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human reproduction **OPINION**

The influence of social factors on gender† health

ESHRE Capri Workshop Group*,‡

*Correspondence address. P.G. Crosignani, IRCCS Ca' Granda Foundation Maggiore Policlinico Hospital, Via M. Fanti, 6, 20122 Milano, Italy; E-mail: piergiorgio.crosignani@unimi.it

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ABSTRACT: 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 about 6 years longer. Thus within various age groups the male:female ratio changes over time. Until age 50 years men outnumber women; thereafter their numbers show a sharp decline. Consequently at age 80 years, there are many more women than men. An estimated 25% of this male excess mortality is due to biological causes, the rest being explained by behavioural, cultural and environmental factors. For both women and men, the main health risks related to lifestyle are smoking, alcohol, unhealthy diet and physical inactivity. In the year 2010, overweight (BMI: 25–29 kg/m^2) and obesity (BMI: >30 kg/m^2) were responsible for over 3 million deaths, with similar relative risks in men and women for overweight and obesity. Smoking and alcohol are the major causes of the global gender gap in mortality. For women in some parts of the world however pregnancy is also hazardous. On a global scale, in 2013 about 300 000 deaths were related to pregnancy, with sub-Saharan Africa registering the highest maternal mortality: over 500 maternal deaths per 100 000 births. Additional woman's health risks arise from gender discrimination, including sex-selective abortion, violence against women and early child marriage. Providers should be aware of the effect that these risks can have on both reproductive and general health.

Key words: health / life expectancy / gender / lifestyle / sex selective abortion / early and child marriage / violence against women

Introduction

More boys are born than girls. The natural sex ratio is ~1.05–1.06, i.e. ~5–6% more male than female births. The overall population sex ratio is a consequence of the sex ratio at birth and life expectancy, and women live longer than men (Barford *et al.*, 2006).

That there is a difference in longevity between males and females has been known since at least the middle of the 18th century. Kersseboom (1740) proposed that mortality of males and females differs 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 (Tabutin, 1978). Recently, however some forecast that the gender gap in life expectancy will tend to close within decades (Mayor, 2015).

The hypotheses advanced to explain male excess mortality can be considered in terms of *biological factors* (inherited risks) and *non-biological factors* (acquired risks).

The biological gender gap in life expectancy is still a difficult research area with the literature limited to a handful of observational studies (Bourgeois-Pichat, 1952; Pressat, 1973; Waldron and Johnston, 1976; Trovato and Lalu, 1996; Luy, 2003), which agree on a modest degree of gender gap with only minor variations. The estimated difference in life expectancy is 1–2 years, the difference found in life expectancy between Catholic cloistered nuns compared with cloistered priests—groups of men and women with very similar lifestyles (Luy, 2003).

This difference in life expectancy corresponds to about 1/3 of that presently observed in most areas of the world.

Lifestyle-associated health risks in women and men

The three major lifestyle factors affecting individual health are excess body weight, smoking and alcohol.

Excessive body weight: consequences according to gender

Overweight [BMI 25–29 kg/m^2] and obesity [BMI 30 and above] have a significant impact on health and were estimated to be responsible for over 3 million deaths globally in 2010 (Ng *et al.*, 2014). Over the last

†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 and Ravindran, 2017.)

‡ The list of The ESHRE Capri Workshop Group participants is given in the Appendix.

three decades, the proportion of individuals globally with a BMI of 25 kg/m^2 or above 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.

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 are at higher risk of all-cause mortality. Compared with women with a BMI of 22.5–24.9 kg/m^2, the reference population, hazards ratios (HR) for death are significantly increased in all those with higher BMI (Table I). Similarly, otherwise healthy non-smokers, overweight and obese men are at higher risk of all-cause mortality (Table I). The excess risk is similar in both sexes (Berrington de Golzalez *et al.*, 2010). Likewise, in comparison with normal weight women, the pooled HR for myocardial infarction in overweight and obese women has been shown to be higher to a similar degree (Thomsen and Nordestgaard, 2014). Thus, although a major—and increasing—cause of mortality for both men and women, there appear to be no differences between the sexes on the effect of obesity on mortality.

Smoking in women and men

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 then decreased from 1980. 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, at least in Western countries (Thun *et al.*, 2012). As illustrated by an analysis of mortality in 30 European countries, smoking-related deaths 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 smoked by women had initially led to the erroneous belief that women were somehow less susceptible to the damages of smoking. However, 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). Indeed relative risks (RR) 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 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 smokers compared with men (Peters *et al.*, 2013c). The Million Women Study, a prospective study including 1.3 million British women, showed that (at age 50–79 years) current 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). As with men, stopping smoking is an effective way to avoid most of the damage, and even cessation at 50 years of age avoids at least two–thirds of the excess mortality seen in women who continue smoking (Pirie *et al.*, 2013).

