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GENDER RELATED HEALTH OUTCOMES: A GLOBAL PERSPECTIVE

ESHRE Capri Workshop Group[1,2]

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1. ABSTRACT

The first signs of separate sexes in many-celled organisms are believed to have emerged around 700 million years ago, however, the influence of gender[3] on human health remains poorly understood.

Male births exceed female births by 5-6% (for a sex ratio at birth of 1.05-1.06) while a women's life expectancy, on a global scale, is 6 years longer. It therefore follows that within various age groups the male:female ratio changes over time. Men outnumber women until the age of 50. Thereafter, their numbers show a sharp decline. Excess mortality in males of this age group is such that in 80 year olds, there are many more women than men. An estimated 25% of this male excess mortality appears linked to biological causes, the rest being explained by behavioral, cultural and environmental factors. For both women and men, the main health risks related to lifestyle are unhealthy diet, physical inactivity, smoking and alcohol, while recent data show that, in women, diabetes is associated with a higher cardiovascular mortality. In the year 2010, overweight (BMI: 25-29) and obesity (BMI: 30 and above) were responsible for over 3 million deaths. Smoking-related mortality accounts for 40-60% of the global gender gap in mortality and alcohol related deaths for 20-30%.

For women in some parts of the world pregnancy can be an extremely risky condition. On a global scale, in 2013 about 300.000 deaths were related to

[3] Sex refers to the anatomy of an individual's reproductive system and secondary sex characteristics (male or female), Gender concerns categories of masculinity and femininity that are learned through socialization, and that are subject to change over time. In most societies there are differences and inequalities between women and men in responsibilities assigned, activities undertaken, access to and control over resources, as well as decision-making opportunities, all of which have an impact on, and are affected by, sexual and reproductive health (WHO (2015a); UN Women, (2015)).
(Extract from Cottingham J. Gender aspects of sexual and reproductive health. In: Quah SR (ed). *Encyclopedia of Public Health*. London: Elsevier; forthcoming.)

pregnancy, with sub-Saharan Africa registering the highest maternal mortality: 510 maternal deaths per 100,000 births. Additional health risks specifically for women arise from instances of gender discrimination including sex selective abortion, genital mutilation (FGM), child marriage, and ('honour' and dowry related) violence against women. Reducing female birth by sex selective abortion will skew the sex ratio to (in some areas of the world) 1.15 or even 1.25. This will create a shortage of young women, disturbing the 'marriage market' of this generation in the affected countries, with a surplus of increasingly anxious young unmarried men. This has considerable social implications, e.g. increased prostitution, sex offenses, rape, importing brides from neighbouring countries, women trafficking and social turmoil, which in turn will affect women's health.

In conclusion, gender based differences in health outcomes are due to biological, environmental and lifestyle factors. Males outnumber women at birth, avoid the complications of pregnancy and social discrimination, but pass away earlier and in larger numbers due to fighting, wars, alcohol and smoking; on a global scale they are less likely to outlive women.

2. INTRODUCTION

The first signs of separate sexes appear in fossil records from around 700 million years ago (Radzvilavicius and Blackstone, 2015), while almost all species of animals and plants now appear as individuals that are either male or female, or sometimes both.

Why evolution produced two sexes remains a mystery but a plausible explanation for the origin of a female germ line was the avoidance of reactive oxygen species (ROS) dependent mutation through the maternal mitochondrial inheritance. Sex

was probably aimed at improving reproductive fitness but is there any correlation between individual health and gender?

More boys are born than girls. The natural sex ratio is about 1.05-1.06, i.e. about 5 or 6% more male than female births. Life expectancy of females however exceeds that of males (Barford et al., 2006).

Interestingly, some scholars forecast that the life expectancy gender gap will close completely within the next decades (Mayor, 2015), whereas others agree that it will further decrease but not below an extent of around three years (Wiedemann et al. 2015). An important question in this context is whether and to what extent a natural longevity advantage for females exists.

The overall natural population sex ratio is a consequence of the sex ratio at birth and life expectancy. In 2015, the global male-to-female sex ratio was 1.014, (i.e. slightly more men in the world than women) but this figure varied hugely with age. At birth and until the age of 1 year the ratio was 1.069, reaching 1 by the age of 50 falling sharply thereafter (US Census Bureau, 2015) such that by the end of life women outnumber men in every population. Why should this be? The hypotheses advanced to explain male excess mortality can be divided into two basic categories, those due to biological factors (largely beyond human control, also called 'inherited risks') and those driven by non-biological factors (i.e. behavioural, cultural and environmental influences ('acquired risks'). It is difficult to quantify the independent impact of each of these.

In this paper we will review some of the data on the differential life expectancies of women and men and consider some health conditions – genetically determined or affected by biological and non-biological factors – in order to explore and understand gender-related differences in mortality.

