ARS TOSCANA
agenzia regionale di sanità

Regione Toscana

LA SALUTE DI GENERE IN TOSCANA

ABSTRACTS IN ENGLISH

Documenti ARS Toscana

numero speciale
maggio 2023

120

nell'ambito
dell'iniziativa regionale

La Toscana delle *donne*
LA RAGIONE DEL VALORE

Collana dei Documenti ARS
Direttore responsabile: Lucia Turco
Registrazione REA Camera di Commercio di Firenze N. 562138
Iscrizione Registro stampa periodica Cancelleria Tribunale di Firenze N. 5498
del 19/06/2006
ISSN stampa 1970-3244
ISSN on-line 1970-3252

La salute di genere in Toscana

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Abstracts in English

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1.1 At what stage is gender medicine today?

The World Health Organization (WHO) introduces the concept of Gender Medicine (GM) and defines it as the study of how (sex-based) biological and (gender-based) socio-economic and cultural differences influence every individual's state of health and health conditions.

GM is neither Women's Medicine nor an independent branch of medicine. Instead, it has an interdisciplinary and innovative dimension, which involves all professionals in the health care. Indeed, differences exist in the development, progression and clinical signs of conditions common to both men and women and they are also present in their response to therapeutic treatment and adverse events associated with it.

Italy was the first European country to guarantee the inclusion of 'gender' in all medical specialties, in clinical drug trials, in the development of diagnostic and therapeutic pathways, and in research, training and dissemination among all healthcare professionals and citizens. It became the first Country in the world with a law and a healthcare plan that promise the development of specificity and gender equity in health.

The Law No. 3/2018 "Delegation to the Government on clinical trials of medicines as well as provisions for the reorganization of health professions and for healthcare management at the Ministry of Health", has been approved and published in the Italian Official Gazette of January 31 2018. This was a crucial step to ensure the provision of effective "personalized therapy". On June 13 2019, the Ministry of Health formally approved a "Plan for the Application and Promotion of Gender Medicine throughout the country" (Article 3, Law No.3, 2018).

The strategic objectives and the actions planned to apply effectively a gender approach in healthcare were outlined in the Law in four focus areas:

A. Clinical pathways for prevention, diagnosis, treatment and rehabilitation
B. Research and Innovation
C. Training/Education and professional updating
D. Communication and information

On January 1 2017, the Italian National Institute of Health (ISS) established the Center for Gender-Specific Medicine, whose main task is the promotion health from a gender perspective.

Tuscany was ahead of the times as it was the first Italian region to introduce the gender element into its Social Health Plan. Indeed, in 2014, the territorial Centre of Health

and Gender Medicine was founded in Tuscany (Ministry of Health, Welfare, Social Health integration for Tuscany). The Centre follows a "networking" organizational model. Its objectives include the development of innovative solutions to access gender-based services, the promotion of gender-based integrated care and treatment pathways, and gender-based healthcare research.

In conclusion, the National Plan is undoubtedly an important outcome, but its implementation will require great commitment from healthcare professionals. Its primary purpose is to include a dimension encompassing sex-based and gender-based differences across all medical areas, which not only accounts for biological and clinical considerations, but also includes cultural and socio-psychological parameters. The final aim is to improve each individual's health through the effective delivery of more efficient personalized medicine to meet each person's real needs.

1.2. Reading data in a Gender perspective

Health equity is concerned with creating equal opportunities for men and women and non-binary people to partake in clinical trials. Until now, women and non-binary people were neglected, but their equitable representation is mandatory for safety, effectiveness, and tolerance of drugs and medical devices. The scare participation of the above population leads to a lack of knowledge (knowledge gap). Although the birth of gender medicine took place more than 30 years ago, recent surveys indicate that it is scarcely used in biomedical research and in daily practice of prevention and care. Indeed, to evaluate the gender sensitive papers, it is necessary to avoid the confusion that still exists today about the terms sex and gender, which are two independent concepts that intersect each other; therefore, it is necessary to verify the exact use of the two terms. It is also necessary to stratify the data by sex and gender, but it is not sufficient because gender requires intersectionality. Data should be obtained from work that considers sex or gender as an experimental variable.

Finally, data analysis should be done by gender-sensitive people, ready to implement the so-called "gendered data innovation".

2.1. Demographic dynamics

On January 1st 2022 the resident population in Tuscany amounts to 3,663,191 people, with 51.5% female and 48.5% male, a proportion maintained constant by years. Since 2015, the population started decreasing, after an increasing trend started

in the early 2000s; the main causes of this decrease are the falling birth rate and the slowdown in the migration flows and, since 2020, Covid-19.

In the next years, Tuscany and the whole Italy will be characterized by the aging of the population; in 2022, the proportion of population aged over 64 is 25.8% (female: 28.2%, male: 23.2%).

Until 35 years of age, male population is larger than the female one, while females overcome men after that age, especially in the eldest age groups.

The different structure of the population by age based on gender is also evident when considering the ratio between elderly people aged 65+ and young people under 15; in 2022, it is 254.9 for females and 186.9 for males.

Differences among sexes arise also in life expectancy at birth and at 65 years old; in both cases, females' is much greater than males'. In 2021, life expectancy at birth for males is 81.2 years old, for females is 85.3 and life expectancy at 65 years old is respectively 19.2 and 22.4.

Since the early 2000s until 2015, the resident foreign population in Tuscany shows an increasing trend. In 2015 it starts a stabilization, with a little contraction in Covid-19 period. Gender differences arises at the beginning of 2007, when female foreign population overcomes the male one.

2.2. Denatality

Italy and Tuscany suffer from birth rates falling; in 2021 6.8 and 6.1 children were born to 1000 inhabitants, while in 2010 they were respectively 9.5 and 8.9. However, in 2021 in Tuscany there were 0.6% more births compared to 2020, even if the number of new-borns is lower than the one in the pre-pandemic period.

Fertility reflects the ongoing falling birth rate, in 2021 with 1.25 and 1.19 mean number of children per woman in Italy and Tuscany, respectively, against 1.68 and 1.32 recorded in 1980.

The falling birth rate phenomenon is attributable in part to a structural effect of the population (there are fewer women in reproductive age now than there were in the 1960s), the slowing down of the in-migration process with the consequent aging of the foreign resident population, and social and economic factors, such as the search for women emancipation. In addition, the Covid-19 pandemic increased the falling birth rate phenomenon.

Data from the assistance birth certificate (CedAP) in Tuscany also show the increasing mean maternal age; in 2001 it was 30.8, and in 2021 it reached 32.7. The same happens with paternal age, from 34 in 2001 to 36.1 in 2021. As a biological consequence, fertility decreases when age increases for both genders.

It is estimated that fertility affects 1 in 7 couples, and it is increasing in the general population as long as common risk factors such as being overweight, smoking habits, and the decision to postpone pregnancy.

In Tuscany families' composition has changed a lot through the years: in 2020-2021 the mono-personal families are 35.7% (they were only 30.5% in 2014-2015), while couples without children decreased from 31.4% to 28.5%.

2.3. Education and Work

Despite the progress made in recent decades in terms of the presence of women in the labour market, the gender gap remains significant. The structural nodes of the gender gap can be summarised as follows: (a) Activity, employment rates remain well below those of men. The national figure is influenced by the strong backwardness of southern Italy. (b) The female condition is still very diversified and some variables such as generational affiliation, educational qualification, and the burden of caring for children and dependent elderly persons play an important role. (c) In the labour market, these differences are intertwined, leading to greater inactivity, intermittent careers, predominance of part-time contracts, segregation in economic sectors with lower wages and fewer career opportunities.

2.4. Mortality

In Tuscany during the period 2016-2018 the overall death rates in males exceeded the female correspondents in all age groups over 9 years of age, with the highest differences in the 20-24 years group (M/F ratio between rates = 3.2).

Proportionate mortality by chapter of the International Classification of Diseases or ICD also differs by gender. In 2016-2018 tumors are the first cause of death in males (33%) and second in females (24%), cardiovascular diseases are the first cause in females (37%) and second in males (31%).

Mortality from leading causes decreased from 1987 to 2018 in both genders, with some exceptions. Men die more than women do from most causes but not, for example, from dementia and Alzheimer, which is a very frequent cause in older women and increases over time.

For some diseases, the female mortality advantage narrowed from 1987 to 2018. They are the diseases whose standardized death rates decrease in males but do not decrease in females (chronic lower respiratory diseases), or even increase (lung cancer

and pancreatic cancer). These diseases share the recognized etiological role of smoking, which spread among Tuscan women about 30 years after men.

3.1. Smoking

Smoking is the leading cause of preventable death, causing more than 8 million deaths annually. The Center for Disease Control and Prevention studies show that it is not always a direct cause of death, but it contributes to the onset of diseases related mainly to the cardio-respiratory system and neoplasms. Negative effects of tobacco affect directly not only smokers, but also people exposed to second-hand smoke, which is highly harmful and has an environmental impact linked to tobacco industry. In 2022 in Italy, smokers are 12.4 million, while 93 thousand people die every year.

In Italy, and in Tuscany too, smoking habit is decreasing from years, thanks to disincentive actions promoted by Institutions aimed to reduce the spread of tobacco-related harm. Measures were adopted even to highlights the consequences of smoking on each life and on public health management, being a major cause of preventable physical harm.

Observing gender trends, we note an increase of smoking among females, in every age. Sometimes women use tobacco more frequently than men do, but they continue to smoke a greater number of cigarettes than female. Therefore, gender differences on tobacco use appear to move to a convergent direction.

3.2. Alcohol

Alcohol use behaviours affect the quality of life in terms of habits, consumption patterns and evolutions to risk drinkers and alcohol abuse. The intake of alcoholic beverages is often the cause or concomitant cause of the diseases onset and produce negative effects on psychophysical conditions, also having consequences on third parties and on relationships.

The social context, culture and religion of the drinkers affect alcohol consumption; even gender difference impact on alcohol use. Historically, in Tuscany alcohol consumption and abuse have always been higher among men. However, in last years, studies suggest an interpretation of a convergence, but still with some differences, between male and female habits.

We assist to an increase of alcohol consumption in the female population with respect to the male one, while the highest intensity of alcohol intake, the frequency

of alcohol abuse and drunkness remain higher in the male community. Considering adolescent population, there is a marked increase of alcohol abuse in young girls too, more than among adult women. In addition to gender, age remains a variable of great impact on consumption habits and pattern. In fact, adolescent people usually drink according to the Nordic model, while older people prefer the traditional Mediterranean way.

3.3. Diet/Food Habits

Food habits constitute an important area of everyday life and are affected by the interconnectedness of many factors, from biological to socio-cultural ones, as the recent pandemic period has also highlighted.

Definitely, gender is one of the variable that defines certain food choices and daily behaviours. Nutrition is a fundamental issue for well-being and health and when adopted with balanced criteria, it contributes to the definition of good physical condition and to the prevention of multiple diseases, even to reduce mortality.

Tuscan food habits tend to be healthy, but still inadequate compared to the WHO's recommendations of five fruits and vegetables servings daily

Gender differences appear in food habits from early youth and increase during the delicate period of adolescence. Girls eat better than boys, they have a good diet characterized by more vegetables, fruits and the balanced consumption of other food groups.

But the correct frequency of food groups consumption is not yet sufficient to describe the good relationship with food, topic addressed in the following chapter.