Table I Hazards ratios for death according to BMI (derived from Berrington de Gonzalez *et al.*, 2010).

BMI (kg/m^2)	All-cause mortality	
	Women	Men
22.5–24.9	1.00 reference	1.00 reference
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)

Outcomes of alcohol consumption in the two sexes

In most parts of the world, women drink less than men, and accordingly suffer fewer health consequences. Nevertheless, alcohol is a major cause of disease and death in women, and some sex-specific diseases (mainly breast cancer) 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 with an almost doubling of mortality in middle age (at 35–54 years, from 20 to 35% cumulative risk of death). Among Russian women, heavy drinking is much less common, but appears to invoke a similar increase in the risk of total mortality (Zaridze *et al.*, 2014).

Drinking alcohol is related to a number of outcomes—some 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 pattern (Bagnardi *et al.*, 2008) and amount of drinking, a valid quantification of the sex differences in alcohol-related disease incidence and mortality exists only for cancer.

In 2002, an estimated 390 000 incident cancers worldwide (3.6% of the total number) were attributable to drinking alcohol—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, occur 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.*, 2016). Table II shows updated estimates of alcohol-attributable cases for all cancers and for alcohol-related cancers.

Cardiovascular diseases: a neglected health risk difference for women

Despite substantial progress in awareness, treatment and prevention of cardiovascular disease (CVD) over the past decades, it remains the leading cause of death and disability worldwide. While considerable efforts to raise awareness of CVD and its symptoms have been made, there is still a widespread 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 with 27% in men (World Health Organization, 2008). 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 of delay in the development of CVD in women relative to men.

'Biological' and 'non-biological factors' may interact in the area of cardiovascular risk and Fig. 1 summarizes the results of recent systematic studies.

Table II Alcohol-attributable cancer cases worldwide by sex (modified from Praud *et al.*, 2016).

Cancer	Men attributable		Women	
	Fraction %	Cases	Fraction %	Cases
Oral cavity and pharynx	44.7	140 416	17.2	22 131
Oesophagus 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	8325
Pancreas	5.4	9584	1.4	2194
Larynx	28.4	39 143	9.7	1821
Breast	NA	NA	7.3	122 010
Total cancer	7.2[a]	535 705	3.5[a]	233 487

SCC, squamous cell carcinoma; NA, not applicable.
[a]Denominator comprises all cancer.

Higher systolic blood pressure and BMI are both important risk factors for CHD and stroke, which are as hazardous in women as in men (Peters *et al.*, 2013a; Mongraw-Chaffin *et al.*, 2015). 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 convincing evidence of higher risks 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 with similarly affected men (Peters *et al.*, 2013c, 2014a). A 37% higher risk of all-cause mortality in women associated with Type 1 diabetes has also been reported, predominantly driven by a higher risk for CVD in women (Peters *et al.*, 2014b).

Health risks specific to women

Pregnancy

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 disappointingly high. Sixty-six percent of all maternal deaths occur in Sub-Saharan Africa, which has the world's highest maternal mortality ratio at 510 deaths per 100 000 live births compared with 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. In contrast, South and East Asia had decreases of over 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 ~40% (Cleland *et al.*, 2012).