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3. EVOLUTIONARY MECHANISM LEADING TO THE SELECTION OF THE FEMALE GERM LINE

Central to the problem of gender is the issue of sex determination and the role of the X and Y chromosomes in sexual differentiation. It is now widely recognized in mammals that male and female gametes are dimorphic with respect to their mitochondria. Mitochondria are essential organelles known primarily for their role in ATP production and secondarily as calcium storage sites and mediators of programmed cell death (Lane, 2005). Mitochondria are endosymbionts derived from bacteria (Archibald, 2014) and adopted during the evolution of eukaryotic cells. While they harbour a genome and transcriptional machinery distinct from nuclear genomic “hosts”, mitochondria express only thirteen of the many hundreds of proteins required to generate ATP via oxidative phosphorylation (Pesole et al., 2012). Importantly, the free radicals or reactive oxygen species (ROS) produced by energized mitochondria are mutagenic to both the nuclear and mitochondrial genomes.

It is generally thought that mitochondrial DNA mutations accumulate within the lifespan of the individual. It has been proposed by Allen and colleagues that risks of oxidative phosphorylation may have led to sexual dimorphisms in the mitochondria of sperm and oocytes. The motility of highly energized sperm contrasting in the special case of the metabolically quiescent oocyte mitochondrial DNA template protected from oxidative damage (de Paula et al., 2013).

Mitochondria are maternally inherited (Mittwoch, 2013) and the gametic dimorphism noted above prompted the segregation of two sexes with two distinct and complementary vehicles, male and female, to reconcile energy conversion

with faithful transmission of mitochondria, with their tiny genomes, between successive generations (de Paula et al., 2013).

According to this theory, the avoidance of ROS-dependent mutation is the evolutionary pressure underlying maternal mitochondrial inheritance.

The role of mitochondria in the story of maternal inheritance punctuates the course of oogenesis and embryogenesis (Van Blerkom, 2004). From the transition of oogonia transit to primordial oocytes, through cell hyperplasia associated with oocyte growth, to the final editing of both numbers and DNA copies during oocyte maturation, these organelles are central to the production of developmentally competent embryos, their contribution being more than merely supporting metabolism (Mao et al 2012). How oocyte mitochondria partition their genomes and membranes remains an open question that could be related to their contribution to embryo life and to human disease (Yaffe, 1999).

Turner and Robker (2015) have recently summarized evidence, largely derived from work with mice, linking insulin resistance and obesity in offspring to stressors imposed on oocytes during their development prior to ovulation. Studies from the same group reported that treatment of obese mice with inhibitors of endoplasmatic reticulum stress ameliorate the transmission of disease predisposition to offspring (Wu et al., 2015). Studies of this kind prompt consideration of gender-specific diseases, such as PCOS in females, that have already been shown to be influenced by androgen exposures at inappropriate times of fetal development. That epigenetic factors, rather than genetic ones, are at play in this and other disease models showing gender bias will be considered below. Besides the mitochondrial origins of gender-related disease states, sex-specific patterns of transcription during embryogenesis have been shown to

impact adult health and disease susceptibility in animal models (Bermejo-Alvarez et al., 2011).

4. THE CONTRIBUTION OF X-LINKED DISEASES

Genes responsible for X-linked conditions are located on the X chromosome. These diseases mostly show recessive inheritance, implying that the gene is expressed in hemizygous males only, since females have two X chromosomes, while males have one X and one Y chromosome. In theory, female carriers, who are heterozygous, will not express the phenotype and only females who are homozygous for the mutation express recessive genes. However, some carrier females who have only one copy of the mutation do show a partial expression of the phenotype, because of skewed X-inactivation.

In Table I a number of well-known X-linked diseases are given.

5. GENDER DIFFERENCES IN LIFE EXPECTANCY: THE EFFECT OF BIOLOGICAL FACTORS

That women live longer than men has been known at least since the middle of the 18th century. Kersseboom (Kersseboom, 1740) proposed that the mortality outcomes of males and females differ sufficiently to justify the use of separate tables for calculating annuities. Excess male mortality was subsequently confirmed following the introduction of official population statistics in western societies, e.g. in Sweden from 1751 onwards (in: Tabutin, 1978).

The hypotheses advanced to explain male excess mortality can be divided into *biological factors* ('inherited risks') and *non-biological factors* ('acquired risks'). It is believed that biological factors have been responsible for only a fraction of the gender gap in life expectancy in high income countries. However, it is difficult to quantify their influence, because it is impossible to carry out relevant

experiments in human beings. Research is therefore limited to a handful of observational studies (Bourgois-Pichat, 1952, Pressat, 1973, Waldron and Johnston, 1976, Trovato and Lalu, 1996, Luy, 2003) which agree on the modest nature of this gender gap with only minor variations in its estimated extent (a difference of 1-2 years in life expectancy) and this, in fact, is the difference found in life expectancy between Catholic cloistered females compared to cloistered males) (Luy, 2003). The extent of the gender gap in life expectancy are causally related and this leads to an estimated impact of biological factors of between 0.8 and 1.6 years in life expectancy at birth. Thus, for gender differences in life expectancy up to six years—i.e. the approximate average extent in contemporary populations of high income countries—, these estimates are very similar to the commonly assumed 25% difference as being caused by biological factors.

6. LIFESTYLE ASSOCIATED HEALTH RISKS IN WOMEN AND MEN

The three major lifestyle factors affecting individual health are:

a) excessive body weight;

b) smoking;

c) alcohol.

a) Excessive body weight: consequences according to gender

Overweight [body mass index (BMI) 25-29] and obesity [BMI 30 and above] have a significant impact on health and were responsible for over three million deaths globally in 2010 (Ng et al 2014). Over the last three decades, the proportion of individuals across the world with a body-mass index (BMI) of 25 kg/m² or greater rose from 29% to 37% in men, and from 30% to 38% in women (Ng et al., 2014). High BMI has become increasingly common, despite the fact that overweight and

obese individuals are at greater risk of adverse long term health outcomes even in the absence of documented metabolic problems.

