

- 1 GENDER RELATED HEALTH OUTCOMES: A GLOBAL PERSPECTIVE
- 2 ESHRE Capri Workshop Group^{1,2}
- 3
- 4 1. Abstract
- 5 2. Introduction
- 6 3. Evolutionary mechanisms leading to the selection of the female germ line
- 7 4. The contribution of X-linked diseases
- 8 5. Gender differences in life expectancy: the effect of biological factors
- 9 6. Lifestyle associated health risks in women and men
- 10 a) overweight and obesity;
- 11 b) smoking;
- 12 c) alcohol consumption.
- 13 7. Cardiovascular diseases: a neglected difference for women
- 14 8. Pregnancy related maternal death: an exclusive female risk
- 15 9. Additional health risks for women:
- 16 a) Sex selective abortion
- 17 b) Female genital mutilation
- 18 c) Early marriage
- 19 d) Violence against women
- 20 10. Conclusion
- 21

¹ Correspondence should be addressed to: P.G. Crosignani, Scientific Direction, IRCCS Ca' Granda Foundation Maggiore Policlinico Hospital, Via M. Fanti, 6, 20122 Milano, Italy, e-mail: piergiorgio.crosignani@unimi.it.

² The list of The ESHRE Capri Workshop Group participants is given in the Appendix.

22 1. ABSTRACT

23 The first signs of separate sexes in many-celled organisms are believed to have
24 emerged around 700 million years ago, however, the influence of gender³ on
25 human health remains poorly understood.

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

40 For women in some parts of the world pregnancy can be an extremely risky
41 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.)

42 pregnancy, with sub-Saharan Africa registering the highest maternal mortality:
43 510 maternal deaths per 100,000 births. Additional health risks specifically for
44 women arise from instances of gender discrimination including sex selective
45 abortion, genital mutilation (FGM), child marriage, and ('honour' and dowry
46 related) violence against women. Reducing female birth by sex selective abortion
47 will skew the sex ratio to (in some areas of the world) 1.15 or even 1.25. This will
48 create a shortage of young women, disturbing the 'marriage market' of this
49 generation in the affected countries, with a surplus of increasingly anxious young
50 unmarried men. This has considerable social implications, e.g. increased
51 prostitution, sex offenses, rape, importing brides from neighbouring countries,
52 women trafficking and social turmoil, which in turn will affect women's health.
53 In conclusion, gender based differences in health outcomes are due to biological,
54 environmental and lifestyle factors. Males outnumber women at birth, avoid the
55 complications of pregnancy and social discrimination, but pass away earlier and
56 in larger numbers due to fighting, wars, alcohol and smoking; on a global scale
57 they are less likely to outlive women.

58 2. INTRODUCTION

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

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

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

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

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

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

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

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

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

107 It is generally thought that mitochondrial DNA mutations accumulate within the
108 lifespan of the individual. It has been proposed by Allen and colleagues that risks
109 of oxidative phosphorylation may have led to sexual dimorphisms in the
110 mitochondria of sperm and oocytes. The motility of highly energized sperm
111 contrasting in the special case of the metabolically quiescent oocyte
112 mitochondrial DNA template protected from oxidative damage (de Paula et al.,
113 2013).

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

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

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

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

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

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

144 4. THE CONTRIBUTION OF X-LINKED DISEASES

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

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

154 5. GENDER DIFFERENCES IN LIFE EXPECTANCY: THE EFFECT OF 155 BIOLOGICAL FACTORS

156 That women live longer than men has been known at least since the middle of the
157 18th century. Kersseboom (Kersseboom, 1740) proposed that the mortality
158 outcomes of males and females differ sufficiently to justify the use of separate
159 tables for calculating annuities. Excess male mortality was subsequently
160 confirmed following the introduction of official population statistics in western
161 societies, e.g. in Sweden from 1751 onwards (in: Tabutin, 1978).