3.4. Physical activity

Physical activity, especially combined with a balanced diet, is essential to have a good health: this guarantees a good relation with food and a healthy lifestyle. Sport activity helps cardiovascular and muscular systems and psychological well-being, but its practising is not widespread throughout the population. For this reason World Health Organization (WHO) has been monitoring the frequency of physical exercise for years denouncing it insufficient in all ages.

We note gender differences in sports. They appear since first years of life and adolescence: female play fewer sports and male usually choose just 2 kind of sport, football and basketball.

We witness the reproduction of two cultural models defined by gender, where sports are considered more appropriate for males and we detect the structure of this stereotype by following the evolution of behaviours in adolescent population. Age is a drop out factor, especially for young girls, they practice less sport as they get older.

In adult population, we can hypothesize a different possibility to access sports due to the different family roles in heterosexual couples: conciliation of work, family and personal life is much more problematic among women compared to men.

Sedentary and insufficient physical activity is confirmed as a significant issue, which is prevalent among women and older people. It is important pay attention to the combination of gender and age: these two aspects could be acted upon starting from the moment of drop out that occurs from a young age.

3.5. Weight and Obesity

Obesity has doubled over the last 4 decades and it is important to stress it, because it is the cause or con-cause of lower life expectancy and a worst quality of life, as it can lead to an onset of diseases. We know that obesity has spread across all age groups of the population, including the youngest, and it has also been affected by the pandemic period and related restrictions.

Weight is one of the useful indicators to examine health status and gives some information about overall health status, although it must be linked with other dimensions related to mental and physical well-being, such as the relationship with food. This approach is particularly important in treating weight in a gender perspective, an area that shows differences between weight trends and eating behaviours.

Actually, studies show that since adolescence women have a healthier diet and remain more frequently into the "normal weight" category. Actually, they acquire more pervasive food control habits that seem to "protect" more against obesity.

On the contrary, they adopt trigger worrying habits in terms of overall well-being from a young age, with the risk of developing eating disorders.

4.1. Cardiovascular Diseases

The interest in gender health and medicine is relatively recent. In cardiology, this need arose earlier than in other fields of medical interest. The study of sex-gender differences is due to the observation of some evidence of the ineffectiveness of some therapies, of outcomes and of the manifestations of cardiovascular diseases in both

sexes. The heterogeneity in the mechanism, manifestation, prognosis and treatment response of CVD is now evident between male and female patients. However, most cardiovascular studies have traditionally focused on male subjects. For many years, cardiovascular pathologies were considered to be of exclusive male relevance. While biological sex influences disease pathophysiology, the psycho-socio-cultural construct of gender may further influence this effect. The constant overlapping of the two concepts of sex and gender has contributed to the confusion. Indeed, gender, which refers to the roles, behaviors, expressions and identities of individuals in society, is an important determinant of CV health and its consideration could help to achieve a broader understanding of the sex differences observed in CVD. Gender is a fluid construct that varies over time, place, and stage of life. Gender may interact with biological sex and other social determinants too, such as ethnicity and socioeconomic standing, to modulate cardiovascular health from conception through early childhood to adolescence and adulthood. In such a varied context, culture and information also play an important role in gender difference. Even now, women themselves are poorly aware that cardiovascular disease is the leading cause of death after menopause for their own sex [1]. Therefore, the reinterpretation of the entire cardiovascular knowledge data in terms of sex-gender difference was and actually remains a clinical and scientific need, but it still represents a cultural and social duty to improve knowledge and clinical performance and to promote preventive strategies in the general population.

4.2.1 Cancer: incidence and survival

In Tuscany about 25,000 new cases of cancer are diagnosed (excluding non-melanoma skin cancer) each year, and growing evidence shows sex-specific differences in the incidence and mortality associated with various cancers. Breast cancer is the most frequently diagnosed cancer in females (28.5% of all female cancers), while prostate cancer is the most commonly occurring cancer in men (17%). Ageing is a known risk factor in the development of cancers and there is a clear increase in cancer incidence with age. Cancer is diagnosed at higher rates in women between 30 to 50 years than in men, since breast cancer is already relatively frequent in this age group. However, incidence rates are significantly higher in males than females with increasing age. If we evaluate trends in the incidence of new diagnoses, incidence rates are relatively stable in men, with a decrease in prostate cancer and lung cancer incidence as an effect of the decrease in tobacco smoking rates, while overall cancer incidence in women is significantly increasing, due to the increased breast cancer and

lung cancer incidence, the latter as a consequence of the recent evolution in smoking habits in women.

Furthermore, incidence rates of melanoma and thyroid cancer, diseases with a good prognosis that are frequent in youngest, are increasing in both genders, while colon rectal cancer is now decreasing thanks to the introduction of organized screening programs. Moreover, with regard to survival analysis, gender is particularly important: overall, the 5-year survival rate for all cancers combined is higher in women than in men and it is increasing compared to the past.

4.2.2 Gender differences in oncology

It is traditionally assumed that men and women are equal in oncology.

As a result, sex differences in treatment effects and in the biology of non-sex-related cancers have largely been ignored in the last decades, and sex is usually not considered in decision making in oncology.

The concept of a sexual dimorphism of cancer, referring to differences in tumour biology between non-sex related cancers arising in men and women is supported by increasing evidence in various cancer types.

In general, women present higher toxicity rates for multiple anticancer drugs.

Given its clinical relevance, the European Society for Medical Oncology (ESMO) decided to address this topic and set up a Gender Medicine Task Force. The aims of this task force are to raise awareness of the presence of potential sex differences in biology and in treatment outcomes of non-sex related cancers and to assess the impact of gender on access, quality of life and long-term consequences of cancer therapies.

4.2.3 Occupational cancers

The estimate of the population attributable fraction for all cancer related to occupations generally ranges between 8 and 2%, 14-3%- for men and 2-1-% for women. The estimate for women was a controversial issue, as differences remain not only for the number of studies in which women are included, but also in presenting in-depth analyses of women, often due to the low number of women included in the studies. Furthermore, considering exposure, the different distribution of women in the production sectors compared to men can lead to different exposures and different ways in which they are exposed. Data from the Tuscany occupational register of Mesothelioma (ReNaM) and the Sinonasal Cancer (ReNaTuNS) recorded high

occupational etiological fraction cancers and the Register of occupational cancers with low etiological fraction (RenaLOCCAM) confirm these differences and the difficulty of defining exposure in women. Data from Malignant Mesothelioma Tuscany Register shows that in women the percentage of "unknown" exposures is much higher than men, considering the Tuscan Registry of Sinonasal Cancer data, among the cases for which an occupational exposure was attributed (certain, probable, possible) 77% are men and 57% women. The Registry of cancers with low etiological fraction, which is based on a different system compared to the previous ones (OCCAM Method), shows for some types of cancer increased risk in women in different economic sectors providing relevant information on cancers by gender, area and productive sectors. Several studies suggest a possible underestimation of occupational risk factors for women supported also by a lack of information on women. The data of the Tuscan occupational registers highlights the need to define exposure in women with greater depth and accuracy. It is desirable that the epidemiological research on occupational cancers take into consideration the possible gender differences and the need of specific studies in sectors where the presence of female workers is greater.

4.2.4 Organized cancer screenings: actions to ensure continuity and promote the implementation of new models

In Italy, a national law included organized screening programs for breast, cervical, and colon rectal cancers among the public health interventions that all the Regions must carry out (DPCM 12/01/2017). Tuscany has well-established screening programs for the three types of cancer from early 2000's. Target populations are 45-74 years-old women for breast, 50-69 years-old women and men for colon rectal- and 25-64 years-old women for cervical cancer screening.

As highlighted by several surveys carried on by National Centre for Screening Monitoring, the COVID-19 pandemic had a strong impact on screening services and in citizen's participation. This pattern was retrievable in several EU countries and regions and in Tuscany as well. Analyzing regional 2021 screening data in comparison with 2020 ones, we observe a good capacity of Tuscan screening programs to recover delays due to the pandemic. We also observe detailed data about invitations and test performed in the three screening programs.

As recommended by the European Council recommendations, new insights about the performance of FIT test from a gender perspective are discussed, with the highlighting of future perspective about new screenings (for gastric, prostate and lung cancer).

4.3.1. Gender difference in the risk of hospitalizations for cardiovascular complications in people with diabetes: the data of ARS databases

Gender difference in people with diabetes at risk of atherosclerotic cardiovascular events (CVE) has been the object of several studies carried out in ARS, mostly linking regional registries hospitalizations with MACRO: a database including people with diabetes resident in Tuscany, mainly identified by administrative data. From these studies, while men have a higher absolute risk of hospitalizations for atherosclerotic CVE, the excess risk associated with diabetes of these complications is constantly higher among women. This is true for heart failure, stroke either first-ever or recurrent, as well as for myocardial infarction. All studies have shown that the 'risk window' for such a greater relative risk of women, as compared to men, opens around the years of menopause and extends until more elderly age strata. In addition, the hospitalizations due to the diabetic foot (a complication that is extremely more prevalent among men), are associated with a greater risk of mortality and of incidence of CVE among women, especially when diabetic foot disease has a mainly vascular origin. In conclusion:

a. diabetes significantly increases the risk of cardiovascular complications and mortality in both sexes, with males having a higher absolute risk of cardiovascular complications,
b. The excess risk of cardiovascular complications (heart failure, ischemic stroke, myocardial infarction) in association with diabetes is greatest among postmenopausal women,
c. In diabetic foot, a complication most common in men, women have a greater relative risk of cardiovascular complications or of all-cause mortality, especially if the diabetic foot disease is secondary to a vascular damage.

These deductions arise from the studies concerning epidemiological review of ARS databases focused on gender differences in cardiovascular complications after diabetes, as published in the last decade.

4.3.2 Osteoporosis

Osteoporosis is a chronic, multifactorial, systemic disease characterized by a reduction in bone mass and deterioration of bone microarchitecture leading to poor quality and decreased resistance of skeletal tissue associated with an increased fracture risk. With respect to the majority of chronic diseases, where the reference standard is the male population and the characteristics of female population are described

as deviations from the male norm, the paradigms for diagnosis and treatment in osteoporosis have been developed for women. The WHO densitometric definition of osteoporosis itself (i.e. bone mineral density, BMD, of 2.5 standard deviations or more below the mean peak bone mass – average of young, healthy adults - as measured by dual-energy x-rays absorptiometry) has been developed and validated for postmenopausal women. Nonetheless, osteoporosis may also affect men. Although BMD is a major determinant for fracture risk, there is no consensus definition for osteoporosis threshold in male subjects. In clinical practice, the WHO densitometric criteria used for postmenopausal women have been applied to men. While oestrogen deficiency represents the major cause for osteoporosis in women, the majority of male osteoporosis is considered to have a secondary cause, such as hypogonadism or corticosteroid therapy. One in three women and one in five men will experience an osteoporotic fracture. Fragility fractures are major causes of increased morbidity and mortality, especially in the elderly. Indeed, mortality rates for fragility fractures are comparable to those of stroke and breast cancer. For this reason, WHO considers osteoporosis second to cardiovascular diseases in terms of critical public health issue.

Osteoporosis is a disease that affects more than 75 million people in Europe, Japan and the United States, and causes each year more than 2.3 million fractures in Europe and the United States. In life course, about 40% of the population suffers for ostehoporosis fracture growing parallel to the increase in expectation life expectancy of the population.