Pooled data from 19 prospective studies involving over one and a half million Caucasian adults show that in otherwise healthy non-smokers, overweight and obese women were at higher risk of all-cause mortality. Compared to women with a BMI of 22.5 to 24.9, the reference population, hazards ratios (HR) for death were significantly increased in all those with higher BMI's (Table II).

In comparison with normal weight women, the pooled hazards ratio for myocardial infarction in overweight and obese women without metabolic syndrome has been shown to be higher (Thomsen and Norgestgaard, 2014) (Table III). In otherwise healthy non-smokers, overweight and obese men were at higher risk of all-cause mortality (Table II). In comparison with normal weight men, the pooled HR for myocardial infarction and ischemic heart disease in obese men were much increased (Table III).

b) <u>Different health outcomes of smoking in women and men</u>

The prevalence of smoking varies substantially according to gender, time period and geographical area. In high income countries the prevalence of male smokers increased dramatically in the first part of the 20th century and decreased again from 1980 onwards. Women started smoking a few decades later than men but continued to do so after rates of smoking in men began to fall (Peto et al. 1992). More recently, smoking has been declining in women as well, at least in Western countries (Thun et al., 2012). As illustrated by an analysis of mortality in 30 European countries, smoking-related deaths currently account for 40-60% of the gender gap in mortality in Western Europe (McCartney et al., 2011).

The review on sex, gender and lung cancer entitled *"Smoke like a man, die like a man"* (Payne, 2001) summarizes the health consequences of smoking in women. In studies investigating both sexes, the shorter duration of the habit and the lower number of cigarettes consumed by women had initially led to the erroneous belief that women were somehow less susceptible to the damages of smoking. However, more recent epidemiologic evidence clearly shows that women are at least as susceptible as men to smoking-related cancers, respiratory diseases, cardio-vascular diseases and other health problems caused by smoking (Surgeon General, 2001). In fact, relative risks appeared to be even higher in women. Although the cumulative exposure to smoking was lower in women than in men, a recent meta-analysis on this topic showed that women smokers had a 25% greater relative risk (RR) of coronary heart disease (CHD) than men, independent of other cardiovascular risk factors (Huxley and Woodward, 2011). In contrast to CHD, there was no clear evidence for a sex-difference in the risk of stroke among women who smoked compared with men who smoked (Peters et al., 2013). The Million Women Study, a prospective study including 1.3 million British women showed that (at age 50-79) smokers had three times the overall mortality of never smokers, and that on average female smokers lose at least 10 years of their lifespan (Pirie et al., 2013). These results are similar to those found in men (Doll et al., 2004). The excess risk appears similar in both sexes, and the higher RR in women is due to the lower baseline risk in non-smokers. As for their male counterpart, stopping smoking is an effective way to avoid most of the damage caused by smoking, and even cessation at 50 years of age avoids at least two thirds of the excess mortality seen in women that continue smoking (Pirie et al. 2013).

c) <u>Outcomes of alcohol consumption in the two sexes</u>

In most parts of the world, women drink less than men, and suffer fewer health consequences as a result. Still, alcohol remains a major cause of disease and death in women, and there are sex-specific diseases (mainly breast cancer) which are particularly relevant for women. In an analysis of mortality in 30 European countries, alcohol-related deaths accounted for 20-30% of the gender gap (McCartney et al., 2011). In Russian male smokers, heavy drinking is associated to an almost doubling of mortality in middle age (35-54 years, from 20% to 35% cumulative risk of death). Among women, heavy drinking is much less common in Russia, but appears to involve a similar increase in risk of total mortality (Zaridze et al., 2014).

Alcohol drinking is related to a number of outcomes– some of which are fatal including accidents, violence, cirrhosis and other liver conditions, several cancers, acute intoxication, psychosis and heart failure. While all of these conditions are related to the quantity and the pattern (Bagnardi *et al.*, 2008) of drinking, a valid quantification of the sex differences in alcohol-related disease incidence and mortality exists predominantly for cancer.

It has been estimated that in 2002 about 390,000 incident cancers (3.6% of the total number) were attributable to alcohol drinking worldwide – 300,000 in men (5.2%) and 90,000 in women (1.7%). Corresponding figures for cancer deaths were over 230,000 (3.5%) – 195,000 in men (5.1%) and 35,000 in women (1.3%, (Boffetta et al., 2006). More than one in four alcohol-related cancers worldwide, and one in five cancer deaths, are in women. The absolute numbers, as well as the proportions, of alcohol-related cancers have been rising in women over the last decade (Praud et al., 2015). Table IV shows updated estimates of alcohol-

attributable cases for all cancers and alcohol-related sites. Overall, about 535,000 cancers in men (7.2% of the total) and 235,000 in women (3,5% of the total) are attributable to alcohol drinking, corresponding to about 770,000 cancer cases in both sexes combined. With reference to cancer mortality, about 480,000 cancer deaths are attributed to alcohol (5,8% of the total), over 360,000 in men (7,8%) and 115,000 in women (3.3% of the of the total). The lower proportion of cancer incidence than mortality in women is due to the weight of breast cancer, which is the major alcohol-related cancer in women, and has comparatively favourable prognosis as compared to other alcohol-related cancers.