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

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

179 6. LIFESTYLE ASSOCIATED HEALTH RISKS IN WOMEN AND MEN

180 The three major lifestyle factors affecting individual health are:

- 181 a) excessive body weight;
- 182 b) smoking;
- 183 c) alcohol.

184 a) **Excessive body weight: consequences according to gender**

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

191 obese individuals are at greater risk of adverse long term health outcomes even in
192 the absence of documented metabolic problems.
193 Pooled data from 19 prospective studies involving over one and a half million
194 Caucasian adults show that in otherwise healthy non-smokers, overweight and
195 obese women were at higher risk of all-cause mortality. Compared to women with
196 a BMI of 22.5 to 24.9, the reference population, hazards ratios (HR) for death
197 were significantly increased in all those with higher BMI's (Table II).
198 In comparison with normal weight women, the pooled hazards ratio for
199 myocardial infarction in overweight and obese women without metabolic
200 syndrome has been shown to be higher (Thomsen and Norgestgaard, 2014) (Table
201 III). In otherwise healthy non-smokers, overweight and obese men were at higher
202 risk of all-cause mortality (Table II). In comparison with normal weight men, the
203 pooled HR for myocardial infarction and ischemic heart disease in obese men
204 were much increased (Table III).

205 **b) Different health outcomes of smoking in women and men**

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

215 The review on sex, gender and lung cancer entitled “*Smoke like a man, die like a*
216 *man*” (Payne, 2001) summarizes the health consequences of smoking in women.
217 In studies investigating both sexes, the shorter duration of the habit and the
218 lower number of cigarettes consumed by women had initially led to the erroneous
219 belief that women were somehow less susceptible to the damages of smoking.
220 However, more recent epidemiologic evidence clearly shows that women are at
221 least as susceptible as men to smoking-related cancers, respiratory diseases,
222 cardio-vascular diseases and other health problems caused by smoking (Surgeon
223 General, 2001). In fact, relative risks appeared to be even higher in women.
224 Although the cumulative exposure to smoking was lower in women than in men,
225 a recent meta-analysis on this topic showed that women smokers had a 25%
226 greater relative risk (RR) of coronary heart disease (CHD) than men, independent
227 of other cardiovascular risk factors (Huxley and Woodward, 2011). In contrast to
228 CHD, there was no clear evidence for a sex-difference in the risk of stroke among
229 women who smoked compared with men who smoked (Peters et al., 2013). The
230 Million Women Study, a prospective study including 1.3 million British women
231 showed that (at age 50-79) smokers had three times the overall mortality of never
232 smokers, and that on average female smokers lose at least 10 years of their
233 lifespan (Pirie et al., 2013). These results are similar to those found in men (Doll
234 et al., 2004). The excess risk appears similar in both sexes, and the higher RR in
235 women is due to the lower baseline risk in non-smokers. As for their male
236 counterpart, stopping smoking is an effective way to avoid most of the damage
237 caused by smoking, and even cessation at 50 years of age avoids at least two
238 thirds of the excess mortality seen in women that continue smoking (Pirie et al.
239 2013).

240 **c) Outcomes of alcohol consumption in the two sexes**

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

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

257 It has been estimated that in 2002 about 390,000 incident cancers (3.6% of the
258 total number) were attributable to alcohol drinking worldwide – 300,000 in men
259 (5.2%) and 90,000 in women (1.7%). Corresponding figures for cancer deaths were
260 over 230,000 (3.5%) – 195,000 in men (5.1%) and 35,000 in women (1.3%, (Boffetta
261 et al., 2006). More than one in four alcohol-related cancers worldwide, and one in
262 five cancer deaths, are in women. The absolute numbers, as well as the
263 proportions, of alcohol-related cancers have been rising in women over the last
264 decade (Praud et al., 2015). Table IV shows updated estimates of alcohol-

265 attributable cases for all cancers and alcohol-related sites. Overall, about 535,000
266 cancers in men (7.2% of the total) and 235,000 in women (3,5% of the total) are
267 attributable to alcohol drinking, corresponding to about 770,000 cancer cases in
268 both sexes combined. With reference to cancer mortality, about 480,000 cancer
269 deaths are attributed to alcohol (5,8% of the total), over 360,000 in men (7,8%) and
270 115,000 in women (3.3% of the of the total). The lower proportion of cancer
271 incidence than mortality in women is due to the weight of breast cancer, which is
272 the major alcohol-related cancer in women, and has comparatively favourable
273 prognosis as compared to other alcohol-related cancers.