According to Istat Multiscopo survey, in Tuscany about 14% of the general female population in declare to be affected by osteoporosis, compared to 2% of males. The prevalence increases progressively with age, in particular for women after age 65, reaching 40% of female population. From 2002 to 2022 in Tuscany about 175,000 hip fractures were related to about 168,000 cases of osteoporosis.

The majority of hip fractures occurred in women over the age of 75, with the incidence having progressively increased over the years. However, the incidence of hip fractures is markedly increased in men over 75 years of age.

Mortality within the year after the fracture is 32.2% for females and 18.2% for males.

4.3.3 Gender related health-urinary incontinence

Definition and classification - The definition of Urinary incontinence (UI) is any involuntary loss of urine. It can be mainly classified as stress, urgency or mixed UI. The overactive bladder syndrome (OAB) is a particular condition characterized by

urgency, with or without UI, usually frequent and nocturnal, in absence of urinary tract infections and other obvious etiology.

Epidemiology - UI is a frequent clinical condition related to age increasing. This includes all ages, with a prevalence of people of over 65 years. The World Health Organization estimates that UI affects 200 million of people. In Italy, UI interests at least 5 million of persons (in particular females).

Pathophysiology - Peculiar risk factors for women are age, pregnancy and labor; likewise, obesity, diabetes, smoking, and neurological conditions could play a crucial role. Risk factors for men are similar, with special reference to iatrogenic cause (e.g. stress urinary incontinence post radical prostatectomy)

Diagnosis - Today UI and pelvic floor dysfunction request collaboration between specialized professionals (gynaecologist, urologist, urogynaecologist colon-proctologist, physiatrician, and neurologist). Communication between general medicine specialized doctors and people affected by incontinence is fundamental. A good anamnesis is the first element for clinical diagnosis. Physical examination and second level (imaging, urodynamic test) exams are crucial for a correct classification.

Therapy - UI management could be conservative with also lifestyle changes, pharmacological and surgical.

Costs and social impact . Direct and indirect costs of UI are considerable. In Italy, the National Health pays more than 2 milliard of euros for UI and its management per year. At the same time, the social and psychological impact has important repercussions on one's family, social and sexual lifestyle, resulting in changing who is affected by it.

4.4. Quality of life, pathologies of elderly and gender

Gender differences in health appear from birth and are associated to life expectancy and health aging of men and women. The Tuscan data confirm the literature evidence regarding gender differences among the elderly. Women live longer, but with disease and disability. The life expectancy at 65 years is 22.4 year for women and 19.2 years for men, but life expectancy in good health is 8.1 years among women and 9.4 years among men. Among men, the higher incidence of cardiovascular diseases and cancer, associated with poor healthy lifestyle habits (tobacco smoke and alcohol in primis) contribute to increase premature mortality. Women live more years with neurodegenerative and rheumatic diseases and they suffer falls and fractures more frequently (associated with a higher frequency of underweight people). They incur disability too, with a higher prevalence of women take in care in residential health

structures. Among women, we must also add to chronic pathologies and disability a greater risk of depression, due to more frequent conditions of disease and loneliness in last life years compared to men. Living with diseases can be seen as a result of the effectiveness of the health service to delay death, but it is necessary to invest more in primary prevention programmes, starting from adulthood, and active ageing to delay the onset of the disease as much as possible and add healthy years of life.

4.5. Rare diseases

Rare diseases (RDs) include a heterogeneous group of clinical conditions, which collectively represent a major public health issue globally, while individually affect a small number of subjects. In the European Union, the definition of RD is any chronically debilitating or life-threatening condition affecting fewer than 5 in 10,000 individuals. In most cases, RDs are genetic conditions classified from serious to very serious that have no definitive cure and can lead to severe consequences.

A population-based registry represents an effective tool for the production of epidemiological indicators linked to patients with RDs living in a defined geographical region. This report shows any gender difference on survival, hospital burden and drug use in patients with RDs living in Tuscany, using a multi-system approach based on the integration of information collected in the Tuscan Rare Disease Registry (RTMR) with data obtained from regional healthcare administrative databases.

Longer survival was observed in females than in males in the groups of endocrine diseases (97.1% vs 92.7%), central and peripheral and central nervous system disorders (69.4% vs 66.4%), respiratory system diseases (66.8% vs 47.6%), diseases of the skin and subcutaneous tissue (75.2% vs 66.7%), and diseases of the musculoskeletal system and connective tissue (78.0 % vs 71.2%).

The hospitalization profile appears substantially similar in females and males. The proportion of female inpatients respect to males was higher in the groups of metabolic (46.3% vs 40.4%) and visual system diseases (10.8 % vs 7.0%).

Overall, the prevalence of drug use was significantly higher in females than in males (87.7% vs 82.6%), particularly among patients aged between 20 and 69 years (89.2% vs 81.4%). Conversely, a higher prevalence rate was observed in males (74.8 vs 69.4%) in the 0-14 age group.

4.6.1.1. COVID-19: infection trends and impact on health

There is evidence in the literature regarding the association between gender and the risk of infection and the development of severe Covid-19 or death.

In Tuscany, the cumulative incidence rate of infections is 45.6% (2020-2022 period). Among females, the incidence rate is 48.4%, among males it is 43.7%. Male mortality is almost double that of females: the cumulative age-standardized mortality rate is equal to 424 deaths per 100,000 males and 227 per 100,000 females, the ratio between the two rates is equal to 1.9. Therefore, the virus lethality is associated with gender. Among males 79 infected per 10,000 died, among females 45 per 10,000, confirming what observed globally for the consequences of contagion: males more frequently have severe and lethal symptoms for their health.

In Tuscany the hospitalization rate standardized by age is 15.5 per 1,000 males and 10.5 per 1,000 females: males have a 48% higher risk of being hospitalised. The 14.2% of hospitalized males had at least one day in the intensive care unit, against 7.9% among females. Compared to females, hospitalized males have higher prevalence for preview diagnoses of diabetes, cardiovascular and cerebrovascular diseases, chronic obstructive pulmonary disease and cancer. After adjusting the comparison of in-hospital mortality by age and comorbidity, there is still a higher risk among males. The adjusted relative risk of death (males vs females) is 1.36 (1.31-1.42).

Our analyses are limited by the lack of information on other known risk factors, such as obesity or smoking and alcohol consumption. Furthermore, our databases do not allow to evaluating the effect of other biological and clinical factors: the role of sex hormones and the ACE2 protein in mediating the immune response and the greater risk, for males, to develop a higher cytokine response. Some studies seem to suggest that a low level of testosterone concentration, typical of elderly men, is one of the determinants of the observed differences. Contextually, another retrospective study demonstrated that increased estradiol to low testosterone ratio is associated with disease severity, level of inflammation, and lethality in males, but not in females, suggesting that sex hormone metabolism disorder could represent a hallmark of the male population. Clinical studies will therefore be necessary to collect biological samples from patients and to measure the association between gender and Covid-19 in our region, where our results are anyway comparable to the national and worldwide scenario.

4.6.1.2. COVID-19 and pregnancy

Firstly described in December 2019 as responsible for severe acute respiratory syndrome (SARS) and then after named Coronavirus disease, SARS-CoV-2 rapidly spread all over the world.

On 12th March 2020, the World Health Organitation (WHO) declared the disease a pandemic.

COVID -19 may be responsible for a spectrum of respiratory symptoms, ranging from a common cold up to a severe pneumonia, acute lung injury (acute respiratory distress syndrome ARDS) and death.

Pregnancy significantly affects the physiology of the respiratory system, reducing the residual volume and increasing the respiratory resistance, besides changes on cardiovascular and immune systems. All of these changes make pregnant women at increased risk of SARS-CoV-2 infection and complications.

Since the beginning of the pandemic, one of the main questions is whether the virus is able to cross the placenta and cause fetal-neonatal infection. Now we know that the virus transplacental transmission appears to be quite rare and SARS-CoV-2 infection is not associated with high levels of viremia.

During the pandemic, the Italian Obstetric Surveillance System (Itoss) task force aimed to trace every woman suffering from SARS-CoV-2 and hospitalized until June 2021, in order to collect information and data on the disease, the way of delivery and the maternal and newborn outcomes.

3306 women with SARS-CoV-2 infection confirmed within 7 days of hospitalization were included in the enrollment period (February 2020-March 2021) and only 12.8% and 3.3% of them had pneumonia and needed ventilator support or access to intensive care unit (ICU) respectively, while 64.3% of them were asymptomatic.

Due to worldwide multiple efforts, safe and effective vaccines have been distributed in Europe and Italy less than one year after the pandemic.

In January 2021 Itoss published the first vaccine recommendations during pregnancy, (recommending the vaccination) only for high-risk categories of pregnant women. The latest recommendation was published on October 2022, advising for a complete vaccination cycle, including the booster doses (third and fourth dose) at any gestational age.

Almost three years after the start of the pandemic, in spite of the presence of vaccines and of the less virulent variants, our clinical practice is still strongly affected by the presence of the virus.

All the efforts and strategies have always taken into account the safety of the mother-newborn dyad, aiming to gain the best outcomes in terms of both body and mental health and pursuing the family bonding since the first minutes after birth.

4.6.1.3. Chronic disease management and the impact of the pandemic

The World Health Organization (WHO) defines Gender Medicine, or rather Gender-specific Medicine, the study of how (sex-based) biological and (gender-based) socioeconomic and cultural differences influence people's health. A growing amount of epidemiological, clinical and experimental data show significant differences between men and women with respect to the development and progression of common conditions, to adverse events associated with therapeutic treatments, to the response to such treatments and to lifestyles. In addition to the social disadvantage with respect to men, women are inclined to get sick more often and take more medications; they are also more likely to experience adverse reactions. From this point of view, government programmatic actions must aim to the promotion of equality and equity between women and men, even in health matters. In this short paper, we want to show any gender differences in the care pathway of Tuscan patients affected from chronic diseases and how much the impact of the pandemic has accentuated gender inequalities in the use of local health services. To summarize, we look at just three diseases: diabetes, Chronic Obstructive Pulmonary Disease (COPD), Chronic Inflammatory Bowel Disease (IBDs). For each one, we calculated a representative process indicator, an outcome and an expenditure indicator in the pre-pandemic period, to show possible gender differences in the care-therapeutic pathway. In order to assess the impact of the pandemic on the management of the diagnostic-therapeutic-care pathway, the percentage changes in the values of the process, outcome and expenditure indicators observed during the pandemic period and those observed in the previous period (year 2020 vs year 2019) were calculated with stratifying for gender.