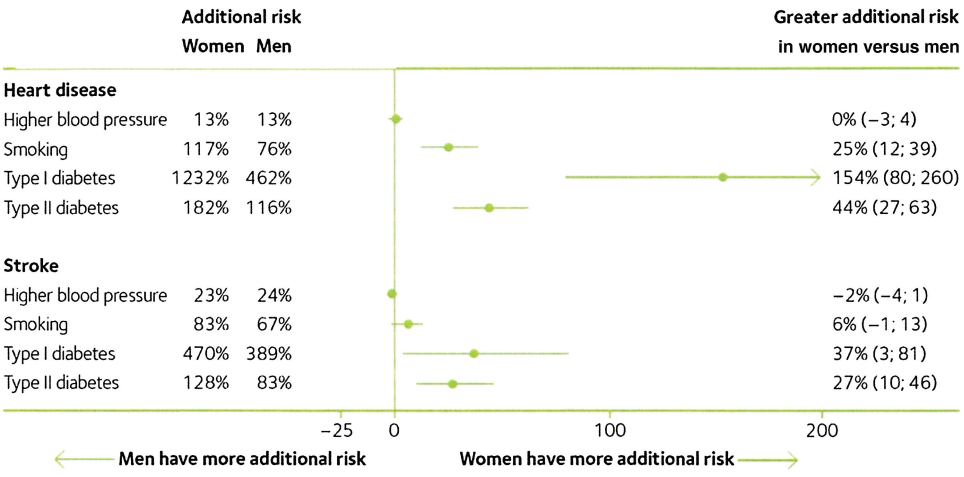

Figure 1 The additional risks of ischaemic heart disease and stroke associated with higher blood pressure, smoking and Type I and Type II diabetes in women compared with men (data from Appelman *et al.*, 2015). The additional risk of ischaemic heart disease and stroke for (i) those with a 10 mmHg higher value of systolic blood pressure; (ii) smoking compared with not; (iii) Type I diabetes compared with not; (iv) Type II diabetes compared with not. Results are shown as the additional risk for women and men and (plotted results and right-hand column) the extra additional risk for women compared with men (e.g. smoking confers 25% more risk of heart disease for women than it does for men). 95% confidence intervals are shown as horizontal lines around the estimates on the graph, and in parentheses in the right-hand column. Additional risk = 100 × (Relative risk − 1); greater additional risk = 100 × (female:male ratio of relative risks − 1).

The second intervention would be to liberalize abortion laws. 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 (Cleland *et al.*, 2012).

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.

Male-to-female sex ratios at birth above 1.07 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).

Countries with a sex ratio over 1.10 include Azerbaijan, Albania, Armenia, China, India, Vietnam and Georgia.

Three specific preconditions favour the practice of sex selection (UNFPA, 2012): first, 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 that sons will work on the family land or in the family business, and stay with their parents after marriage, offering them physical protection and economic support. Daughters however are married off (after payment of a dowry) and move away from their family to live with their husband's relatives (Guilmoto, 2013) so they are expensive and contribute nothing. Second, it should be *necessary*; small-family norms represent a distinct precondition for sex selection; otherwise, parents would simply have additional births in order to achieve their gender objective. China is an example of a country where political directives (the 'one-child family' rule) have induced an artificial demographic fertility decline (Guilmoto, 2013). Third, sex selection should be *feasible*; parents need to have easy access to acceptable and efficient methods (UNFPA, 2012). Bongaarts describes 'a large pent-up demand for sex selection' and suggests a potential for future increases in 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' (Bongaarts and Guilmoto, 2015).

Violence against women

Violence against women is defined as 'any act of gender-based violence that results in, or is likely to result in, physical, sexual or psychological harm or suffering to women, including threats of such acts, coercion or arbitrary deprivation of liberty, whether occurring in public or in private life.' (United Nations, 1993). It includes female genital mutilation (FGM). Intimate partner violence (IPV) is the commonest type of cruelty prevalent in every country and society worldwide (United Nations, 1993). It often remains hidden; few women report IPV to the police. The World Health Organization estimates that between 15 and 71% of women experience physical and/or sexual violence from an intimate partner at some time in their life (Garcia-Moreno *et al.*, 2005). IPV may be perpetrated by partners of both sexes, and may occur in same sex relationships but women in heterosexual relationships are the commonest victims. Accurate figures for the prevalence of FGM and IPV are lacking since, for obvious reasons, they often are unreported. Estimates are likely to be conservative.

Forms and prevalence of violence against adult women

A recent study involving 66 countries shows that more than one-third of female killings are carried out by an intimate partner (Stöckl *et al.*, 2013). In Europe, the highest rates are registered in the poorest countries (World Health Organization, 2013) (Fig. 2).

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 the so-called 'honour killing' victims may be as high as 5000 (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 8083 dowry deaths (UNFPA, 2000). While this represents a 1.8% decline of deaths over the reported deaths for 2012 (8233), the number of cases of 'cruelty by husband or his relatives' increased by 11.6% from 89 546 in 2009 to 118 866 in 2013.

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, such as Turkey, have changed their laws to reflect these human rights standards (Turkish Penal Code, 2004).

Early and child marriage: the most frequent violence against young girls

Early marriage, e.g. marriage occurring before the age of 18 years, with or without parental and/or judicial consent, is often associated with adolescent pregnancy with its attendant, high maternal mortality and morbidity. Below the age of 15 years early marriage can have disastrous consequences on the development and health of adolescents who may leave school without an education, thus becoming more vulnerable later in life. When the spouse is older and possibly polygamous, violence and sexually transmitted infections are common (Raj *et al.*, 2009; Loaiza, 2012).

