S&G and present it to the CPME Board for approval.

Examples of Good Practice

<u>Ethics Committee Guidelines of the Medical University of Vienna</u>

Ethics Committees play an important role in protecting the health and well-being of clinical trial participants. However, Ethics remains a national issue and can, therefore, not be harmonized by the EU Clinical Trial Regulation. Since a primary aim of clinical research is to provide scientific evidence

leading to improved standard of care, it is important to determine whether the intervention or therapy being studied affects women or men differently. The Ethics Committee of the Medical University of Vienna Guidelines are an example of good practice for other Ethics Committees in Europe to include women in clinical trials. (1).

Best Practice in the United States

A) *NIH Revitalization Act*: In 1993, the NIH addressed the exclusion of women from biomedical and clinical studies through the Act, which called for women and minorities to be included in all human subject research in adequate numbers to allow for valid analyses in phase III clinical trials. The NIH explicitly stated that cost was not an acceptable reason for excluding women and minorities (2).

B) *Office of Women's Health*: The FDA's Office of Women's Health protects and supports women's health through policy and science, including advocating for women participation in clinical trials and for sex, gender and sub population analysis (3, 4).

C) *FDA Drug Trial Snapshots*: The FDA Action Plan, published in 2014, sets out important steps for making clinical trial data across the demographic spectrum of sex, race/ethnicity and age more transparent and publicly available. The Action Plan asks for subgroup data to be analysed, thus ensuring the safety and effectiveness of the medicinal product in a wider population. The Snapshots provide easy to understand information at a glance: including demographic breakdown by sex, age, and ethnicity and providing efficacy and safety results sorted demographically (5).

Health Canada Guidance Document

In 2013, Health Canada issued a Guidance document to address the under representation of women in clinical trials. It states that if data from early phase trials do not indicate potential sex-related differences, it cannot be assumed that clinically relevant differences do not exist. The Guidance document recommends that the statistical section of the study protocol for Phase III trials include pre-specific plans for asserting sex related differences and includes provisions for including pregnant and breastfeeding women (6).

Workshop outcomes and further steps towards implementation

Expert discussions in two workshops and the final Roadmap conference agreed on the following recommendations for improving medicines regulation in Europe:

- Given that the scientific knowledge on sex differences is now well known and a more supportive legislative environment in Europe is about to come into force, the time has come to address remaining barriers and move from the description of sex differences to a more systematic approach of implementation into regulatory and clinical practice for the benefit of patients and, ultimately, to improve health and healthcare for all.
- The experts worked together to devise recommendations on how to best move forward from the current situation in the EU to integrate sex and gender into medicines regulation. There were six main, concrete recommendations for future activities to achieve this aim.
- Firstly, Ethics Committees should develop guidelines that require the inclusion of women in clinical research, utilising insight from good practice example from the Medical University of Vienna.
- Secondly, the European Medicines Agency (EMA) should follow the FDA Snapshot initiative by making sex-specific data more readily available and transparent.
- Thirdly, IMI-2 to address Sex & Gender and Age issues in their research programmes, bringing together, researchers, industry, EMA and other key stakeholders to analyse existing barriers for the recruitment and retention of women and older people in clinical trials and to develop a robust methodology for subgroup analysis.
- Fourthly, Rigorous sex- and age-specific Pharmacovigilance reporting should be improved.
- Fiftly, congenital anomalies are rare, and many medication exposures in pregnancy are rare, therefore European collaboration in Pharmacovigilance is essential in order to facilitate the collection of sufficient data for effective and timely Pharmacovigilance.
- Finally, the European Medicines Agency together with key stakeholder should draft dedicated guidelines on sex and gender analysis of differences in clinical trials along the lines of Health Canada.

4.1.4 Potential Impact

Interaction of sex and gender influence all aspects of innovation in science as well as medicine. Science that informs medicine, including the prevention, diagnosis, and treatment of diseases must consider the crucial impact of sex and gender, an endeavour known and widely accepted as gender medicine. The EUGenMed Project will lead to a significant innovation in European medicine by introducing sex and gender aspects into medical practice, biomedical research, drug development, medical education and medicines regulations in order to improve European citizens' - women's and men's - health and to strengthen Europe's standing in biomedicine.