No valid data are available on sex-differences in other alcohol-related diseases and deaths, in particular on liver disease and accidents. However, in most high income countries cancer accounts for over 50% of the total burden of alcohol-related diseases and deaths (Corrao et al., 2004), and differences specific in all other diseases can only partly modify the sex differential in alcohol-related diseases and deaths.

Moderate alcohol consumption may have a favourable impact on CVD and death and on total mortality (Doll et al., 2005; Giacosa et al., 2013), but any putative benefit is likely to be greater in men who are middle aged or older, and who have higher rates of incidence and mortality from CVD than women.

7. CARDIOVASCULAR DISEASES: A NEGLECTED HEALTH RISK DIFFERENCE FOR WOMEN

Despite substantial progress in the awareness, treatment, and prevention of cardiovascular disease (CVD) over the past decades, it remains the world's leading, and arguably most preventable, cause of death and disability. While considerable efforts to raise awareness of CVD and its symptoms have been

made, there is still a wide-spread perception, particularly in lower and middle-income countries, that it is a disease that predominantly affects men. However, as women have a greater life expectancy than men, the cardiovascular burden in absolute terms, is actually greater in women than in men; in 2004 almost 32% of all deaths in women were due to cardiovascular causes compared to 27% in men. These estimates, and the notable sex-difference in cardiovascular burden, are likely to increase further due to population aging, a higher life expectancy and the decade delay in the development of symptomatic CVD in women relative to men. "Biological" and "non biological factors" may interact in the area of cardiovascular risk and Figure 1 summarizes the results of recent systematic studies.

Higher levels of systolic blood pressure and body mass index (BMI) are important risk factors for coronary heart disease (CHD) and stroke, which are as hazardous in women as in men (Mongraw-Chaffin et al., 2015; Peters et al., 2013a). Sex differences in the risk of CVD associated with smoking are likely to be due to different smoking habits (Peters et al., 2013b) while there is a convincing evidence of higher risk associated with diabetes in women. Two recent meta-analyses have shown that women with diabetes had a 44% higher excess risk of CHD, and a 27% higher excess risk of stroke as compared to similarly affected men (Peters et al., 2013c; Peters et al., 2014a). A 37% higher risk of all-cause mortality in women associated with type I diabetes has also been reported, predominantly driven by a higher risk for CVD in women (Peters et al., 2014b).

8. PREGNANCY RELATED MATERNAL DEATHS: AN EXCLUSIVE FEMALE RISK

In 2013 around 290,000 maternal deaths occurred globally. Although this represents a decrease of 45% since 1990, the level of maternal mortality in many countries continues to be unacceptably high. Sixty two percent of all maternal

deaths occur in Sub-Saharan Africa, which has the world's highest maternal mortality ratio (MMR) with 510 per 100,000 live births compared to the global average of 210 deaths per 100,000 live births. This region has also experienced one of the slowest rates of decline in maternal mortality, with an average decrease of 2.9% between 1990 and 2013 when compared to South and East Asia which have seen decreases by about 4.5% over the same time period (World Health Organization, 2014).

High rates of maternal mortality (and morbidity) are clearly a gender issue and could potentially be resolved by two simple interventions . The first is family planning. In the last two decades increasing contraceptive use has reduced maternal deaths in developing countries by around 40% (Cleland et al., 2012). Yet today more than 200 million women in the developing world who want to avoid pregnancy do not use modern contraception. Fewer than 70% of postpartum women wanting contraception have access to it. It has been estimated that if the demand for family planning was met, 54 million unintended pregnancies, and more than 79,000 maternal deaths could be avoided annually (Cleland et al., 2012).

The second intervention would be to liberalise abortion. More than one third of pregnancies in the world each year are likely unintended (68 million) and 44 million pregnancies end in induced abortion, half of those unsafe. Around 47,000 women die from unsafe abortion every year (13% of all maternal deaths worldwide) and another 5 million women suffered significant disability (Sedgh et al., 2012). The fact that access to safe abortion can save maternal lives is evident from the fact that liberalisation of the abortion law in South Africa in 1997

resulted in a 91% decrease in the number of abortion related deaths (Benson et al., 2011).

9. ADDITIONAL HEALTH RISKS SPECIFIC FOR WOMEN

There are a number of examples of health risks that are specifically due to gender discrimination affecting the health and life expectancy of women (Sen, 1992; Bongaarts, 2013).

a) Social sex-selective abortion

In many societies a preference for sons is a long-standing cultural tradition that often leads to higher mortality among girls and women than among boys and men.

- Sex-ratio at birth (SRB)

Male-to-female sex ratios at birth above 1.07 usually are considered to be the result of prenatal sex selection and selective abortion. Some parts of the world, particularly China and India have witnessed increased rates of sex-selective abortion. In China the sex ratio rose from 1.07 in 1982 (when there was virtually no prenatal sex selection) to 1.20 in 2005 (Li, 2007). In India, the corresponding figure increased from 1.09 in 1982-1984 to 1.14 in 2003-2005 (Kulkarni, 2007). According to the most recent reliable figures, countries with a sex ratio over 1.10 are Azerbaijan, Albania, Armenia, China, India, Vietnam and Georgia.