The main determinants of early marriage are poverty and low socioeconomic status (often in rural areas), poor education of both the parents and the adolescents themselves, and archetypical social norms prevailing in the region or country, including a strong gender inequality and inappropriate legislation or disregard of the legislative framework.

Overall, one in three girls in low-income countries will have been married before they are 18 years old, and one in nine girls before their 15th birthday. In 2014, the overall number of women married before age 18 years worldwide was estimated as 720 million. South Asia, in particular India, is especially affected, and contributes 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

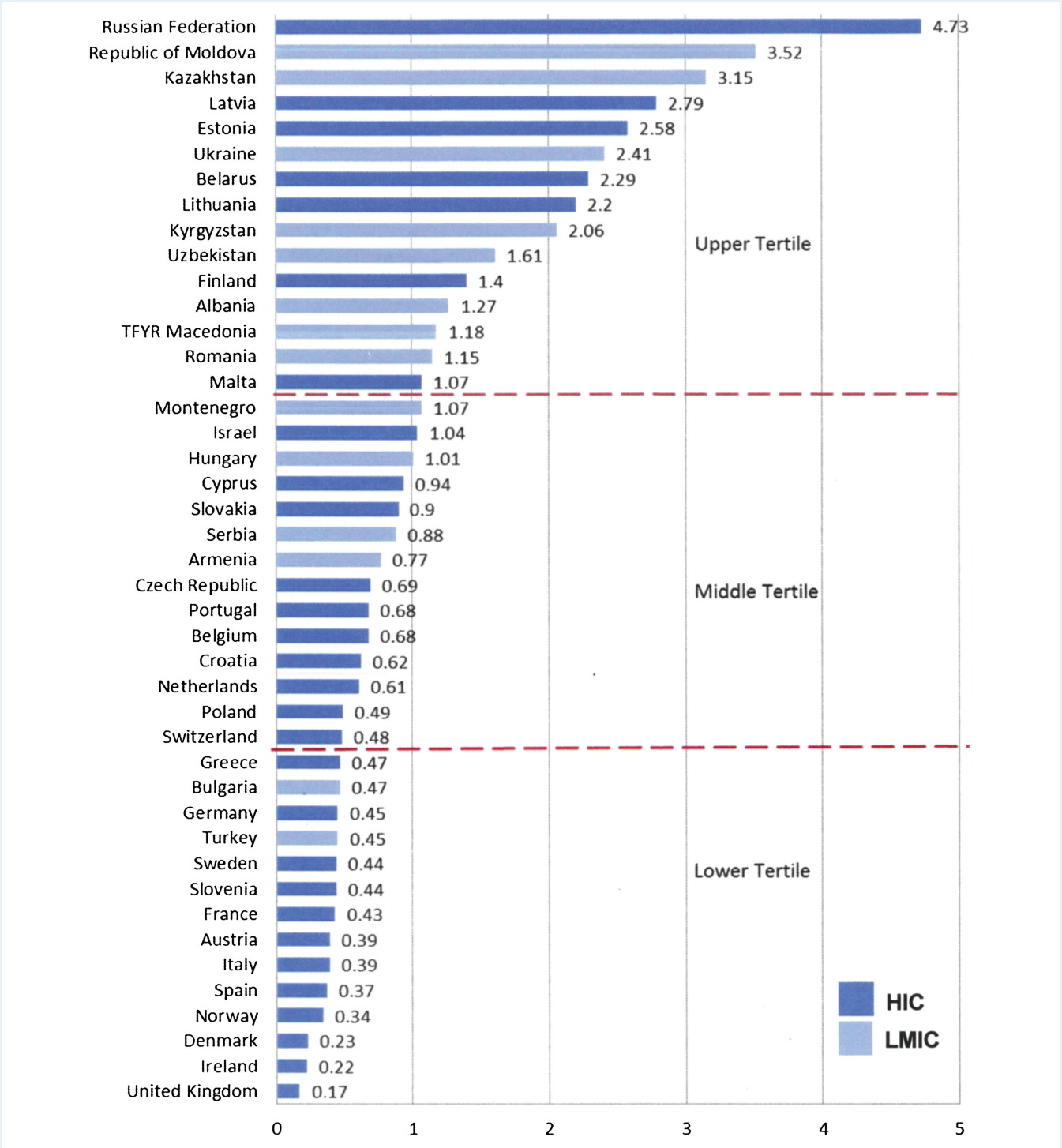

Figure 2 Mortality rates in women aged 15–69 years due to assault in the European Region by country income level per 100 000 population (data from World Health Organization, 2013). HIC, high-income countries; LMIC, low- and middle-income countries.