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

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

284 7. CARDIOVASCULAR DISEASES: A NEGLECTED HEALTH RISK DIFFERENCE 285 FOR WOMEN

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

290 made, there is still a wide-spread perception, particularly in lower and middle-
291 income countries, that it is a disease that predominantly affects men. However,
292 as women have a greater life expectancy than men, the cardiovascular burden in
293 absolute terms, is actually greater in women than in men; in 2004 almost 32% of
294 all deaths in women were due to cardiovascular causes compared to 27% in men.
295 These estimates, and the notable sex-difference in cardiovascular burden, are
296 likely to increase further due to population aging, a higher life expectancy and the
297 decade delay in the development of symptomatic CVD in women relative to men.
298 "Biological" and "non biological factors" may interact in the area of cardiovascular
299 risk and Figure 1 summarizes the results of recent systematic studies.
300 Higher levels of systolic blood pressure and body mass index (BMI) are important
301 risk factors for coronary heart disease (CHD) and stroke, which are as hazardous
302 in women as in men (Mongraw-Chaffin et al., 2015; Peters et al., 2013a). Sex
303 differences in the risk of CVD associated with smoking are likely to be due to
304 different smoking habits (Peters et al., 2013b) while there is a convincing evidence
305 of higher risk associated with diabetes in women. Two recent meta-analyses have
306 shown that women with diabetes had a 44% higher excess risk of CHD, and a
307 27% higher excess risk of stroke as compared to similarly affected men (Peters et
308 al., 2013c; Peters et al., 2014a). A 37% higher risk of all-cause mortality in
309 women associated with type I diabetes has also been reported, predominantly
310 driven by a higher risk for CVD in women (Peters et al., 2014b).

311 8. PREGNANCY RELATED MATERNAL DEATHS: AN EXCLUSIVE FEMALE RISK

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

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

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

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

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

341 9. ADDITIONAL HEALTH RISKS SPECIFIC FOR WOMEN

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

345 **a) Social sex-selective abortion**

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

349 - Sex-ratio at birth (SRB)

350 Male-to-female sex ratios at birth above 1.07 usually are considered to be the
351 result of prenatal sex selection and selective abortion. Some parts of the world,
352 particularly China and India have witnessed increased rates of sex-selective
353 abortion. In China the sex ratio rose from 1.07 in 1982 (when there was virtually
354 no prenatal sex selection) to 1.20 in 2005 (Li, 2007). In India, the corresponding
355 figure increased from 1.09 in 1982-1984 to 1.14 in 2003-2005 (Kulkarni, 2007).

356 According to the most recent reliable figures, countries with a sex ratio over 1.10
357 are Azerbaijan, Albania, Armenia, China, India, Vietnam and Georgia.

358 What all these countries have in common is a strong patrilineal family structure,
359 combined with a permissive attitude towards abortion, and rapidly declining birth
360 rates. There are three specific preconditions that favour the practice of sex
361 selection (UNFPA, 2012): 1. It should be *advantageous*; parents will resort to sex
362 selection only when they perceive clear benefits in having (usually) boys rather
363 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

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

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

398 **b) Female genital mutilation**

399 In some parts of the world, many mothers believe that Female Genital Mutilation
400 (FGM) is a rite of passage necessary to optimise marriage prospects, preserve
401 virginity and promote femininity. Defined as any ceremonial or non- medical
402 alteration of the female genitalia, the extent of the procedure varies considerably
403 from partial excision of the clitoris to total excision of labia minora, labia majora
404 and clitoris with narrowing of the vaginal orifice (World Health Organization,
405 2010). Immediate complications of FGM include bleeding, infection, pain,
406 retention of urine, and death. Late complications include urinary complications,
407 scarring, pain, infertility and sexual dysfunction.