What all these countries have in common is a strong patrilineal family structure, combined with a permissive attitude towards abortion, and rapidly declining birth rates. There are three specific preconditions that favour the practice of sex selection (UNFPA, 2012): 1. It should be *advantageous*; parents will resort to sex selection only when they perceive clear benefits in having (usually) boys rather than girls. Thus there is a strong son preference in India where it is anticipated

364 that sons will work on the family land or in the family business, stay with their
365 parents after marriage, offering them physical protection and economic support.
366 Daughters are married off (after payment of a dowry) and move away from their
367 family to live with their husband's relatives (Guilmoto, 2013). 2. It should be
368 *necessary*; small-family norms represent a distinct precondition for sex selection;
369 otherwise, parents would simply have additional births in order to achieve their
370 gender objective. China is an example of a country where political directives (the
371 "one-child family" rule) have induced an artificial demographic fertility decline
372 (Guilmoto, 2013). Left to chance one in four couples in a two-child family and -
373 half of couples with a one-child policy would have no son. 3. Sex selection should
374 be *feasible*; parents need to have easy access to acceptable and efficient methods
375 (UNFPA, 2012). Son preference is common in many low and middle income
376 countries. This affects the health of the unborn child as well as that of the
377 mother. Bongaarts and Guilmoto (2015) used Demographic and Health Surveys
378 to explore sex composition preferences. Estimates of desired sex ratio at birth
379 (DSRB) were available for women in 61 countries and for men in 45 countries. In
380 29 countries the DSR exceeded 110 but there was a wide margin between the
381 desired sex ratio and the observed sex ratio in all countries. Although many
382 couples state a preference for sons the observed sex ratio is around average. The
383 gap varies from country to country perhaps because access to sex-selection
384 technology (ultrasound) and/or safe abortion varies. Moreover, for many couples,
385 abortion may be unacceptable. Bongaarts and Guilmoto (2015) describe 'a large
386 pent-up demand for sex selection' and suggests a potential for future increases in
387 sex ratios if and when the 'medical, technical, ethical, social, and economic

obstacles that now prevent sex selection are removed and if nothing is done to raise gender equality'.

Sex selective practices have significant implications for the future. High sex ratios at birth irrevocably lead to high adult sex ratios. Selectively reducing female birth will create a shortage of young women disturbing the 'marriage market' of this generation in the affected countries, with a surplus of increasingly anxious young unmarried men. This may have considerable social implications, e.g. increased prostitution, sex offenses, rape, importing brides from neighbouring countries, women trafficking and social turmoil, which in turn will affect women's health. (Hvistendahl, 2011)

b) <u>Female genital mutilation</u>

In some parts of the world, many mothers believe that Female Genital Mutilation (FGM) is a rite of passage necessary to optimise marriage prospects, preserve virginity and promote femininity. Defined as any ceremonial or non- medical alteration of the female genitalia, the extent of the procedure varies considerably from partial excision of the clitoris to total excision of labia minora, labia majora and clitoris with narrowing of the vaginal orifice (World Health Organization, 2010). Immediate complications of FGM include bleeding, infection, pain, retention of urine, and death. Late complications include urinary complications, scarring, pain, infertility and sexual dysfunction.

WHO estimates that between 100 million and 140 million girls and women world-wide have been subjected to FGM. Most commonly practised in North, West and East Africa in Somalia, Guinea, Egypt, Mali, Eritrea, Sudan (World Health Organization, 2008) – an estimated 500,000 of women living in Europe have undergone the procedure (Garcia-Moreno et al., 2005). The prevalence of FGM

varies dramatically among ethnic and religious groups and also according to rurality, income and education (Mitis et al., 2015). Social traditions and belief that religion requires FGM are major reasons for its continuation.

- Recent trends

Several reports showed that the prevalence of FGM has declined in the past two decades. On December 2012 the United Nations voted to ban FGM in all of its member countries (Gracia, 2004).

c) <u>Early and child marriage</u>

Early marriage, e.g. marriage occurring before the age of 18, with or without parental and/or judicial consent, is often associated with health problems such as adolescent pregnancy with its attendant complications, high maternal mortality, sexual violence and STIs. It represents a violation of the Convention of the Rights of the Child (UNICEF, 2005). It also constitutes a major threat to the development and education of the adolescent.

- Determinants

The main determinants of early marriage are: poverty and low socioeconomic situation (often in rural areas), poor level of education of both the parents and the adolescents themselves, archetypical social norms prevailing in the region or country, including a strong gender inequality and inappropriate legislation or disregard of the legislative framework. Gender is an issue as well: boys are also married as children, but in a disproportionally low rate.