A healthy population and sustainable healthcare systems are necessary for smart, sustainable and inclusive growth. Population ageing and changes in the social determinants of health have increased the coexistence of disease burdens related to health, nutrition, and infections, and the emerging epidemic of chronic and non-communicable diseases (NCDs) such as diabetes, asthma and coronary artery diseases. Chronic diseases are responsible for a large part of illness, disability and mortality in the EU for woman and men. Today, we know that one-size medicine does no longer fit all and a more targeted approach is needed. The EUGenMed work to encourage research to include Sex & Gender in protocols and design of research proposals and subsequently the wide dissemination of research results that includes these perspectives, will contribute to a fair and just society helping to reduce health inequalities and promote access to high quality healthcare for EU citizens.

EUGenMed project emphasises the need for well-educated health professionals and health workforce. If we are to improve the healthcare of all European citizens and reach the European Union's goal of achieving an increase of two healthy years for our ageing population by 2020, it is urgent to implement sex and gender training into medical education curricula.

We expected a major impact on medical societies, academia, regulatory bodies, funding agencies, industry, non-governmental organisations and government, in summary on the whole scientific and broader regulatory communities, which was achieved. It was the gathering together of representatives of the broader societal stakeholders and influencers that was the catalyst for awareness and advocating for acceptance of the importance of sex and gender.

The outcome from the EUGenMed project is now available and will contribute to other EU Innovative initiatives such as EUPATI and IMI, the Innovative partnership on Active and Healthy Ageing, Joint Action on Chronic Diseases among others.

Impact on medical societies

In clinical medicine, sex and gender (S&G) aspects were not frequently considered due to a lack of knowledge and subsequently of sex and gender related guidelines. The participants recognized the necessity to communicate their knowledge in particular to this scientific community, to present findings at congresses, to publish summaries, to present knowledge to medical societies and be included in their guidelines. As a consequence, all workshops decided to publish papers, which is the prime instrument to influence medical societies. The first paper has recently been published in the European Heart Journal ***(Annex 6a: Ref. 1)***.

- Publication: Gender in cardiovascular disease, V. Regitz-Zagrosek et al, European Heart Journal 2015, http://dx.doi.org/10.1093/eurheartj/ehv598
  This publication will have major impact on guideline committees and clinical work in Europe.
- Publication: Transdisciplinary criteria for the inclusion of sex and gender into diagnostic algorithms, Oertelt Prigione et al, in preparation
- Publication: Sex and Gender in Basic research, V Regitz-Zagrosek et al in preparation

The vision is to act together with the major cardiological societies. One of the biggest medical societies in Europe is the European Society of Cardiology. It has more than 90,000 members in 56 member states, more males than females. Its annual congresses reach about 30,000 participants every year. We continuously enforced the discussion with the European Society of Cardiology boards to include statements on sex and gender specific aspects in cardiovascular disease in women and men in its guidelines and to promote academic careers of women in cardiology. Indeed, ongoing discussion with European Society of Cardiology at very different levels were successful. In previous congresses, there was very sparse coverage of S&G aspects. However, at the most recent congress in London, eight different sessions were dedicated to S&G topics, one session planned by the EUGenMed

coordinator and two by the coordinator as a speaker. In addition, a significant number of sessions discussed S&G aspects. Discussions have also been started by the EUGenMed coordinator to install a WG on S&G at European Society of Cardiology in research and more activities to include S&G in different guidelines.

Furthermore, societies for gender research are well suited distribution channels, even though their reach out is more limited and specific. Main players are International Society of Gender Medicine (IGM), the Canadian Heart Research Centre (CHRC) and the American Organization for the Study of Sex Differences (OSSD. Sex and gender differences were integrated into the IGM congress September 2015 in Berlin (www.igmcongress.com) in 3 main sessions. A whole session with FDA participation was devoted to S&G differences in drugs. The program of the congress is attached. More than 200 scientists visited the congress.

Next steps will be participation at the "2015 APS Conference: Cardiovascular, Renal and Metabolic Diseases: Physiology and Gender" (November 17-20, 2015 in Annapolis, Maryland, USA), submission of sessions to OSSD congress 2016 and the basic research congresses of 2016 and AHA (BCVS).