The Regional Health Agency of Tuscany (ARS) implemented a system for the identification of prevalent cases of the main chronic diseases using administrative data. Estimates of patients affected by the main chronic diseases and process, outcome and expenditure indicators are available on the MaCro portal. These indicators are useful to monitor the treatment pathways of the disease (https://www.ars.toscana.it/banche-dati/MACRO). What do the results show us? In 2019, diabetes is more frequent among men than among women, in all age classes, except for the youngest age group, where a higher prevalence is observed in women. The Guideline Composite Indicator (monitoring of glycated haemoglobin, lipid profile, microalbuminuria, creatinine and ocular fundus) is higher in men than in women, showing differences in the quality of care between genders. The difference is particularly high in the youngest and oldest age groups. The rate of access to the emergency room is higher in men than in women in all age groups, except the youngest; this is probably due to more frequent complications in men. Per capita expenditure for district care is

higher in men than in women in all age groups. The pandemic caused a major reduction in the process indicator among women than among men, as well as in access to emergency room and in the per capita spending on territorial assistance. In 2019, COPD is more frequent among men than among women, and this difference is more evident among the elderly. In 2019, the percentage of COPD patients who performed at least one spirometry was higher in men than in women. The emergency room admission rate for patients with COPD is higher for men in all age groups. Similarly, the expenditure for district care per capita also shows higher values for men, in all age groups. Comparing 2020 with 2019, the overall impact of the pandemic produces a greater reduction of the process indicator in women. The rate of access to the emergency room and the per capita expenditure for district care decrease more significantly in women. In 2019, IBDs are more frequent among men than among women, in all age groups. The percentage of IBDs patients who performed at least one gastroenterology visit decreases as age increases and has higher values in men. The rate of access to the emergency room increases with age, and is higher in men with the exception of 16-44 years old. Per capita expenditure for district care is higher in men than in women, especially in the elderly. The pandemic caused a major reduction among men than among women in the process indicator, as well as in access to emergency room. The per capita expenditure for district care decrease more significantly in women.

4.6.1.4 The psychological and psychosocial well-being of healthcare professionals in the University Hospital of Careggi during the COVID-19 emergency: results of the first survey, initiatives to support operators and future developments

We developed this study as part of the activities of the Regional Reference Center on Relational Criticalities (RCRC), a team of psychologists and psychiatrists who belong to the Departmental Operating Structure for Clinic and Organizations, Careggi University Hospital of Florence. RCRC is part of Careggi Hospital Management staff and is involved in the Clinical Government of Tuscany Region, Italy (DGR n.73 / 2018). Since its foundation in 2007 (DGR n.356/2007), the CRCR deals with the organizational well-being of Hospitals and structures of the Regional Health System, promoting the psychological well-being of health care professionals, through tools such as research, planning, consultancy and training.

It is within this mandate that, in order to better understand what actions the Careggi Hospital should have implemented to support its health care professionals

in such a complex moment such as the COVID-19 pandemic, both in the short and in the long term, we decided to investigate which individual or context-related factors could intervene in determining the response of health care professionals in terms of stress, anxiety, depression and general well-being.

4.6.2 HIV/AIDS

New diagnoses of Hiv infection notified in Tuscany were stable from 2009 to 2016.

In recent years, particularly in 2020 and 2021, numbers are decreasing: 154 cases (rate: 4.2 per 100,000 residents) in 2020, down 14% from 2019, when there were 180 cases and down 56% from 2016 when there were 351 cases; 148 cases in 2021 (rate: 4.0 per 100,000 residents) down another 4% from 2020.

76.8% of cases are male (ratio male/female: 3.3:1), with an incidence rate of 6.5 per 100.000 residents, against an incidence rate of 1.8 per 100.000 in women.

The majority of HIV+ has to be ascribe to sexual risk behaviours. Heterosexual intercourse are the most frequent way of infection in women (87.1%). In males, the infection is both homosexual (MSM: men who have sex with men) and heterosexual: 51.7% and 36.6% respectively.

About the reasons of Hiv testing, 61.8% of patients has the test at the moment of the diagnostic hypothesis of an HIV related pathology, while only 33.6% of patients has the test spontaneously because of perception of a risk behaviour. Again, this observation underlines how the attitude of people towards HIV has dramatically changed, no more perceiving the infection as a real danger for self- health and life.

Besides these first two reasons of testing, women have test also because of a gynaecological consultation during pregnancy (15%). In fact, Hiv screeening is part of the expected program of exams during pregnancy.

Often the awareness of Hiv + overlaps with the diagnosis of Aids, because of the presence of an Aids defining opportunistic infection or neoplasia at the moment of the first medical consultation. This worrying delay in diagnosis, related to the poor knowledge of the issue and of risk behaviours, leads to the observed spread of the infection by sexual transmission, particularly in heterosexual population.

Hiv acquisition risk is modified by sex hormones and vaginal microbiome, with the latter acting through both inflammation and local metabolism of pre-exposure prophylaxis drugs. Female sex associates with enhanced risk for non-AIDS morbidities, suggesting different inflammatory profiles in men and women.

4.6.3 Notifiable infectious diseases

The differences observed between males' and females' health are mainly attributable to biological and socio-cultural factors. Among these, according to a gender approach, age, comorbidities, genetic predispositions, geographic distribution of pathogens and lifestyles are just some of the main determinants that have an impact on health.

On the one hand, biological aspects influence susceptibility to infection, pathophysiology, immune response, clinical presentation, disease severity, response to treatment, and vaccination . On the other hand, socio-cultural aspects, and in particular behaviours, are able to influence both the risk factors for health and the exposure to infections, because of their being often so profoundly different in the two genders. Females have a stronger immune system than males, which is able to provide them greater protection against the attacks of pathogens; indeed male sex (human and animal) is more likely to develop infectious diseases than the female one.

Although scientific evidence suggests that gender differences have an important impact on the transmission, course and outcome of some infectious diseases, most surveillance systems have not yet adapted to respond this need.

Disaggregated data by gender are rarely published among the information reported, just as information relating to pregnancy status and other characteristics associated with women's reproductive factors are sporadically collected and disseminated. This limits the possibility to understand the gender dynamics of the disease, to identify vulnerable groups and to develop effective responses.

The main indicators referring to infectious disease cases reported in Tuscany for the most interesting pathologies (whose data recorded on digital support are available) are presented below. Specifically, the number of cases notified to the reporting system in the last five-year (period 2017-2021) has been compared with those relating to the previous five-year (period 2012-2016). Mortality for the same pathogens (period 2012-2018) was also analysed with data from the Regional Mortality Register.

In Tuscany, the proportion for most infectious diseases is higher for males than for females. In the last five-year period (2017-2021), the differences are mainly marked for Tuberculosis and Legionellosis, both with percentages close to 68% for males, Listeriosis (63%), Cutaneous leishmaniasis (87.5%), Visceral leishmaniasis (75%), Acute hepatitis A (72.5%), Acute hepatitis B (76.3%), Acute hepatitis C (73.1%) and Haemophilus influenzae (72.2%).

A statistical significance of the results between the two genders has been recorded in the above said diseases, except for Haemophilus influenza. These discrepancies are not confirmed in the previous five-year period 2012-2016 for Visceral leishmaniasis, Listeriosis, Acute hepatitis A and Haemophilus influenzae, pathogens for which

aligned values are observed in the two genders, thus suggesting more appropriate cautions in their overall assessment in a gender perspective.

On the contrary, during 2017-2021 diseases that reveal the greatest percentage, differences in favour of females are Tetanus, Non-tuberculous mycobacteriosis and Rickettsiosis, but this prevalence is confirmed only for Tetanus in the previous five-year period.

Based on deaths recorded in Tuscany in the period 2012-2018, the small numbers of deaths caused by most infectious diseases did not lead to statistically significant results. Therefore, these results were not commented on.

Conversely, statistically significant results have been found for Tuberculosis and Legionellosis, both showing higher mortality levels in men than in women. Particularly, the proportions by gender were 60.9% males against 39.1% females for Tuberculosis, with mortality rates of approximately 0.5 per 100,000 inhab. for males and 0.3 per 100,000 inhab. for females.

Instead, the proportions were 66% males against 34% females for Legionellosis, with rates generally between 0.2-0.3 per 100,000 inhab. for males and 0.1-0.2 per 100,000 inhab. for females.

In summary, regarding the majority of infectious diseases - especially the bacterial ones - in Tuscany a significantly higher number of notified cases were found in males than in females, with significantly higher values among cases of Tuberculosis, Legionellosis, Leishmaniasis cutaneous, acute hepatitis B, acute hepatitis C.

Instead, analysing the mortality of infectious diseases from a gender perspective, the small number of deaths allow assessments only for Tuberculosis and Legionellosis, where for both deaths referring to males are significantly higher than those to females are.

4.6.4 Sexually Transmitted Diseases

According to the scientific publication of the World Health Organization (WHO), the spread of sexually transmitted infections (STIs) is very elevated in the world, with 376 million new cases every year.

With 172 million new diagnoses each year, Chlamydia trachomatis (Ct) infection is confirmed as the most frequently detected STI of bacterial origin in the world, followed by Neisseria gonhorroeae (86.9 million new cases each year) and Treponema pallidum (syphilis), with 6.3 million new cases each year.

The lack of knowledge on the subject of STIs, the occasional use or non-use of condoms and the number of sexual partners are some of the main sources of risk

capable of increasing the probability of contracting a sexual infection. Although these factors may be considered non-specific, much of the literature identifies certain subgroups of the population as being at "greater risk", including: females, adolescents and male homosexuals.

Despite the widespread diffusion of these infections, the notification and monitoring systems are not always exhaustive. In Italy, where STI surveillance has been active since the early 1990s, a monitoring system based on data from local clinical centers (sentinel centres) and microbiology laboratories has been activated to mend the underestimation of notified cases. The aforementioned survey shows that, in 2020 in Italy, the main diagnosed infections were confirmed as anogenital warts (Hpv viral infections) and bacterial infections from treponema pallidum, Ct and Ng. In both genders, the most represented age group continues to be between 25 and 44 years (60.9% of reports), while greater differences are observed in the more extreme age groups. Women appear to be more affected by STIs already at a younger age (15-24 years), with as many as 25.3% of reports compared to 12.1% observed among men (average value). On the contrary, among the over45s, men are most involved with an average value of 26.9% compared to 16.5% observed among women.

The broad interest of young people is also confirmed by the survey Epidemiology of Determinants of Road Accidents in Tuscany (Edit), which continues to detect in 2022 a low use of condoms in the 14-19 age group (63.6% declare having used it during the last sexual intercourse), a value which drops to 56.5% in the female gender (males: 70.6%).

4.7 Mental Health

When we speak about mental health disorders, there are both biological and social aspects capable of producing marked gender differences during certain phases of life.

Through the analysis of the distribution of mental disorders in the general population living in Tuscany, we observe a greater interest in the female sex, both in young people and adults. The Tuscan Edit 2022 study found a high level of distress in 52.7% of females (14-19 age group), compared to 20.8% of males, as well as in the analysis of eating disorders (males: 18.6% vs. females: 50.5%).

In 2020 the study carried out in Tuscany and focused on the general population, but particularly on the adult one, recorded a lifetime prevalence of at least one mental disorder equal to 28.5%, with a difference between the two sexes of ten percentage points (males: 23.3% vs. females: 33.2%).

Data referring to the population who had access to the Regional Health Service for a mental health problem show that males are more interested in disorders, with onset

in early childhood and in local services (males: 294.7 vs. females: 205.1 per 10,000 residents) and in hospitalization (males: 75.3 vs. females: 60.9 per 10,000 residents). This difference is not confirmed in adulthood, where both territorial and hospital prevalence don't show significant differences, even if females reveal greater adherence to treatment with higher values in territorial care (males: 70 vs. females: 80.1 females per 100,000 residents with at least 4 performances in the year).

Pharmacological treatment also appears in line with this result; where the prevalence of use in the female gender is double than that of males (females 10.7% vs. males 5.7%), with a stable trend over time.

The crueler suicide methods adopted by males makes this gender more exposed to mortality from this cause (males: 12.4 vs. females 3.6 per 100,000 residents).