- Epidemiological situation across continents and countries

Overall, one out of three girls in developing countries will have been married before they are 18, and one out of nine girls will have been married before their 15th birthday. In 2014, the overall number of women married before age 18

worldwide was estimated to 720 millions. South Asia, in particular India, is especially hit, and provide 42% of all early marriages. East Asia and the Pacific (25%), Africa (18%) and Latin America and the Caribbean (9%) account for most of the other affected regions (Loaiza, 2012; UNICEF, 2001; Office of the United Nations High Commissioner for Human Rights, 2014). However, the rates of girls married before age 18 as compared to the total number of married women is highest in Africa: in Ethiopia, Niger, Chad, Guinea, and Malawi, more than 50% of girls marry before age 18. Worldwide, 12 per cent of women were married or in union before age 15 (Figure 2). In most countries, on all continents, a downward trend has been observed over the last 10-15 years.

- Impact on development and health

Early marriage, especially below the age of 15 has disastrous consequences on the development and health of adolescents who may leave school without an education thus becoming more vulnerable later in life. Early marriage is also often accompanied by one or more pregnancies and – where the the spouse is older and possibly polygamous – violence and sexually transmitted infections (Loaiza, 2012; Raj et al., 2009).

- Public health, policies and interventions

Educational interventions have been developed at several levels, such as within the school and the community (Erulkar and Muthengi, 2009). As a response to poverty, cash transfer strategies have been developed, which have proven effective in improving retention in the school system and delaying marriage (Chandra-Mouli et al., 2013).

Many countries have adopted the age of 18 as the minimum age of marriage, but in many instances, communities, especially in rural areas, ignore the law. The

463 enforcement of adherence to the legal frame is an important part of the
464 prevention of early marriage. Also, countries should remove the legislation that
465 discriminates between men and women in terms of the minimum legal age for
466 marriage.

467 **d) Violence against women**

468 Violence against women is defined as “any act of gender-based violence that
469 results in, or is likely to result in, physical, sexual or psychological harm or
470 suffering to women, including threats of such acts, coercion or arbitrary
471 deprivation of liberty, whether occurring in public or in private life.” (United
472 Nations, 1993). It includes FGM, while intimate partner violence (IPV) is the
473 commonest type of cruelty prevalent in every country and society worldwide
474 (United Nations, 1993). It often remains hidden; few women report IPV to the
475 police. WHO estimates that between 15% and 71% of women experience physical
476 and/or sexual violence from an intimate partner at some time in their life (Garcia-
477 Moreno et al., 2005). IPV may be perpetrated by partners of both sexes, and may
478 occur in same sex relationships but women in heterosexual relationships are the
479 commonest victims.

480 - Prevalence

481 A recent meta-analysis of 155 population surveys in 51 countries provides
482 reliable estimates of the lifetime prevalence of IPV in women aged 15 or more
483 (Gracia, 2004). The global prevalence is 30%; while the corresponding values for
484 low- and middle-income countries of Europe, and high-income countries are
485 25.4% and 19.3% respectively. Table V shows that more than a third of female
486 killings are carried out by an intimate partner, accounting for 2000 annual

deaths in Europe. Figure 3 illustrates the mortality rates registered recently in the European countries.

- Honour violence

Societal expectations of masculine and feminine behaviour, often referred to as "gender roles," are ubiquitous. In some countries, these roles are associated with distinct forms of active and passive "honour", whereby men are supposed to be assertive and respond with violence to slights upon their own, or their families' "honour" and women are expected to maintain their own honour through conformity to social norms of feminine behaviour. In such a context, a man has an explicit role to meet the expectations of the community and the family, and to respond, potentially with violence, if this does not happen. The United Nations Population Fund (UNFPA) estimates that the annual worldwide number of so-called "honour killing" victims may be as high as 5,000. (UNFPA, 2000)

- Dowry violence

Dowry violence, in which young brides are tortured, killed, or pushed to commit suicide if the size of their dowries is considered inadequate, is common in some countries like Bangladesh, India and Pakistan,. In 2013, the Indian National Crime Records Bureau reported 8,083 dowry deaths (UNFPA, 2000). While this represents a 1.8% decline of deaths over the reported deaths for 2012 (8,233), the numbers of cases of "cruelty by husband or his relatives" increased from 89,546 in 2009 to 118,866 in 2013 (11.6% increase), indicating the much larger phenomenon of maltreatment of women as lower-valued human beings, despite a high economic growth and a rapidly expanding middle class with a more modern social outlook

- Trends

International human rights bodies strongly recommend that states pass legislation “to remove the defence of honour in regard to the assault or murder of a female family member” (United Nations Committee on the Elimination of Discrimination against Women, 1992). At the national level, some countries, like Turkey, have changed their laws to reflect these human rights standards. (Turkish Penal Code, 2004).

9) CONCLUSION

Males outnumber women at birth, avoid the complications of pregnancy and social discrimination, but pass away earlier and in larger numbers due to fighting, wars, alcohol and smoking; on a global scale they are less likely to outlive women. Gender based differences in health outcomes are due to biological, environmental and lifestyle factors. Many of these differences are relative rather than absolute.