In summary, we have been contributing in 2015 to 3 major congresses in clinical, basic and population health research

- European Society of Cardiology congress, London 2015
- Congress of the International Society of Gender Medicine, Sept 2015 Berlin, **(**sessions: Gender in drug development and therapy – Follow-up on EUGenMed, chairs: Karen Nieber, Vera Regitz-Zagrosek; Public Health and medical education – Follow-up on EUGenMed, chairs: Ineke Klinge, Alan White; Basic research and Cardiovascular Disease - Internal Medicine Follow up on EUGenMed, chair: Georgios Kararigas)
- "2015 APS Conference: Cardiovascular, Renal and Metabolic Diseases: Physiology and Gender" (November 17-20, 2015 in Annapolis, Maryland, USA). The EUGenMed coordinator is co-organizer of the congress. The main topic is sex in basic research.

Not only the cardiologists in the European Society of Cardiology but also doctors in other disciplines, general physicians and other medical professionals are requiring more and more information on sex and gender. Our materials will be ready to affect their daily medical practice. In Germany, a specification in gender medicine by the German Society of Gender Medicine (DGesGM e.V.) already exists *"Specialist in Gendermedicine" by DGesGM (Gendermediziner DGesGM^{R}).* The generation of policy briefs on CVD, Stroke, Diabetes, Asthma and Lung Cancer (***Annex 1***) will be instrumental to keep theses audiences informed. They will be distributed through EIWH-, GIM, IGM, EUGenMed and EUGenNet homepage.

Impact on public health research institutes and policy

Given the marked sex and gender differences in risk factor prevalence, associations with NCDs and population attributable risks, explicit gender-sensitive prevention approaches are indicated. Likewise, although a number of gender sensitive Public Health Policies have been developed and implemented in the last two decades, research on impact and efficiency of such approaches and on risk factor control and management is very scarce and there is a lack of critical discussion on the methodology of gender-sensitised interventions. The impact of our work is threefold: (1) existing evidence-based knowledge concerning sex and gender aspects of risk factors for NCDs has been assembled, (2) current gaps concerning sex and gender aspects have been identified, (3) a catalogue of practical steps (strategies) for implementation of available knowledge on the relevance of sex and gender in public health practice has been designed. This catalogue comprises the following key issues:

(1)An agreement among all participants in the workshop to consider ethical and systemic principles as elementary reasons for implementation of gender-sensitive public health

(2)The need for the inclusion of the vastest possible number of stakeholders in change and implementation processes deemed particularly relevant for public health

(3)Special consideration should be given to the development of more effective channels of communication between public health researchers/practitioners and politicians and the media since many of the relevant topics are unknown beyond the community of peers.

(4)Lessons learned from best practice examples of community-oriented implementation strategies (e.g. within the Football Fans in Training Program (Hunt et al. Lancet, 2014) should be further developed

As a result, defined implementation steps for gender-sensitive public health were developed by the group and structured in accordance with the 72 implementation steps from the taxonomy of the US ERIC (expert recommendations for implementing change) project (Powell BJ, Implementation Science; 2015). We expect that our full catalogue will be of utmost relevance to all different actors in the public health field be they researchers, educators or policymakers.

The following articles and congress presentations are in progress:

- Publication: Sex and gender aspects of risk factors for non-communicable diseases across Europe, V. Elisabeth Zemp-Stutz, Ineke Klinge et al, in preparation
- Publication: Doing gender medicine: Reflections on sex and gender in medicine and public health, Lucie Dalibert, in preparation
- Publication: Implementation steps towards gender-sensitive policy and practice, Sabine Oertelt-Prigione, in preparation
- Publication: Integrating Sex and Gender into Medical Education in Europe, the European Institute of Women's Health, in preparation
- Planning sessions at congress of the International Society for Gender Medicine in Berlin, Sept 2015 (www.igmcongress.com/)
- Submitted abstracts to Gender Summit 2015, EUPHA 2016 and EASST 2016

Impact on Academia

During the project lifetime, the **Medical University of Innsbruck** awarded an honorary doctorate to Vera Regitz-Zagrosek, recognising her achievements in gender medicine.

Charité - Universitätsmedizin Berlin recognised the relevance of gender medicine by awarding a guest professorship on this topic to project partner Ineke Klinge at the Institute for Gender in medicine.

When EUGenMed started it was clear that some European universities were willing to build curricula in gender medicine; Charité Berlin, Medical University of Innsbruck, Maastricht University, University of Vienna and Karolinska Institute had courses. Our project contributed to build structured curricula, with well-defined learning goals, contents, facts and courses. Teaching materials have been contributed by EUGenMed members and dissemination of materials was done via EUGenMed channels. The legitimation by a European group will help to introduce the qualification of "gender medicine" into medical board certificates and into continuing medical education thereby promoting similar structures in other countries.