(UNICEF, 2001; Loaiza, 2012; Office of the United Nations High Commissioner for Human Rights, 2014).

While many countries have adopted the age of 18 years as the minimum age of marriage, communities, especially in rural areas, often ignore the law.

Conclusion

Boys outnumber girls at birth. Men avoid the complications of pregnancy and social discrimination, but die earlier and in larger numbers due to biological factors, 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, lifestyle and social factors. Many of these differences are relative rather than absolute. Reproductive healthcare providers are well informed of the effects of pregnancy on morbidity and mortality in many countries but may be less aware of the detrimental effects to health of gender specific social factors such as domestic and honour violence and early child marriage. Providers need to be sensitive to the role that such factors may have in women presenting to them for investigation and treatment.

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Appendix

A meeting was organized by ESHRE [August 28–31, 2015] to discuss the above subjects. The contributors included: M. Aboulghar (Editor-in-Chief, Middle East Fertility Society Journal, Cairo, Egypt), D.F. Albertini (Director Division of Laboratories, Center For Human Reproduction, New York, USA), J.F. ALLEN (Research Department of Genetics, Evolution and Environment, University College London, London, UK), S. Bhattacharya (Professor of Reproductive Medicine, Head of Division of Applied Health Sciences and Director Institute of Applied Health Sciences, School of Medicine and Dentistry, University of Aberdeen, Aberdeen Maternity Hospital, Foresterhill, Aberdeen, UK), J. Cottingham Terralis C, 110 rue Nelson Mandela, 74160 St Julien-en-Genevois, France J.L.H. Evers (Department of Obstetrics and Gynaecology, Maastricht University Medical Centre, Maastricht, The Netherlands), J.P.M. Geraedts (Department of Genetics and Cell Biology, University Maastricht, The Netherlands), A. Glasier (Simpson Centre for Reproductive Health, University of Edinburgh, UK), K. Hunt (MRC/CSO Social and Public Health Sciences Unit, University of Glasgow, Glasgow, UK), J. Hussein (Scientific Director Immpact, University of Aberdeen, Health Sciences Building Foresterhill, Aberdeen, UK), C. La Vecchia (Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milano, Italy), W. Luy (Mortality Research Group, Vienna Onstitute of Demography, Austrian Academy of Sciences, Vienna, Austria), P.-A. Michaud (Faculty of Biology & Medicine, University of Lausanne, Independent Consultant in School & Adolescent Health and in Medical Education, Bussigny, Switzerland), E. Negri (Department of Epidemiology, IRCCS - Istituto di Ricerche Farmacologiche 'Mario Negri', Milano, Italy), S.A.E. Peters (Research Fellow in Epidemiology, The George Institute for Global Health, Nuffield Department of Population Health, Oxford Martin School, University of Oxford, Oxford, UK), D. Sethi (Programme Manager Violence and Injury Prevention, Division of Noncommunicable Diseases and Life-Course, UN City, Copenhagen, Denmark). The discussants included: D.T. Baird (Centre for Reproductive Biology, University of Edinburgh, UK), P.G. Crosignani (IRCCS Ca' Granda Foundation, Maggiore Policlinico Hospital, Milano, Italy), P. Devroey (Centre for Reproductive Medicine, Universitair Ziekenhuis Vrije Universiteit Brussel, Belgium), K. Diedrich (Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Germany), R.G. Farquharson (Liverpool Women's Hospital, Department of OB/GYN, Liverpool, UK), L. Fraser (Reproduction and Rhythms Group, School of Biomedical and Health Sciences, Kings College London, UK), L. Gianaroli (SISMER, Reproductive Medicine Unit, Bologna, Italy), K. Lundin (Reproductive Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden), A. Sunde (Department of Obstetrics and Gynaecology, University of Trondheim, Norway), J.S. Tapanainen (Department of Obstetrics and Gynaecology, University of Helsinki, Helsinki University Hospital, Helsinki, and Department of Obstetrics and Gynaecology, University of Oulu, Oulu University Hospital, Oulu and Medical Research Center Oulu, Oulu, Finland), B. Tarlatzis (Unit for Human Reproduction, 1st Department of Obstetrics and Gynaecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece), A. Van Steirteghem (Centre for Reproductive Medicine, Universitair Ziekenhuis Vrije Universiteit Brussel, Belgium), A. Veiga (Director R+D Hospital Universitari Quiron Dexeus, Barcelona, Spain), A. Volpe (Dipartimento Integrato Materno Infantile, Università di Modena, Italy). The report was prepared by all participants.

Authors' roles

All lecturers and discussants contributed to the preparation of the final manuscript.

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Conflict of interest

None declared.

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