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607 ouderdom. Hier is bygevoegt een proeve van de constante ondervinding, dat
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792 **Table I.** Clinical characteristics of the most common X-linked diseases (Online Mendelian
793 inheritence in men (OMIM). A knowledgebase of human gene and genetic disorders:
794 http//www.mcj.mlm.mih.gov/omim. 2015; Orphanet the portal for rare disorders:
795 http//www.orpha.net).
796

	Incidence	Male patients	Female carriers
Fragile X syndrome	Affects up to 1/2,500 males and 1/4,000 females. Most frequent genetic cause of mental retardation in males.	Results from CGG expansion in FMR1 gene. Long face, large ears, connective tissue abnormalities. Macro-orchidism. Characteristic behaviour.	An expansion of the CGG repeat from 55 to 199 copies in women is associated with ovarian dysfunction in about 20% of carrier women. More than 200 CGG copies results in fragile X syndrome.
Red-green color vision deficiency	Present in about 1/12 of all males and about 1/200 of all females.	Genetic changes involving the OPN1LW or OPN1MW gene cause red-green color vision defects. These changes lead to an absence of L or M cones or to the production of abnormal opsin pigments in these cones that affect red-green color vision.	
Glucose 6 Phosphate Dehydrogenase Deficiency	Affects 0.5-26% of the population and an estimated 420 million individuals in the world	Most often patients are asymptomatic. However, acute hemolytic anemia, can appear following ingestion of certain foods (fava beans), taking certain common drugs (some antimalaria drugs, sulphamides, analgesics), or in the course of an infection.	In heterozygous females the disease has a variable expression, and is often absent or moderate
Duchenne Muscular Dystrophy	Affects about 1/3,600 boys.	Caused by a mutation in the gene which codes for dystrophin. Early childhood onset, muscle weakness leading to wheel chair dependency and death at about 25 years.	Echocardiographic examination abnormal in 36 % Dilated cardiomyopathy in 8% of DMD carriers Left ventricle dilatation in 18 % Only 38 % normal
Haemophilia A	Clotting factor VIII deficiency occurs in about 1/5,000 to 1/10,000 males.	Symptoms are internal or external bleeding episodes. Without treatment life expectancy is about 10 years. With treatment it is almost normal.	Female carriers have increased bleeding tendency as well.
Haemophilia A	Clotting factor IX deficiency occurs in about 1/20,000 to 1/30,000 males.	Idem	Idem
Fabry disease	Deficiency of the enzyme alpha galactosidase A, present in between 1/40,000 and 1/120,000 males	Wide range of systemic symptoms. Life expectancy for males was 58.2 years, compared with 74.7 years in the general population. The most common cause of death was cardiovascular disease, and most of those had received kidney replacements.	For females life expectancy was 75.4 years compared with 80.0 years in the general population.
Complete Androgen Insensitivity	Estimated incidence is between 1/20,000 and 1/99,000 live male births	Individuals with complete androgen insensitivity syndrome are born phenotypically female, without any signs of genital	Normal

		masculinization, despite having a 46,XY karyotype and testes.	

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799 **Table II.** Hazards ratios for death according to BMI (Berrington de Gonzalez et al.,
800 2010).

BMI	All-cause mortality	
	women	Men
22.5-24.9	*ref.*	*ref.*
25.0-29.9	1.13 (1.09, 1.17)	1.17 (1.12, 1.23)
30.0-34.9	1.44 (1.38, 1.50)	1.43 (1.36, 1.50)
35.0-39.9	1.88 (1.77, 2.00)	1.95 (1.79, 2.12)
40.0-49.9	2.51 (2.30, 2.73)	2.86 (2.51, 3.25)

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803 **Table III.** Pooled hazard ratios (95% CI) for myocardial infarction and ischemic
804 heart disease in overweight and obese women and men without
805 metabolic syndrome (Thomsen and Norgestgaard, 2014)

	Myocardial infarction		Ischemic heart disease	
	women	men	women	Men
Overweight	1.62 (1.09, 2.40)	1.09 (0.81, 1.48)	1.12 (0.92, 1.37)	1.08 (0.90, 1.77)
Obese	1.91 (1.12, 3.27)	1.83 (1.19, 2.82)	1.18 (0.88, 1.58)	1.77 (1.36, 2.31)

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Table IV. Alcohol-attributable cancer cases worldwide by sex (Praud et al, 2015).

Cancer	Men		Women	
	Attributable Fraction %	Cases	Attributable Fraction %	Cases
Oral cavity and pharynx	44.7	140,416	17.2	22,131
Esophagus SCC	51.8	143,963	28.3	34,035
Colon and rectum	15.0	111,555	2.3	14,019
Liver	13.0	71,595	12.8	28,952
Gallbladder	25.3	19,449	8.2	8,325
Pancreas	5.4	9,584	1.4	2,194
Larynx	28.4	39,143	9.7	1,821
Breast	NA	NA	7.3	122,010
TOTAL CANCER	7.2*	535,705	3.5*	233,487