For example, Charite has fully integrated sex and gender into the medical curriculum and has published these achievements" ***(Annex 6a: Ref. 8)***.

During the lifetime of EUGenMed, the board of doctors in Austria, Österreichische Ärztekammer (ÖÄK, www.aerztekammer.at), developed a diploma in gender medicine, closely related to the German "Gendermediziner DGesGM^{R}". Our associated expert Margarethe Hochleitner in Innsbruck was significantly involved in advocating for this degree.

Universities of Vienna, Padua, Innsbruck, Rome, Stockholm, Maastricht and Nijmegen have been in contact with our project partners and have also made great progress in establishing courses in gender medicine and to install related professorships. EUGenMed coordinator Vera Regitz-Zagrosek has been invited to present their developments based on the EUGenMed project in the US: at the gender education summit teaching conference at Mayo at October 16th 2015.

Project partners Vera Regitz-Zagrosek and Ineke Klinge have been invited to present EUGenMed at the Gender Summit *Mastering gender in research performance, contexts, and outcomes 6-7 November 2015*. Ineke Klinge was also invited to share EUGenMed insights at: Ready for Dialogue: Conference on the Gender Dimension in Science and Research Dialogue, on 5 November 2015, Berlin

As a result of the workshop on medical education, the European Institute of Women's Health (EIWH) has been working closely with organisations to integrate sex and gender into medical education across Europe. AMEE (An International Association for Medical Education) has fully supported a special report on sex and gender in medical education. Janusz Janczukowicz of AMEE and Petra Verdonk are creating a Special Interest Group Gender and Diversity. Janczukowicz is also writing paper for integrating S&G into medical education for AMEE special meeting in September with the support of the AMEE Board. Moreover, many gender and cultural diversity sessions will be included for the first time at in 2016 at AMEE's annual conference in Barcelona in 2016. The EIWH will be involved in this conference and may be joining the AMEE Gender Group.

In addition, as a follow-up to the EUGenMed workshop on medical education, the European Medical Students' Association (EMSA) has taken on the subject of S&G integration in medicine to be brought to a larger audience of students, spreading the awareness and getting them involved. The EMSA organised an entire session dedicated to this topic, occurring on the 17th September during our General Assembly, including discussing the EUGenMed Project. Kristina Mickeviciute, the EMSA Vice President for External Affair, has been active encouraging the integration of S&G into medical education and supporting the EUGenMed Project.

In more detail, the following recommendations for dissemination were agreed at the workshop on medical education.

- Generate and widely distribute accessible and inclusive materials and publications on the sex and gender in medical education.

  Materials - such as policy briefings, background documents, reports and other publications - should explain the importance of integrating S&G medical in education, including best practice, existing policy and effective steps for action. These documents should be written in clear language to ensure accessibility as well as diffusion.

- Work with educators and students to integrate sex and gender in medical education thereby adjusting curricula to improve its content.

  Inform students and educators on the importance of integrating sex and gender into medical education. Promote the diffusion of best practice and lessons learned from the experiences at institutional, local and national levels. Evidence should be used to improve patient outcomes. Interactive education should be encouraged when possible.

- Improve communication of the importance of sex and gender in medical education, expanding to a wide audience.

  Education and dissemination efforts must include a broad audience of all the key stakeholders in the medical field from research to all medical professionals to policy-makers.

- Educate medical professionals on the importance of sex and gender in the prevention, development, diagnosis and treatment of various conditions in medical training.

  Medical education continues after the completion of medical school. Medical training should include education for experienced practitioners through efforts such as symposiums on sex and gender in medical education in professional conferences.

- Support EU-wide collaborative efforts and programmes that promote the integration of sex and gender into medical education and training.

  Sex and gender has been integrated into various curricula throughout Europe. There is no European mandate in medical education, but cross-national collaboration should be encouraged. Set up a European stakeholder group on sex and gender in medical education.

In order to work towards achieving these goals, some commitments were made by various participants at the workshop. Steps towards implementation include but are not limited to:

- The Standing Committee of European Doctors (CPME) agreed to use their network to disseminate workshop findings and to launch a working group on sex and gender in medicine. The EIWH has provided information to support internal discussions and the adoption of a policy paper.