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

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

416 - Recent trends

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

420 **c) Early and child marriage**

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

427 - Determinants

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

434 - Epidemiological situation across continents and countries

435 Overall, one out of three girls in developing countries will have been married
436 before they are 18, and one out of nine girls will have been married before their
437 15th birthday. In 2014, the overall number of women married before age 18

438 worldwide was estimated to 720 millions. South Asia, in particular India, is
439 especially hit, and provide 42% of all early marriages. East Asia and the Pacific
440 (25%), Africa (18%) and Latin America and the Caribbean (9%) account for most
441 of the other affected regions (Loaiza, 2012; UNICEF, 2001; Office of the United
442 Nations High Commissioner for Human Rights, 2014). However, the rates of girls
443 married before age 18 as compared to the total number of married women is
444 highest in Africa: in Ethiopia, Niger, Chad, Guinea, and Malawi, more than 50%
445 of girls marry before age 18. Worldwide, 12 per cent of women were married or in
446 union before age 15 (Figure 2). In most countries, on all continents, a downward
447 trend has been observed over the last 10-15 years.

448 - Impact on development and health

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

455 - Public health, policies and interventions

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

461 Many countries have adopted the age of 18 as the minimum age of marriage, but
462 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

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

489 - Honour violence

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

500 - Dowry violence

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

511

512 - Trends

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

519 9) CONCLUSION

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

526

527

528

529 REFERENCES

- 530 Appelman Y, van Rijn BB, ten Haaf ME, Eric Boersma E, Peters SAE. Sex
531 differences in cardiovascular risk factors and disease prevention.
532 *Atherosclerosis* 2015, in press.
- 533 Archibald, JM (2014) One plus one equals one. Symbiosis and the evolution of
534 complex life. Oxford University Press, Oxford.
- 535 Bagnardi V, Zatonski W, Scotti L, La Vecchia C, Corrao G. Does drinking pattern
536 modify the effect of alcohol on the risk of coronary heart disease? Evidence
537 from a meta-analysis. *J Epidemiol Community Health* 2008;**62**: 615-619.
- 538 Barford, A., et al. (2006). "Life expectancy: women now on top everywhere."
539 *British Medical Journal* 332: 808.
- 540 Benson J, Andersen K, Samandari G Reductions in abortion-related mortality
541 following policy reform: evidence from Romania, South Africa and Bangladesh.
542 *Reprod Health* 2011; 22; 8:39
- 543 Bermejo-Alvarez P, Rizos D, Lonergan P, Gutierrez-Adan A. Transcriptional sexual
544 dimorphism during preimplantation embryo development and its
545 consequences for developmental competence and adult health and disease.
546 *Reproduction* 2011;141:563-570.
- 547 Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis
548 RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB, Beeson WL, Clipp SL,
549 English DR, Folsom AR, Freedman DM, Giles G, Hakansson N, Henderson
550 KD, Hoffman-Bolton J, Hoppin JA, Koenig KL, Lee IM, Linet MS, Park Y,
551 Pocobelli G, Schatzkin A, Sesso HD, Weiderpass E, Willcox BJ, Wolk A,
552 Zeleniuch-Jacquotte A, Willett WC, Thun MJ. Body-Mass Index and Mortality
553 among 1.46 Million White Adults. *N Engl J Med* 2010;363:2211–2219.
- 554 Boffetta P, Hashibe M, La Vecchia C, Zatonski W, Rehm J. The burden of cancer
555 attributable to alcohol drinking. *Int J Cancer* 2006;**119**: 884-887.
- 556 Bongaarts J. The Implementation of Preferences for Male Offspring. *Population*
557 *and Development Review* 2013;39:185-208.
- 558 Bongaarts J, Guilimoto C. How many more missing women? *Lancet*.
559 2015;386:427
- 560 Bourgeois-Pichat J. Essai sur la mortalité "biologique" de l'homme. In: *Population*
561 *1952*;7(3):381-394.
- 562 Butchart A, et al. *Preventing intimate partner and sexual violence against women.*
563 *Taking action and generating evidence.* Geneva, World Health Organization,
564 2010.
565 (http://whqlibdoc.who.int/publications/2010/9789241564007_eng.pdf,
566 accessed 9 June 2015).
- 567 Chandra-Mouli V, Camacho AV and Michaud PA. WHO guidelines on preventing
568 early pregnancy and poor reproductive outcomes among adolescents in
569 developing countries. *J Adolesc Health*. 2013;52:517-22.
- 570 Cleland J, Conde-Agudelo A, Peterson H, Ross J, Tsui A. Contraception and
571 health. *Lancet* 2012;380 :149-56.
- 572 de Paula WBM, Lucas CH, Agip A-NA, Vizcay-Barrena G, Allen JF. Energy,
573 ageing, fidelity and sex: oocyte mitochondrial DNA as a protected genetic
574 template. *Phil Trans R Soc B* 2013;368;20120263.
575 <http://dx.doi.org/10.1098/rstb.2012.0263>.