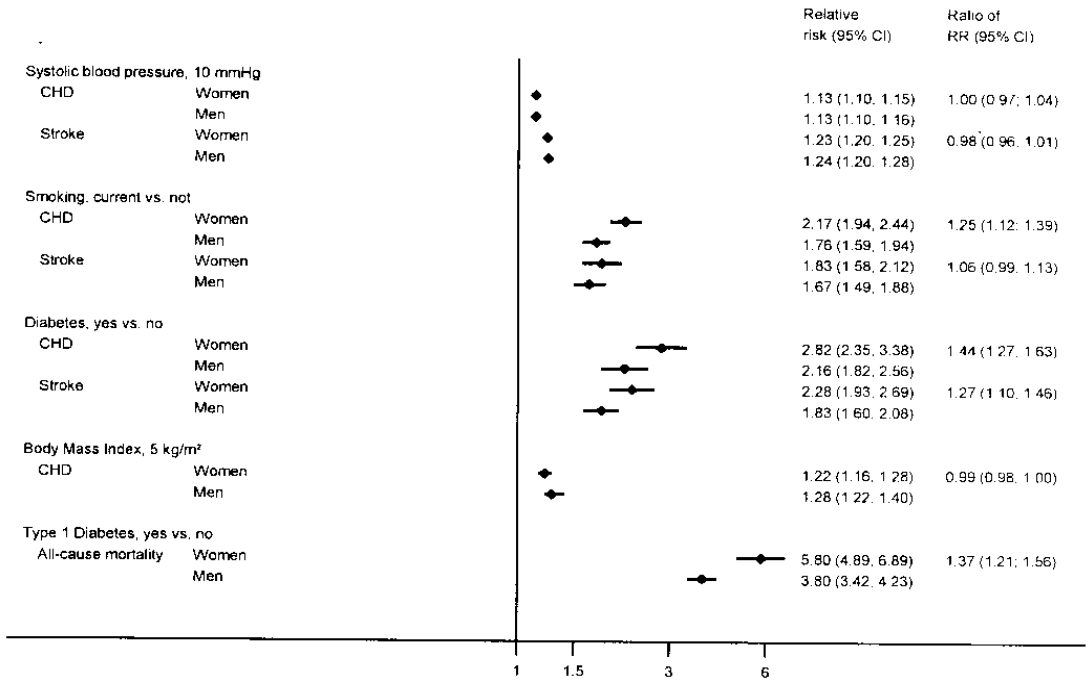
SCC: squamous cell carcinoma. NA: not applicable

*Denominator comprises all cancer.

Table V. Global prevalence of intimate partner (I.P.) homicide in 66 countries (Stokl et al., 2013).

Region	Female homicide		Male homicide	
	cases (No.)	I.P. portion	cases (No.)	I.P. portion
Worldwide	133.691	47.4	373.077	6.5
High income countries	115.515	48.6	364.410	6.6
Africa	6.219	44.8	235	4.4
Americas	9.658	42.6	4.580	4.0
Low and middle income Europe	200	20.4	226	3.7
Southeast Asia	80	62.1	334	1.0
Western Pacific	1.132	20.2	3.292	1.6

Figure 1. Summary results from meta-analyses of sex differences in the association between cardiovascular risk factors and following events (Appelman et al., 2015)



Boxes and bars represent relative risks and 95% confidence intervals for women and men. Ratio of RR represents the female:male ratio of relative risk for CHD, stroke, and all-cause mortality

849 Figure 2. UN Demographic and Health Survey, 2000-2010. European Training in
850 Effective Adolescent Care Health (EUTEACH).

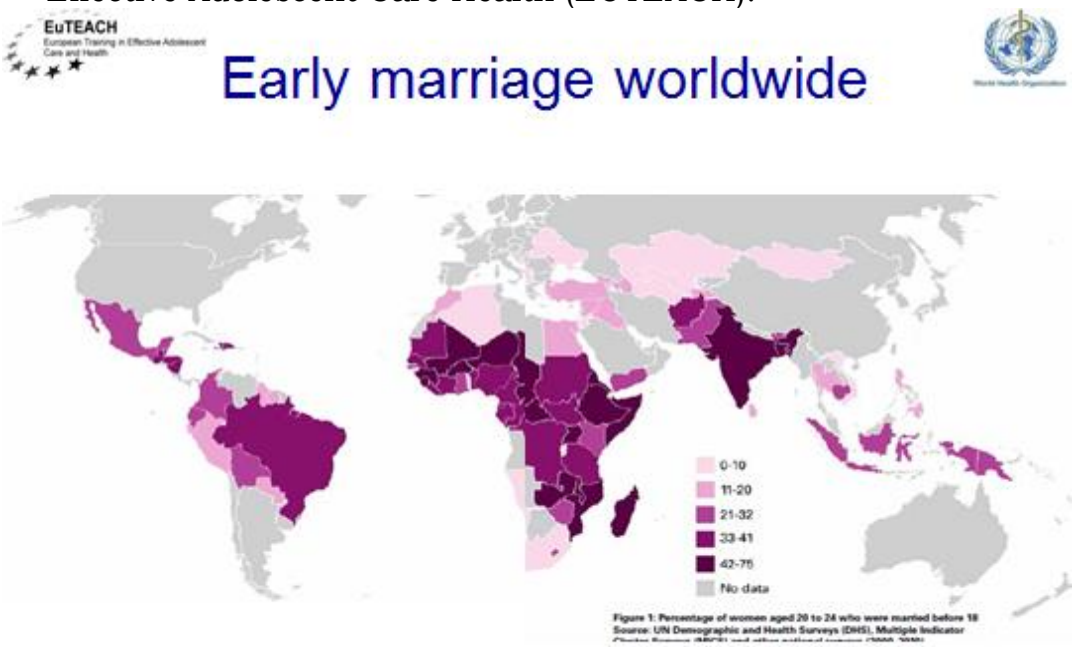


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Figure 3. Mortality rates in women aged 15-69 years due to assault in the European Region by country income level per 100 000 population (REFERENCE - Sethi).