4.8 Illegal substances and gambling

The analysis of psychotropic substances consumption shows that the number of people using substances increased from 226 million in 2010 and to 284 million in 2020. This spread is also due to a significant increase in the global population. The phenomenon has always been characterised by meaningful gender differences. It mainly affects men, as confirmed in the World Drug report 2022. However, the last edition of EDIT 2022 study shows a decrease in consumption of psychotropic substances in Tuscan adolescent population, with some differences among boys and girls related also to the choice of substances.

Next to psychotropic substances consumption, gambling disorder is considered a pathological addiction by the Diagnostic and Statistical Manual of Mental Disorders, which recognizes it as a problem that interferes with different areas of life, family and relationships, work and study. As such, ludopathy impairs the mental and physical well-being of those affected and is often linked to other psychiatric conditions. The prevalence of gambling mainly concerns men, also in the adolescent population of Tuscany: the analysis registers a decrease and shows a prevalence among boys, especially on the Lie/Bet Questionnaire, while the indicator of ludopathy risk with a value 4 times is higher in male habits.

4.9.1 Road accidents

According to the World Health Organization (WHO), between 20 and 50 million people are injured in road accidents every year, with a significant portion suffering from disabilities and about 1.3 million dying. The economic cost of road accidents

is significant, with expenses for medical care and loss of work from those involved in severe accidents amounting to about 3% of each country's Gross Domestic Product.

Gender differences analysis suggests that women are less involved in road accidents compared to men, because women spend less time driving , they are more cautious and have less dangerous behaviour while driving . Women tend to drive at lower speeds , have greater respect for road rules, and have a lower propensity to drive under the influence of alcohol or drugs . As a result, women are responsible for fewer road accidents.

According to Istat report, during 2021 in Italy and also in Tuscany, all indicators related to road accidents increased generally in compared to the previous year. Specifically, 13,596 accidents with injuries were recorded, causing 17,510 injuries and 190 deaths. The analysis by gender shows that 62.2% of the injured and 82.1% of the dead are males, confirming male dominance in severe injury cases. About this topic, although Istat published data provides little gender-disaggregated information, it's possible to explore differences between men and women using indicators from regional health sources, such as the Emergency room (ER), Hospital Discharge, and Mortality.

In 2021 an analysis of the health consequences of road accidents shows that 61,467 Tuscany residents (crude rate of 1,664.5 per 100,000 inhabitants) were admitted to Emergency room with a diagnosis of a traumatic injury, which is a significant increase from the approximately 50,000 in 2020 (+23.3%). The majority of the visits were male (55.3%) and the most affected age group was between 15 and 29 years (crude rate of 2,703.5 per 100,000 inhab.). The trend of higher ER admissions by males has been consistent since 2010, with constant differences between genders. The same pattern of higher rates by males is confirmed for all ages, except for the 65-79 years group, where females have a slightly higher rate. Looking at more severe events, in 2021 in Tuscany road accidents resulted in 2,536 hospitalizations, with a rate of 68.7 per 100,000 inhab., an increase from the 2020 rate of 63.4, but still lower than the 2019 rate (80.9 per 100,000 inhab.).

67% of the hospitalized were males, with higher rates in all age groups, with the largest differences observed in the 15-29 years and 80+ years groups. Finally, the number of deaths from road accidents is decreasing over time, with a more pronounced reduction for males, but with a higher death rates trend for males for all age groups.

Epidemiology represents an important side of the topic. Aiming to give an overall picture of the phenomenon also behaviours have to be taken into account. In 2005, Ars started the conduction of a study (Edit) to investigate the determinants of road accidents among high school students in Tuscany. From 2022, the most recent results showed that 26.6% of the 7,000 respondents had a driver's license, with 35% of males and 17.7% of females possessing one. 35.8% of the respondents reported driving a vehicle regularly, with a higher percentage of males (44.5%) compared to females (25.4%). The study revealed that 34.9% of regular drivers reported having an

accident in their lifetime, with higher percentages for males (38.2%) than for females (27.7%). The results showed that male driving behaviours had a greater impact on road safety, with smartphone use being the most common distraction (4.2%) during accidents. Moreover, the study results highlighted a convergence of risky behaviours between the two genders over time.

In summary, males show a greater involvement in every sphere of road accidents than females. Based on the results of the Edit study, the risk behaviours adopted by Tuscan adolescents while driving show however an overall alignment between the two genders, suggesting that in the forthcoming years, frequencies will no longer be higher only for males.

4.9.2 Domestic accidents

Domestic accidents (DA) are accidental events that occur to persons in homes, mainly due to falls, poisonings, burns, cuts and injuries causing temporary or permanent impairment of a person's health due to various kinds of injuries. In most industrialized countries, these events are one of the leading cause of mortality and morbidity in all age groups. People at higher risk of DA are those who spend a lot of time at home, such as homemakers, children and the elderly.

According to the Istat Multipurpose survey "Aspects of daily life" , in Italy in 2021 it was estimated that 633,000 people (10.6 per 1,000 inhabitants) had a domestic accident during the 3 months prior to the interview, for an amount of 743,000 accidents. In 2021, as seen in the previous surveys, the most involved persons are still those over 80 years of age (30.1 per 1,000 inhab.), followed by 70-74 years old (13.8 per 1,000 inhab.) and 75-79 years old (12.9 per 1,000 inhab.).

The categories with the highest incidence are retirees (16.3 per 1,000 inhab.) and homemakers (14.9 per 1,000 inhab.). Gender data reveal that men are involved in 7.6 accidents per 1,000 inhab., while women 13.5 accidents per 1,000 inhab.. In the same year in Tuscany, persons who got accidents in the last 3 months prior to the interview were 54,000 (corresponding to an estimated amount of about 216,000 persons for 2021), while the number of accidents was 66,000 (corresponding to an estimated amount of about 264,000 accidental events for 2021).

The shortage of the indicators provided by Istat, the general lack of data available and the limited number of published studies in this field represent a barrier to understanding and identifying those at greatest risk of DA. Regional health sources, particularly Emergency room, Hospital discharges and Mortality provide an important added value to the analysis.

In 2021 in Tuscany, there have been about 106,800 emergency room visits for domestic accidents with traumatic diagnoses, a 6.1% increase from 2020, when there were 100,700 visits. Women represent the highest frequency, with 3,095 visits per 100,000 inhab. (55.2% of the total) compared to 2,678 visits per 100,000 inhab.. After 65 years, the frequency of hospital visits for women exceeds those of men, reaching 2 visits for women against 1 visit for man after 80 years. The main diagnoses for women were "concussions" (26.4% of the total), while it was "concussion without loss of consciousness" (12.7% of the total) and "injury to the fingers of the hand without mention of complications" (7.5% of the total) for men.

Looking at more severe events, in 2021 in Tuscany the number of hospitalizations for domestic accidents with traumatic diagnoses was about 8,800, a decrease from 2020 when there were 10,000 hospitalizations.

65.5% of hospitalizations involved women, whose mainly involved age group was the elderly (80+ years), with 4,859 hospitalizations, 75% of which involved women. Finally, the mortality trend based on data from the Regional Mortality Register between 2010 and 2018 shows an average of about 180 deaths among Tuscan residents per year due to domestic accidents, with a mortality rate of 5 deaths per 100,000 inhabitants. Data do not show the prevalence of one gender over the other.

In summary, domestic accidents are accidental events with the highest frequencies recorded by female gender, probably driven by the category of homemakers accounting for many of the cases. Again, females are the most affected group, showing higher frequency in different settings, such as emergency rooms and hospitalizations. Mortality data do not confirm the major involvement of women in this field, highlighting overall aligned death rates between the two genders.

4.10 Accidents and occupational diseases

It is well known that in the workplace there are clear gender differences regarding the job characteristics and the associated risks and harms. The analysis of the data collected by the Italian Funds for Occupational Injuries and Diseases (Inail) on occupational injuries in Tuscany during 2010-2020 shows a downward trend, that decreases significantly in males, while it is more stable in females, with an increase in 2020 due to the widespread COVID infections in the sector of healthcare, where the female gender is prevalent.

In relation to the occupational sectors, we observe the "occupational segregation" phenomenon, males have higher injury rates in Industry and Constructions respect to females, while the injury rates are higher in females in Healthcare sector or Services. With respect to time of the injuries occurrence within the 24 hours, we observe a

different distribution of the frequency curves, probably due to a different organisation in the two sexes (part-time or 8.00-14.00 prevalent in women for example). If we only consider serious occupational injuries, the trend shows a decreasing tendency in both males and females, although more in males. Analysing data on occupational diseases, an increasing trend is detected during 2010-2020, while it tends to decrease over the last two or three years and in particular in 2020, the year in which the effect of the pandemic was also evident due to the significant reduction in all routine healthcare activities. This is more evident in males than in females, for whom the trend in occupational diseases recognised by Inail has remained more stable. The analysis of occupational diseases by production sector shows that the Mining, Construction and Manufacturing sectors are more affected for males, and the Manufacturing, Service and Healthcare sectors for females. Musculo-skeletal diseases are prevalent in both males and females, especially in women, whereas cancers and respiratory diseases are more frequent in males, given the close association of these pathologies with the sectors of Industry where the male workforce is prevalent. Diseases linked to psychosocial risk factors are more frequent in women.

Among occupational diseases, there were 559 complaints of work-related stress in the period under review, with a very low percentage of recognition by Inail (17%). The limited number of complaints of work-related stress may be linked to the phenomenon of under-reporting (lack of information to the worker, fear on the part of the worker of losing his job or of coming into conflict with the employer or colleagues), however, it is also evident that the small number of cases that are recognised as work-related by Inail assessment is also low. However, the complaints are predominantly from the female sex (55.8%), with a substantially stable trend from 2010 to 2020, although fluctuating due to small numbers. The occupational sectors in which this occupational disease is most frequently reported are Manufacturing, especially for males, Healthcare and Public Administration for females, then Public Administration, for which, however, no differences are detected on the basis of gender.

4.11 Autoimmune diseases

Autoimmune diseases (AD) are a heterogenous group of about 80 different conditions characterized by a disruption of the immune system, which causes a loss of immune self-tolerance. AD are chronic diseases, affecting about 5% of the general population in developed countries, leading to a shorten lifespan expectation and deeply interfering with daily activities and quality of life. Females are generally more affected than males, with a 3:1 ratio, considering all AD diseases together.

AD can be distinguished in organ specific and systemic. Among the first, we must mention Hashimoto thyroiditis or Graves-Basedow disease, type I diabetes, Addison disease, primary biliary cholangitis or autoimmune hepatitis, celiac disease, and inflammatory bowel diseases (e.g., Crohn disease or ulcerative colitis). Other organ-specific AD are multiple sclerosis or myasthenia gravis. On the other hand, rheumatoid arthritis, spondyloarthropathies, connective tissue diseases (e.g., systemic lupus erythematosus, Sjogren syndrome and systemic sclerosis) and systemic vasculitides belong to the group of systemic AD.

The pathogenesis of these complex diseases is poorly understood, however it is generally accepted that a genetic background, together with environmental factors (e.g., ultraviolet rays, smoke, and hormones in particular) can trigger an altered immune response, leading to autoimmunity.