- Janusz Janczukowicz and Petra Verdonk are creating a Special Interest Group Gender and

Diversity for AMEE (An International Association For Medical Education). AMEE has supported a special report on sex and gender in medical education. Janczukowicz is also writing paper for integrating on the topic for AMEE special meeting. Moreover, many gender sessions will be included for the first time at in 2016 at AMEE's annual conference with the help of the EIWH.

- European Medical Students' Association (EMSA) committed to spreading the awareness and increasing involvement. The EMSA organised an entire session dedicated to this topic, including discussing the EUGenMed Project.

Katrín Fjeldsted, President of the Standing Committee of European Doctors (CPME) supported the findings of the Medical Education workshop and put them into practice by using their network to disseminate workshop findings. As a result CPME has launched a working group on sex and gender in medicine. The EIWH has provided information to support internal discussions and the adoption of a policy paper.

Impact on regulatory bodies

Given that the scientific knowledge on sex differences is now well known and a more supportive legislative environment in Europe is about to come into force, the time has come to address remaining barriers and move from the description of sex differences to a more systematic approach of implementation into regulatory and clinical practice for the benefit of patients and, ultimately, to improve health and healthcare for all. Expert discussions in two workshops and the final Roadmap conference agreed on the following recommendations for improving medicines regulation in Europe:

- Ethics Committees should develop guidelines that require the inclusion of women in clinical research, utilising insight from good practice example from the Medical University of Vienna.
- The European Medicines Agency (EMA) should follow the FDA Snapshot initiative by making sex-specific data more readily available and transparent.
- IMI-2 to address Sex & Gender and Age issues in their research programmes, bringing together, researchers, industry, EMA and other key stakeholders to analyse existing barriers for the recruitment and retention of women and older people in clinical trials and to develop a robust methodology for subgroup analysis.
- Rigorous sex- and age-specific pharmacovigilance reporting should be improved.
- Congenital anomalies are rare, and many medication exposures in pregnancy are rare, therefore European collaboration in pharmacovigilance is essential in order to facilitate the collection of sufficient data for effective and timely pharmacovigilance.
- The European Medicines Agency together with key stakeholder should draft dedicated guidelines on sex and gender analysis of differences in clinical trials along the lines of Health Canada.

Regulatory agencies such as the European Medicines Agency (EMA) will have to implement the new Clinical Trials Regulation by May 2016, which stipulates that women and older people people have to be included in clinical trials and any exclusion has to be justified. This will make more information available on how a medicine works in women and older people. Hildrun Sundseth, EIWH President, has presented the EUGenMed project to the European Medicines Agency's Patient and Consumer Working Party. She sits on the EU Taskforce for developing the Guidelines for summaries of clinical trials for lay persons as stipulated by the new legislation and has ensured that Sex and Age are included in the clinical trial summaries to be made publicly available on the new European Portal and clinical trials database. This will make information on how many women have been included in clinical trials transparent and publicly available. As recommended by the EUGenMed final conference, the US Snapshot idea graphic will be included in the lay person summary.

Impact on funding agencies

Horizon 2020 has three objectives for gender equality the third being integration of the gender dimension, now firmly established throughout the programme. To facilitate this objective over 100 topics in work programme 2014-15 were 'flagged' meaning that researchers were to consider if and in what sense sex and gender were relevant to the content of their research. Answers to this question were evaluated under the excellence criterion. Yet there is room for improvement. It is the mandate of the H2020 Advisory Group on Gender (chaired by partner Ineke Klinge) to provide advice to the

Commission on integrating the gender dimension in research and innovation content. In preparation of WP 16-17 the Advisory Group on Gender prepared a note: For a better integration of the Gender dimension in work programme 2016-2017. Many specific suggestions were made, among other things, real new innovative suggestions stemming from ongoing EUGenMed workshops.

During EUGenMed's lifetime an interesting development in the US took place: in 2014 the NIH issued new guidelines is to balance sex in basic and animal research as a funding criterion. A further context relevant for EUGenMed are the Canadian Institutes of Health (CIHR) guidelines on how to integrate sex and gender aspects in research issued in 2010. Applicants have to answer these compulsory questions with good arguments. Monitoring the effect of these guidelines, yielded positive effects: i.e. more proposals addressed sex and gender aspects

S&G should be integrated in basic research projects, as in RADOX (RADical reduction of OXidative stress in cardiovascular diseases, Grant no: 316738).