576 Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to alcohol
577 consumption: a prospective study among male British doctors. *Int J*
578 *Epidemiol* 2005;**34**: 199-204.

579 Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50
580 years' observations on male British doctors. *BMJ* 2004;328:1519.

581 Garcia-Moreno C, Jansen HAFM, Ellsberg M, Heise L, Watts C. WHO Multi
582 country study on Women's health and Domestic Violence against women.
583 Geneva, World Health Organization, 2005.
584 (http://www.who.int/gender/violence/who_multicountry_study/Introduction-Chapter1-Chapter2.pdf, accessed 4 June 2015).

586 Giacosa A, Barale R, Bavaresco L, Gatenby P, Gerbi V, Janssens J, *et al.*. Cancer
587 prevention in Europe: the Mediterranean diet as a protective choice. *Eur J*
588 *Cancer Prev* 2013;**22**: 90-95.

589 Gracia E. Unreported cases of domestic violence against women: towards an
590 epidemiology of social silence, tolerance, and inhibition. *Journal of*
591 *Epidemiology and Community Health*, 2004, 58:536-537.

592 Guilmoto CZ: Sex imbalances at birth in Armenia; demographic evidence and
593 analysis. IRD/CEPED, Yerevan/Paris, 2013.

594 Hill C, Laplanche A. [The French drink too much alcohol]. *Presse Med* 2010;**39**:
595 e158-164.

596 Human Mortality Database 2009. University of California, Berkeley (USA), and
597 Max Planck Institute for Demographic Research (Germany). Available at
598 www.mortality.org or www.humanmortality.de (data downloaded on 31 July
599 2009).

600 Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart
601 disease in women compared with men: a systematic review and meta-analysis
602 of prospective cohort studies. *Lancet* 2011;378:1297-1305.

603 Hvistendahl M. Unnatural selection. Public Affairs Books, New York, 2011.

604 Kersseboom, Willem. Observatien, waar in voornamentlyk getoont word wat is
605 gelyktydigheid, dewelke vereischt word in alle calculatien, die tot voorwerp
606 hebben de probable levenskracht van persoonen van eenigen voorgestelden
607 ouderdom. Hier is bygevoegt een proeve van de constante ondervinding, dat
608 die van de vrouwelyke sexe doorgaans maar eenige weinige jaaren
609 doormalkander langer leven, dan die van de mannelyke. The Hague: Jan van
610 den Bergh, 1740.

611 Kulkarni PM. Estimation of missing girls at birth and juvenile ages in India.
612 UNFPA, New Delhi, 2007.

613 La Vecchia C. Alcohol in the Mediterranean diet: assessing risks and benefits. *Eur*
614 *J Cancer Prev* 1995;**4**: 3-5.