4.12.1 Pregnancy

Talking about women's health, their reproductive status is always at issue. We know also that women's reproductive health status depends on the quality of health care in every country. So far, the focus on pregnancy health care can reflect how a country can look forward. Moreover, many pathologies that arise in women during pregnancy can predict her future health status and/or of her baby; for example, in the case of gestational diabetes, as treatable as it is, the risk that the mother and the baby develop insulin intolerance is present. The fact that pregnancy highlights certain vulnerabilities does not mean condemning the development of pathologies in the future, but the possibility of recognizing the potential future risks. Usually, these risks can be avoided with adequate lifestyles or, at least, early intercepted with adequate controls. Therefore, "postpartum clinics are dedicated to the prevention of future pathologies", to identify specific paths for each patient who developed pathology during pregnancy and can be at risk in the future. The cornerstones of pregnancy service in Tuscany is a network of health care professionals, general managers, and regional policy-makers called "pregnancy booklet". This system guarantees maternal and infant care to the entire population, as well as it tries to prevent the main problems that can arise. Giving a birth is always a happy and highly desired event throughout Italy and in Tuscany. In fact, voluntary abortions are declining because of efforts to prevent unintended pregnancies. Over time, the incidence of pregnant women over than 40 years old has increased, together with the number of women conceiving through assisted reproduction techniques (ART). The use of ART may lead to multiple and unsafe pregnancies. The assistance standard during pregnancy in Tuscany is high and 95.4% of women with a physiological pregnancy carry out

the tests prescribed by the pregnancy guidelines and follow the regional protocol. In addition, an improvement in assistance during pregnancy has reflected a constant reduction of hospitalization, which can be helpful to allow women remaining to their home and inside their emotional nucleus. Pregnancy can represent an extraordinary opportunity to protect women's health, revealing all the possible issues that can be corrected with proper controls and, at the same time, with good lifestyles. Otherwise, chronic disease can be developed at later stages of life and can affect women's lives negatively at different levels.

4.12.2 Postpartum depression

Postpartum depression (PPD) is defined as the occurrence of a depressive disorder during pregnancy or after childbirth. The pathogenesis of perinatal and postpartum depression is yet unknown; in literature it is said that genetic, hormonal and psychosocial stress factors play an important role in the insurgence of this pathology.

Recent studies show a prevalence of this phenomena varying from 6.5% to 20%. Early identification of the female population at risk of perinatal psychic and psychosocial distress, as long with their risk factors, is essential to take care of them promptly during and before pregnancy.

On 204,282 women who gave birth in Tuscany between 2014 and 2021, 16.7% had at least one mental health problem within the 10 years before and 1 year after partum; 13% had problems only before partum, 2.4% had problems both before and one year postpartum and 1.3% postpartum only.

A higher risk to develop postpartum depression in one year after delivery was detected in mothers with history of mental health problems before pregnancy (Odds ratio; OR: 10.21; 95% CI: 9.65-10.7) and in mothers who gave birth to a dead-born children (3.54; 2.42-5.15). Other risk factors beign more than 34 years old at birth, being not employed, being obese before pregnancy, smoking during pregnancy being alone or with a trusted person (who is not the father) in the delivery room and having delivered a premature born children. On the other hand, having a foreign citizenship (0.68; 0.62-0.73), being multiparous, (0.82: 0.77-0.86) and being between 18-29 years old at birth seem to decrease the risk of developing PPD.

Tuscany adopts various strategies to identify women at risk of developing postpartum depression in time. In particular, in the central healthcare district (ASL Centro) during the delivery of the pregnancy booklet, pregnant women also receive the Whooley Questionnaire (Whooley Questions for Depression Screening) and, if women result positive to the screening, a psychologist contacts them to look

more closely into their situation. Dealing with the screening, the central healthcare district (ASL Centro) administrated 5,560 questionnaires between September 2020 and December 2021. 6% of women resulted at risk of developing depression but 41 of them didn't want to be contacted by the psychologist. 48.42% of the contacted women were suggested and started individuals or couples interventions.

4.12.3 Mood disorders in future fathers

In a modern gender perspective, perinatal psychology has recently focused on fathers' internal experience and their dynamics with becoming mothers and newborns, underlying the importance of including future fathers in services supporting becoming parents.

Fathers experience many internal changes in the development of parenthood, as well as mothers. In the past, males' emotional experiences of becoming fathers have not been described and spoken, but lately men are expressing more of their feelings and internal experiences. Moreover, perinatal literature has underlined the importance of fathers in supporting mothers and in the healthy development of the child. Sometimes the complexity of the process of parenthood can expose men to uneasiness, insecurity and some others emotion that can develop in health disorders.

The Paternal Perinatal Depression (Baldoni and Ceccarelli, 2010) includes depressive symptoms that can develop since the beginning of pregnancy to the first year of life of the newborn and on. Males' symptoms can come out less as depressive symptoms, but express more anxiety or come out as behaviour symptoms such as impulse loss of control, excessive physical activity, addiction development, search for sex activities outside the couple or Abnormal Illness Behaviour. Nowadays the clinical correct definition of such condition is Paternal Perinatal Affective Disorder, PPAD.

Recent studies show a prevalence of this phenomena varying from 8 to 10,4%; in Italy from 9 to 12% (Baldoni, 2020). The most common risk factors are early or late age, individual psychological features such as history of mental health problems, family conflicts, being unemployed and factors associated with the experience of pregnancy and birth.

Institutions and health services must take into account the importance of well-being of future fathers and develop attention to the early identification of fathers at risk of developing mental health problems to increase help during the process of becoming parents to the families.

4.12.4 Coagulative alterations in women of child-bearing age

Changes in hemostatic balance can occur in women of reproductive age and, in particular, during pregnancy and exogenous administration of estrogen containing medication, such as oral contraceptives.

These therapies may increase the thrombotic risk.

In normal pregnancy, there are changes in the hemostatic system determining hypercoagulability, a condition due to a marked increase in the procoagulant activity in maternal blood by factors VII, X, VIII, fibrinogen and von Willebrand factor increase, and decrease in physiological anticoagulants (reduction in protein S activity and acquired activated protein C (APC) resistance). Moreover, other components may be responsible for the hypercoagulable state, such as the components of hereditary thrombophilia (factor V Leiden, the G20210A mutation of the prothrombin gene, and physiological coagulation inhibitor deficiencies). The overall fibrinolytic activity is impaired during pregnancy because of the reduction of tissue plasminogen activator (t-PA) levels, and increase of plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI 2) levels. Overall there is increased thrombotic risk throughout gestation.

The use of exogeneous hormones to achieve pregnancy in women undergoing ovarian stimulation for assisted reproductive technologies (ART) can be associated with both arterial and venous thrombotic complications. During this process, hormonal therapy induces increase of coagulation factors (vWF, VIII, V factors, of fibrinogen, as well as an altered APCR, a reduced activity of antithrombin, of proteins C and S) and impaired fibrinolysis by reduction of PAI-1 levels, thus resulting in increased risk of thrombotic events. This risk appears to be very similar to that observed during physiological pregnancy. Nevertheless, in ART, the thrombotic events (especially venous thrombosis) can present in unusual sites (vessels of the neck and the cerebral venous sinuses, and upper extremities).

Finally, the use of oral contraceptives represents a well-established risk factor for venous thromboembolism, as it causes alterations in anticoagulant system, thus favoring the development of venous and arterial thromboembolic complications even in young women. This effect may be enhanced in the presence of genetic components such as hereditary thrombophilia, or acquired lifestyle risk factors, in particular body overweight, obesity, smoking habits, or in the presence of female prevalent cardiovascular risk factor, such as migraine with aura.

4.12.5 Menopause and risk of future diseases

Menopause is not a disease, but a physiological moment of transition in a woman's life that coincides with the end of her fertility. However, the diseases potentially related to menopause should be a focus of collective prevention and information to reduce comorbidities in the medium and long term and ensure a good quality of life.

With the current life expectancy in Italy, about one third of a woman's life is spent in menopause. Quality of life at this stage has thus become increasingly important and highlighted the need for a personalized therapeutic approach, not only for the resolution of climacteric symptoms, but also for the prevention of diseases related to the cessation of ovarian function. In fact, the hormonal changes associated with menopause due to the loss of the endogenous estrogenic protective effect, leads in itself to a potential increase in cardiovascular risk (heart attack, cerebral stroke, hypertension) and osteoarticular diseases.

Alongside the increased risk conferred by traditional cardiovascular factors, menopause, especially if early onset, rises as an unalterable gender-specific risk factor in female sex [3-5]. The presence of a relative increase in circulating androgens, due to the change in the ratio of testosterone to estradiol, has been associated with an increased risk of metabolic syndrome, weight gain with accumulation of body fat, especially on the abdomen [6-10]. Estrogen deficiency results at the bone level in accelerated age-related bone loss, particularly at the level of trabecular bone. This loss is responsible for the typical fragility fractures mainly in the vertebrae and distal radius.

Among the earliest and most frequent symptoms, we find vasomotor symptomatology (hot flashes, night sweats) that can affect up to 80% of perimenopausal women and almost 20% of them are in a severe form. Vasomotor symptomatology can be both a metabolic and cardiovascular risk factor.

The genitourinary syndrome of menopause involves the whole range of pelvic disorders related to hormone deficiency, such as urogenital atrophy, urinary incontinence, recurrent and interstitial cystitis.

Menopause in itself is not a disease and does not require therapy, but rather hormone replacement (HRT), where its indication is identified [11].

HRT represents the pharmacological intervention that can modify the short, medium and long-term effects of estrogen deficiency, typical of the menopausal period. However, HRT should always be considered as part of an integrated approach to the person, including those indications and recommendations such as to promote a healthy lifestyle, adequate diet and moderate exercise. It is also able to prevent osteoporosis and related fractures, has a positive effect on risk factors for cardiovascular and metabolic disease, as well as on quality of life.

Among adverse events that aggravate quality of life, one of the negative prognostic factors is menopause induced by adjuvant therapy after malignancy, especially for younger women at psychological level.

In recent years, there has been a significant increase in the incidence of iatrogenic menopause, often at a relatively early age. This increase is due to a new and growing population of young, non-oncologic women, who go through iatrogenic menopause (prophylactic adnexectomy), caused by BRCA1/BRCA2 genetic mutation for ovarian and/or breast cancer and other malignancies. It is therefore necessary to restore psychophysical functions that may be compromised by oncological therapies from an integrated medicine perspective; in this sense, complementary medicines, included in the regional integrative LEAs and supported by increasing scientific evidence of efficacy and safety, have an increasingly wide use in these patients: in fact, they are part of the therapeutic approaches recognized by the Menopause Guidelines of the Tuscany Region (2015) while DGR No. 418/2015 defined their integration modalities in the Regional Oncology Network.

5. The *Codice Rosa* network and gender violence

The Codice Rosa network indicates the ways women victims of gender based violence (Woman Section) and people who suffer violence due to vulnerability or discrimination (Hate Crime Victims section) can access to the care pathway.

Moreover, the Codice Rosa is the tool for alerting and activating future local care pathways, with the aim to guarantee care continuity and follow up for the victims.

Born in 2009 in Grosseto, the Codice Rosa became a local project in Tuscany and was structured as a real network involving all the local hospitals, with the signature of a protocol of agreement between Tuscany Region and the General Attorney of the Republic of Florence.

The Codice Rosa is a time dependent network, able to provide quick responses to the care needs of abused people. This is possible through the acknoledgement of violence and the realization of particular care pathways, specifically created for gender based violence: abused children, people with disability and sexually discriminated people.