National funding agencies like the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) and the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) are interested in funding gender-balanced programs, but are looking for guidance on how to introduce sex and gender aspects into their research projects. We have identified a need by these agencies for structured, evidence-based sex and gender information, recommendations and best practice examples. EUGenMed has continuously worked with US groups to funding agencies.

In the Netherlands a recent development has been the compilation of a "Knowledge Agenda" by the Alliance for Gender and Health. This agenda brings existing knowledge on sex and gender aspects of many diseases together, identifies priorities for research and makes the case for implementing the existing knowledge. The Minister of Health has committed to finance a research program at ZonMW (the funding agency).

Besides The Dutch Heart Foundation has consulted both Vera Regitz-Zagrosek and Ineke Klinge on the strategic priorities for funding for 2016.

Our project has encouraged a common approach to sex and gender research. By bringing together major protagonists under EUGenMed, we have produced a consensus document in the form of a Road Map. This has improved Europe's leadership in sex and gender medicine and enhanced the leadership of European research and competitiveness in world markets. Sex and gender groups from different continents like North and South America and Canada, from different African nations and different Asian countries have shown interest in the development of gender medicine in Europe, are coming to European congresses and are ready to export the gender knowledge in the medical fields into their societies. An example is the adoption of the Gendered Innovations project in South Korea, where new case studies have been produced, adding to the worldwide relevance of gender medicine In this respect, Europe acts as a pacemaker and driving force and its strategic, exemplary innovations in gender medicine are leading the way.

Impact on industry

Industry is searching for novel concepts and strategies in drug development. Since the philosophy of "one drug and dose for all" is being replaced by targeted approaches, industry is looking for concepts to develop drugs for different target groups, for women, men, for post- and pre-menopausal women. During EUGenMed's lifetime we set up a co-operation with Bayer to develop animal models for S&G differences. The project is ongoing and hopefully will set the basis for gender research projects that could be developed together with EPFIA and IMI (Innovative Medicines Initiative). Industry is interested in learning how to develop animal models for different hormonal stages in women as well as in men, and to learn about drug development in male and female animals without doubling all efforts. Therefore, intelligent, gender-sensitive approaches do have a significant market in industry.

Clinical studies so far are not organised in a gender-balanced manner. Regulatory authorities and the big medical journals claimed repeatedly that the inclusion of women should be improved. However, industry lacks knowledge and strategies how to include adequate numbers of both genders into the respective clinical studies. EUGenMed is developing gender-balanced strategies and information or toolboxes that give advice how to achieve adequate gender-balance in medical studies.

EUROPEAN Gender Network (EUGenNet)

In order to reach out to a larger group of stakeholders we presented the EUGenMed project in September 2015 at the International congress of Gender Medicine (www.igmcongress.com) organized together with the International Society of Gender Medicine (IGM). 3 sessions were dedicated specifically to the outcomes of the EUGenMed project. More than 200 scientists from all over the world visited this event and discussed the EUGenMed findings and conclusions.

The sustainability of the EUGenMed project was also discussed at this congress of the International society of gender medicine in Berlin. Subsequently a EUROPEAN Gender Network (EUGenNet) was founded to follow the goals of EUGenMed and to disseminate its results and to continue working into the same direction. More than 71 participants already registered for active cooperation in EUGenNet ***(Annex 8: EUGenNet stakeholder list)***.

EUGenNet will act in close cooperation with International Society of Gender Medicine (IGM) and hold sessions at their congresses. It is the goal of the EUGenNet to act at the same time as an open group and as an effective communication structure. Bylaws have been proposed that shall unify these goals. Linked sections at the GIM and IGM homepage shall be dedicated to exchange within EUGenNet. Partners will interact by email and meet personally at the IGM conferences. Due to a lack of direct resources, donations will been used to pay membership fees within IGM. Regular newsletter will keep all partners informed and call them to common action, if necessary. We just used this forum to invite all partners to register as gender experts in the Horizon2020 program.

The formation of this EUROPEAN Gender Network (EUGenNet) will consolidate and give a firm foundation to the existing collaboration and give the opportunity to the diverse partnership formulated under EUGenMed to work in a very structured way on the implementation of the outcome from this project at EU- and at a national level.