The network goals are:

- Allow an early acknoledgement of the violence cases, both on local and in hospital basis, in particular in emergency departments;
- Coordinate the different institutions and professionals, in order to guarantee a quick and effective response to the victim, starting from his/her access into the emergency room;

- Guarantee a local care pathway once the victim is released from the hospital, based on the assessment of the victim's individual needs, also concerning his/her protection;
- Guarantee uniformity of interventions in local hospitals;

A Chief chairs the board of the regional network of Codice Rosa and three area boards of Codice Rosa, one for each area of the healthcare system in Tuscany and finally, the Codice Rosa local networks, operating in each hospital of the region.

In particular, the regional board of Codice Rosa has developed a series of guidelines concerning violence, which have been approved with a decree by Tuscany Region in 2019.

These guidelines concern about:

- Regional indications for emergency rooms about violence and sexual abuse on adults;
- Regional indications for emergency rooms about violence and sexual abuse on children;
- Regional indications about the correct way of gathering evidence and the chain of custody;
- Regional indications for the 118 workers in the Codice Rosa network;
- Regional indications about the composition of the assessment team.

The 14th regional Report published in 2022 by the regional observatory about gender based violence in Tuscany indicates that the number of admissions in 2021 increased by 14,6% compared to the previous year. This is mainly due to the pandemic, which limited the access to hospitals.

In 2021, 1647 adult admissions were registered for the Woman pathway and for the hate crime victims pathway; in both cases the number of women outweighed the number of male victims, reaching 80%.

Regarding children, the admissions number has increased by 21.7%, mainly in the age between 12 an 17.

We can understand from these data how the admissions are considerably increasing. Moreover, the fast turn over of emergency rooms health professionals and the fundamental role of the local care system in discovering violence cases highlight the need of more personnel trained on the subject.

For this reason, the training of health workers is the first action that has to be undertaken, in order to prevent violence and protect the victims.

6. Gender Identity

Gender Incongruence (GI) is a marked incongruence between the assigned gender at birth and the one experienced by an individual. Some people with GI may desire

gender-affirming hormonal treatment (GAHT), in order to align their body with their gender identity. In this case, transgender individuals' needs should be actively explored by clinicians, offering an individualized approach. In fact, trans AMAB (assigned male at birth) people may request different degrees of feminization and/or de-masculinization; whereas trans AFAB (assigned female at birth) people may desire different degrees of de-feminization and/or masculinization. Although non-binary transgender individuals represent a growing body of clients referring to specialized gender clinics, in the last years literature mainly focused on standardized GAHT in binary transgender people. To date, no standardized hormonal treatment protocols for non-binary transgender individuals have been described in the literature and there is a lack of data regarding their efficacy and safety. For this reason, benefits and risks of such treatments should be extensively discussed with patients.

7.1 Female sexual dysfunction and neoplastic diseases

Thanks to the use of multimodal treatments, early diagnosis and new therapeutic frontiers, patients with a precedent history of cancer can live longer "alongside" their disease. Thus, there is a need for constant attention in the treatment of "collateral damage" which can permanently compromise survivors' life quality, though linked to a positive therapeutic effect. It is no longer enough to deal with the issue of sexual dysfunctions focusing merely on anatomical damage to organs and functions. The mechanisms implicit in sexuality, in health as in sickness are complicated and often hard to define – they involve psychological, relational, biological, cultural, ethnic, and religious spheres. Thus, in addition to the dramatic bodily changes, such as scars and amputations, that are a veritable representation of the disease, there are also negative experiences of fear, pain, and fatigue that influence interpersonal relations between couples and with family members and colleagues at work. For this reason, along with strictly medical interventions (gynaecological, urological, endocrinological, and rehabilitative), it is necessary to break down the communication barriers that confine the cancer patient within her solitude and to speak concretely and reassuringly to direct her to parallel therapeutic paths of support and counselling aimed specifically to help her regain a satisfying sexual life.

7.2 Sexual dysfunctions and pharmacotherapy for sexuality

Erectile dysfunction (ED) is one of the most common male sexual dysfunction, with a prevalence range of 30-52% in men aged 40-80 years. The diagnosis is usually made by the collection of a detailed medical and personal history, together

with physical and biochemical examination of the patient. Since ED is nowadays considered as a marker of systemic endothelial dysfunction, penile color Doppler ultrasound represents the gold standard for the instrumental diagnosis of vasculogenic ED, and it is also useful for the stratification of the cardiovascular risk of patients.

ED usually presents a multifactorial pathogenesis, characterized by organic (enodcrine or nonendocrine), psychological and relational factors. Therefore, men with ED benefit from multimodal management strategies, including lifestyle modification, pharmacological treatment and psychosexual counselling.

Oral phosphodiesterase-5 inhibitors (PDE5-i) represent the first-line medical therapy for ED; when PDE5-i are ineffective or contraindicated, medical indications are injected vasodilator agents, vacuum erection devices and surgical therapy.

Premature ejaculation and delayed ejaculation highly represent prevalent male sexual dysfunctions as well, however evidence about their definition and treatment are poorer, with the necessity of further studies to better understand them.

8.1 Pediatric gender health: differences start at birth (or before)

Despite different trends followed by birth rates over time in Tuscany, sex ratio in newborns has remained relatively unchanged, each year on average for every 100 newborns of female sex there are 106 of male sex. This unbalanced sex ratio at birth compensates for a slight but clear disadvantage in terms of mortality and morbidity of the male sex, which begins early in life and persists throughout development into adolescence and adulthood. The data from Tuscany Region, in line with international evidence, show an increased risk of maternal and fetal complications during the later stages of pregnancy in pregnancies of male fetuses, such as preterm birth and recourse to caesarean section delivery. During the course of development, male children showed higher mortality and hospitalization rates at 12 months of age, 1-4 years of age, and at 5-14 years of age than those found in females. Since these data are referred to the early stages of life, they probably highlight a biological disadvantage in the male sex compared to the female sex, the causes of which remain to be clarified.

8.2 Child abuse

The phenomenon of children involved in acts of mistreatment and sexual abuse is one of the most consistent and significant areas for actions of security and protection and requires specific and different interventions.

Since 2005, the Meyer Pediatric Hospital hosts a working group called "Group Abuse Childhood and Adolescence (GAIA)", that is involved in the multidisciplinary management across hospital activity of children victims of suspected abuse and ill-treatment.

The Resolution of the General Director of the Meyer Pediatric Hospital approved in 2010 recognizes to GAIA the mandate to provide efficient reception and diagnostic classification of suspected child victims of abuse; to prevent and early assess the signs of distress and / or risk related to a suspected abuse; to suggest care pathways and activate judicial course.

Different professionals compose GAIA: pediatricians, pediatric gynecologists, psychiatrists, psychologists, psychotherapists, nurses, social workers.

Judicial authorities, other hospitals and extra - hospital services, pediatricians/ doctors and school authorities and, above all, victims' families can activate directly GAIA.

Since 2013, the Meyer Pediatric Hospital has been involved in the fulfillment of the regional project aimed to defend the weakest population groups exposed to violence – Codice Rosa.

GAIA has significantly increased the workload.

9.1 Migration flows and gender

Migration is a phenomenon that affected increasingly large numbers of people all over the world. Mobility from one country to another is due to different needs and motivations, depending on the country of origin. Poverty, climate change, political instability, as well as the labour market are factors that can lead a person to migrate to another country looking for better living conditions.

The World Migration Report 2022 highlights that, in 2020, 3.6% of the global population (N=281 million) were international migrants. In this scenario, Italy is a country strongly affected by the migration phenomenon, with more than 5 million foreigners living on the first of January 2022. However, foreigners on the national territory do not always meet the necessary requirements to stay in the country and, therefore, a large part of this population is considered illegal. In 2021, in Italy there were more than 90,000 applications for regularisation of foreign citizens, but only a small number of residence permits were issued.

Tuscany also has a strong presence of non-regularised foreigners, with 7% of the total national migration flow staying in the territory. The analysis of the foreign population resident in Tuscany by gender also confirms the Region as one of the first in the entire national territory for foreign presence. With over 400,000 foreign

residents, Tuscany registers a higher percentage of women (51.7%) than men (48.2%).

The analysis by age shows a homogeneous distribution by gender, with a greater concentration of this population in the 30-49 age range, highlighting a young population.

Gender differences arise considering the nationalities of origin present in the territory. Indeed if males come more often from China (18.6%), females come instead from Romania (22.4%), denoting a different mobility in the two genders according to different needs, such as work.

In fact, the labour market represents an area strongly marked by gender, both because of the different types of jobs held by men and women, and because of their exposure to different risks. The annual report published by the Ministry of Labour and Social Policies shows a higher number of work-related accident reported by men (9,745) than by women (N=5,707).

In brief, it is fundamental to consider gender differences for a better understanding of the phenomenon and pay more attention to the needs of all citizens, improving integration and intercepting the difficulties they face.

9.2 The health of foreign population

The health condition of foreign population living in Tuscany is different from that of the resident one; this difference is due to socio-cultural and demographic factors, such as age and lifestyle.

However, as the time spent in the country of arrival increases, the habits of the two populations tends to overlap progressively, leading to similar health problems.

Besides the differences between Italians and foreigners, the gender issues has become increasingly relevant over the years, generating for example differences in access to health care services for the foreign population, but also different diseases and health problems.

The areas where the main gender differences are found are maternal and child health, where foreign residents women are more affected by voluntary interruptions of pregnancy, with significantly higher rates than those of Italian women (foreigners: 12.5 per 1,000 women; Italians: 4.5 per 1,000 women). Moreover, prevention habits during pregnancy are also a topic that distinguishes the two populations differently, with foreign women being at greater risk of not intercepting early risk situations for their newborn children, because of their poor compliance to medical check-up.

In addition, it is well known that foreign people tend to identify First Aid as the first point of reference for care access, (access rate: 284.8 testifies the high rates of access), despite the lower average rate of the resident population (access rate: 287.1).

The analysis of the primary causes of access also shows differences in the two genders, highlighting how men are more affected by causes of hospitalisation for traumatism than women (males: 40.2; females: 29.9). This is partly due to the different risk factors the two genders are exposed to, such as the workplace. On the other side, foreign women appeal more to hospitalisation than foreign men, mainly for pregnancy complications causes (foreigners: 27.5 for 1.000 residents; Italians: 18.9 for 1.000 residents).

Nevertheless, there are no other particular gender differences between men and women.

Finally, talking about prevention in a gender perspective, there are strong differences between Italians and foreigners in participation to screening programmes. In particular, women's screening programmes such as mammography and cervical screening still have very low rates of adherence by foreign women, testifying the need for greater awareness among this population.

10.1 Hospitalization in a gender perspective

A gender-sensitive hospitalization approach can be useful to identify sub-optimal use of hospital resources, when gender differences in recovering should not be exclusively due to epidemiological gender factors rather than issues of equity of access. According to a rather scarce specific scientific literature, the analysis of the hospitalization experience and its survival outcome are conducted observing the dynamics of hospitalization gender according to age and specific services used, with the identification of differences in ordinary admissions, Day hospital admissions and urgency of interventions over the five-year period 2017-2021. The result picture coming from the provided data seems to outline a use of hospital according to the different phases of life. In fact, at different times, men and women are exposed to different assistance needs: the former tending to be staying into the hospital when older, and the latter tending to be generally more present in the hospital and susceptible to more urgent interventions

10.2 First aid and Emergency departments

The importance of gender medicine is increasing also in the treatment of some specific acute pathologies in first aid and in emergency departments, where gender differences in terms of mortality are significant.