EUGenNet will add to keep Europe at the forefront of innovation in biomedical S&G research, in clinical medicine, in public health, basic research, medical education and medicine regulations. Science needs to increase understanding of S&G differences and how this knowledge can be applied to the next generation of medical interventions. Our roadmap and developed materials will impact future research priorities and facilitate the integration of sex and gender in the design and process of health research and the training of future scientists, and medical professionals. In this respect, Europe continues to serve as a global leader in addressing sex and gender inequities in health.

The case for gender medicine as an independent discipline

There is an ongoing discussion how to implement research and clinical and teaching aspects of gender medicine; if such a discipline as gender medicine is needed or if gender aspects can be sufficiently covered by mentioning them in all disciplines. There is no doubt, that sex and gender aspects should be discussed and mentioned in almost all clinical disciplines (blue columns /vertical row in in figure 3). The question is, who is implementing them, who can assure research and clinical and teaching quality as well as recognition of overarching viewpoints and concepts. For these tasks, experts in gender medicine are needed.

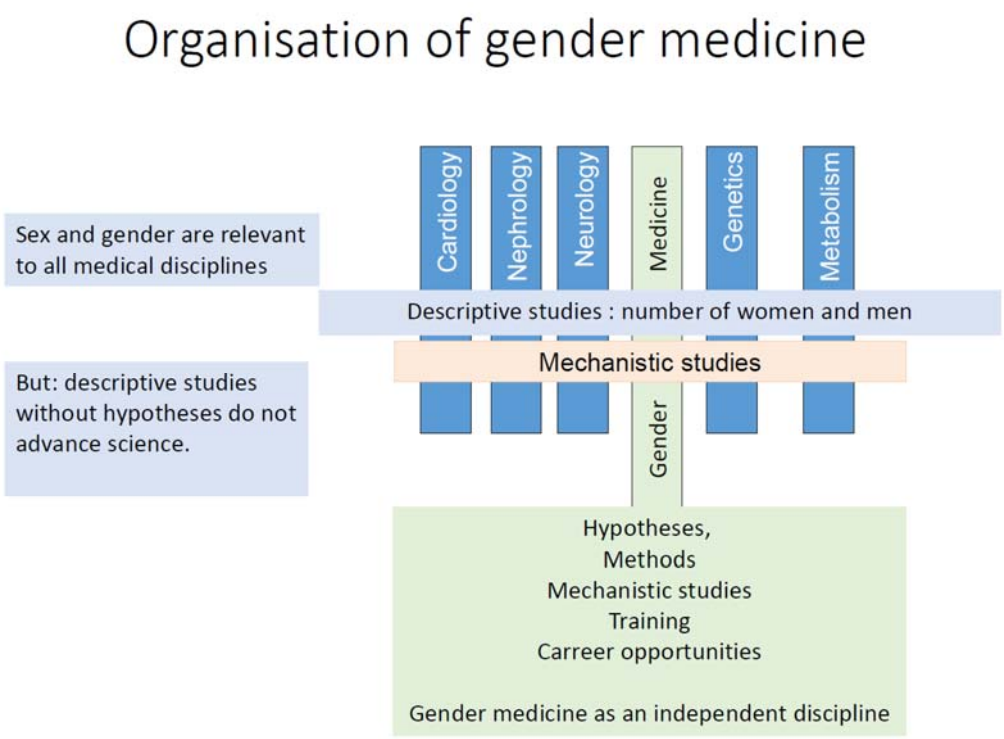

Fig 3: Gender medicine is important in all medical disciplines in a cross-sectional manner, but must also be developed as an independent discipline in order to assure mechanistic, high quality research.

Sex is a biological concept, based on mechanisms that lead to sexual disparity. These mechanisms are not specific for a discipline, e.g., cardiovascular or renal or other diseases, but they rather represent general concepts like effects of sex chromosomes or hormones. The same is true for gender. Gender roles are determined by society and education. Male or female behaviour is not specific for a group of diseases, e.g. neurological or metabolic diseases; it is rather disease independent and due to societal influences and individual response. Thus, for the study of sex and gender (S&G) overarching concepts are needed. Own hypotheses, research questions and strategies, methodological approaches and training strategies must be developed independent from disciplines. High investments in methods must be possible and rewarded. Junior scientists and advanced scientists must find career opportunities for themselves. For the formation and training of gender experts, specific structures are needed.

For these reasons, gender medicine as an independent discipline must be developed with its own institutes and resources and gender researchers must be supported to build a scientific community.

4.1.5 Address of project public website

Project website: www.eugenmed.eu

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