For example, cardiovascular diseases represent the main cause of death in women in the late years, because in females they appear without evident symptoms. This is

the reason why it is important to use a different approach in organising the treatments and care activities in the Emergency departments.

In 2021, according to administrative data, 1,165,767 people needed primary care from the hospital, with accesses rising after the decline due to effects of the Sars-CoV-2 epidemic.

Previously, the attendance in emergency department (ED) was 1,5 millions. The ratio between males and females does not change over time (51% male, 49% females), but age class observes different behaviours: males visit ED more than females up to the age of 79, except for age 25-39 (55% of females). Women aged over 79 are the most frequent ED users (58%) and those aged 95 and older are the main users (70%).

According to access causes, excluding the ones strictly connected to gender, more frequent diagnosis are abdominal pain (60%) and headache (75%) for women; renal colic (70% M) and open wound of fingers (69%) for men. Traumatisms represent the recurring cause of access by far for both genders, but they are characterized by injuries of any type (fractures, bruises, wounds…) in different parts of the body.

In particular, women are mainly injured by femur fracture (in all its parts) and by arm and forearm long bones fractures, while males' lesions occur in all other parts of the upper limbs (hands, wrist, elbow, scapula and clavicle), as well as eye injuries for external cause and traumatisms of the cornea.

Among some little but socially relevant groups of injuries, we highlight anorexia nervosa (97% of 60 cases), poisoning by sedatives and hypnotics or other drugs (64% of 1,000 cases) and the diagnoses requiring the activation of the alert code for violence and abuse of adults and minors. These accesses amount to 1,445, the proportion between adult men and women is 1:3 (1,304 cases), while females represent 66% (141 cases) among the underage population. More in detail, sexual abuse accounts for 6% for adults (75 cases) and 30% for children (42 cases), and they are more frequently directed to females (88% in the adult population and 95% in that of minors).

Women result more frequently hospitalized than men (16% F vs 14% M), while males have a greater propensity to leave the ED before closing the medical record, being more frequently discharged to outpatient facilities (1.4% M vs 1.1% F). Home discharge is anyway the most frequent outcome, almost 76% for both gender groups.

Finally, reported data can depict a scenario where the gender of patients accessing the Tuscan Emergency departments could make specific care paths more preventable, facilitating the organisation of care.

10.3.1 Drug use

The pattern of medication use in general population is often significantly affected by gender differences, due to biological aspects related to sex as well as socio-economic,

cultural and lifestyle differences. In this context, regional administrative healthcare data represent an important source of information to understand and quantify gender differences in drug utilization in the Tuscan population.

Therefore, the administrative healthcare database of Tuscany was used to select all subjects enrolled in the regional healthcare service and identify within each of the first four levels of the Anatomical-Therapeutic-Chemical (ATC) classification, the five classes of drugs reimbursed by the National Healthcare Service that showed in 2021 the greatest gender differences in terms of absolute value of prevalence of use (|Δ|) measured as the number of users per 1,000 inhabitants. For such drug classes, we observed also the mean number of packages dispensed per user during 2021.

According to the I° ATC level, the greatest differences in prevalence of use were observed for drugs acting on nervous system (ATC N), alimentary tract and metabolism (ATC A), systemic hormonal preparations, excl. sex hormones and insulins, (ATC H), genitourinary system and sex hormones (ATC G) and antiinfectives for systemic use (ATC J). For all these drug classes, excluding ATC G, the observed prevalence of use was higher in women than men. In particular, when medicines were grouped according to the IV° ATC level (pharmacologic-therapeutic criterion), the greatest gender differences in terms of prevalence of use were observed for vitamin D and analogues (ATC A11CC: men= 34.8; women= 131.8 users per 1,000 inhab.), alpha-adrenoreceptor antagonists (ATC G04CA: men= 79.9; women= 1.0 users per 1,000 inhab.), thyroid hormones (ATC H03AA: men= 19.8; women= 88,5 users per 1,000 inhab.), selective serotonin reuptake inhibitors (SSRI) (ATC N06AB: men= 43.4; women= 96.4users per 1000 inhab.) and other antibacterials (e.g. mainly represented by fosfomycin for non complicated urinary tract infections) (ATC J01XX: men= 18.7; women= 57.9 users per 1,000 inhab.). In general, with respect to the drug classes considered above, women show a higher prevalence of use, although with a mean number of packages dispensed per user during the year of observation that almost overlap between the two genders. The only exception to this general pattern is represented by genitourinary drugs and sex hormones (ATC G), for which both the prevalence of use and the mean number of packages dispensed per user were significantly higher in men than women (prevalence of use |Δ|=64.4; packages per user |Δ|=6.8) basically due to drugs used for benign prostatic hypertrophy, a disease of the male genital tract.

In conclusion, the analysis described above highlighted the five classes of drugs, reimbursed by the National Healthcare Service, that showed the greatest gender differences in terms of patterns of use in the Tuscan population. The gender differences observed in the utilization of thyroid hormones, drugs for benign prostatic hypertrophy, antibacterial such as fosfomycin, and vitamin D and analogues, can be mainly attributed to biological differences between sexes. Conversely, gender-related

differences are more likely to have the greatest impact on the observed pattern of use for drugs acting on the central nervous system, such as SSRI antidepressants.

10.3.2 Response to drugs and gender

Both preclinical (animal and cell studies) and clinical investigations neglected women. But the pharmacological response depends on sex and gender, since pathophysiological dissimilarities between men and women significantly influence the pharmacokinetics and pharmacodynamics of drugs. However, pharmacological response is also strongly affected by gender. For example, it is influnced by age, social and economic status, level of education, religion, being a care giver, geographical localization, ethnicity and etc.. Therefore, gender pharmacology indicates that pharmacological response is holistic and personalized at the same time. Sex and gender also influence the consume of drugs, as made clear by the example given relating to the consumption of antibiotics in the Tuscan Region, which is sex-gendered and age dependent. Interstingly, COVID-19 has changed the consume of antibiotics in a similar way in both sexes, while the appropriate use is reduced especially in women. It is necessary to introduce a sex and gender approach to increase appropriateness in all individuals towards the reduction of inequalities in health and care.

10.4 Health workers and gender

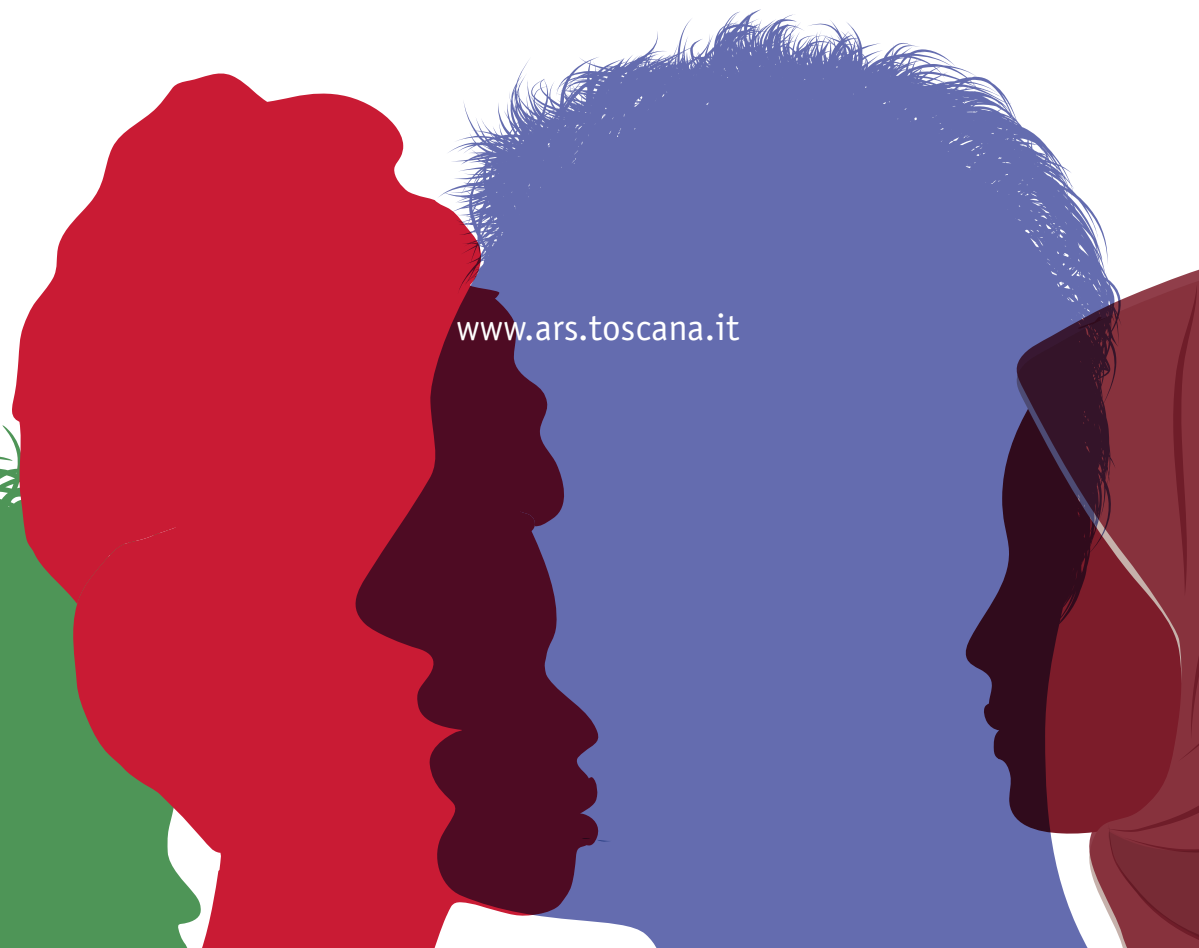
In this chapter, we want to summarize the bibliography respect to the variable gender into the physician-inpatient-caregiver relationship. We can see that the inpatient gender and the caregiver gender are important to determinate the behaviour of these characters, but it is also important the gender matching of both in the couple inpatient-caregiver. Furthermore, it is really necessary to understand how physician gender impact the attitude and the technical acts in the relationship with patient and, also in this case, how the matching of the physician, inpatient and caregiver gender manipulate the medical relationship. This can also happen because of the expectations that the characters have with respect to the gender, combined with the role covered by the subject, for example a male doctor or a female doctor. We quote a monocenric study made in a hospital of Tuscany, where we investigate the communication between physician, caregiver and inpatient respect to the gender.

11. Organ transplantations

Organ donation and transplantation are the essential prerequisite to respond to patients affected by severe end-stage organ dysfunction. Between 2002 and 2020, the total number of potential donors was 6,296, with 3,377 actual donations. In both cases, there is a younger male predominance at 54%, with respect to women. Among the causes of brain death, the most frequent is cerebral haemorrhage (3,958 cases), for which female gender is only slightly more represented (2,031 cases, 51.3%). For all other causes, males are more represented.

In the same period, 5,733 organ transplants were performed in Tuscany, 3,922 men (68.4%) and 1,811 women (31.6%). Women undergo transplantation at a younger age than men do, for every type of intervention. Overall, the average age of transplant recipients is 49.7 years for women and 52.4 years for men. The average waiting time on the transplant list is 378.9 days for women and 303.5 for men. In the last two years (2021 and 2022), this difference has been eliminated.

The 5-year survival rates among those operated between 2012 and 2020 show very similar data between gender for kidney transplants, higher among women for liver and lung transplants, and higher among men in the case of heart transplants.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