615 La Vecchia C, Bosetti C, Bertuccio P, Castro C, Pelucchi C, Negri E. Trends in
616 alcohol consumption in Europe and their impact on major alcohol-related
617 cancers. *Eur J Cancer Prev* 2014;**23**: 319-322.

618 Li S. Imbalanced sex ratio at birth and comprehensive intervention in China.
619 www.unfpa.org/gender/case_studies.htm presented at 4th Asia Pacific
620 Conference on Reproductive and Sexual Health and Rights, Hyderabad, India,
621 29-31 October 2007 (accessed 19 May 2015), 2015

622 Lane N (2005) Power, sex, suicide: Mitochondria and the meaning of life. Oxford

623 University Press, Oxford.

624 Loaiza E. Marrying Too Young, End Child Marriage. 2012:76 pp.

625 Luy M. Causes of male excess mortality: insights from cloistered populations. In:

626 Population and Development Review 2003;29(4):647-676.

627 Mao, J, Whitworth KM, Spate LD, Walters EM, Zhao J, Prather RS. Regulation of

628 oocyte DNA mitochondrial copy number by follicular fluid, EGF, and

629 neuregulin 1 during in vitro maturation affects embryo development in pigs.

630 Theriogenology 2012;78:887-897.

631 Mayor S. Lifeexpectancy gender gap will close in England and Wales, study

632 predicts. BMJ 2015;350:h2322.

633 McCartney G, Mahmood L, Leyland AH, Batty GD, Hunt K. Contribution of

634 smoking-related and alcohol-related deaths to the gender gap in mortality:

635 evidence from 30 European countries. Tobacco Control 2011;20:166-168

636 Mitis F, Sethi D, Crispino V, Galea G. European facts and the Global status

637 report on violence prevention 2014. Copenhagen, WHO Regional Office for

638 Europe, 2013.

639 ([http://www.euro.who.int/_data/assets/pdf_file/0007/265750/European-](http://www.euro.who.int/_data/assets/pdf_file/0007/265750/European-facts-and-the-Global-status-report-on-violence-prevention-2014-Eng.pdf?ua=1)

640 [facts-and-the-Global-status-report-on-violence-prevention-2014-](http://www.euro.who.int/_data/assets/pdf_file/0007/265750/European-facts-and-the-Global-status-report-on-violence-prevention-2014-Eng.pdf?ua=1)

641 [Eng.pdf?ua=1](http://www.euro.who.int/_data/assets/pdf_file/0007/265750/European-facts-and-the-Global-status-report-on-violence-prevention-2014-Eng.pdf?ua=1), accessed 9 June 2015).

642 Mittwoch U. Sex determination. EMBO Reports 2013;14:-592.

643 Mongraw-Chaffin ML, Peters SA, Huxley RR, Woodward M. The sex-specific

644 association between BMI and coronary heart disease: a systematic review and

645 meta-analysis of 95 cohorts with 1.2 million participants. *The lancet Diabetes*

646 *& endocrinology* 2015.

647 Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC,

648 Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T,

649 AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W,

650 Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J,

651 Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH,

652 Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne

653 SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL,

654 Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N,

655 Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A,

656 Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M,

657 Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim

658 D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li

659 Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah

660 GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand

661 D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO,

662 Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya

663 K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L,

664 Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S,

665 Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE,

666 Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC,

667 Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ,

668 Gakidou E. Global, regional, and national prevalence of overweight and

669 obesity in children and adults during 1980-2013: a systematic analysis for
670 the Global Burden of Disease Study 2013. *Lancet* 2014;384:766-781.

671 Office of the United Nations High Commissioner for Human Rights. Preventing
672 and eliminating child, early and forced marriage. 2014:18 pp.

673 Online Mendelian inheritance in men (OMIM). A knowledgebase of human gene
674 and genetic disorders: <http://www.mcj.nlm.nih.gov/omim>. 2015.

675 Orphanet the portal for rare disorders: <http://www.orpha.net>.

676 Payne S. 'Smoke like a man, die like a man?': a review of the relationship between
677 gender, sex and lung cancer. *Soc Sci Med* 2001;53:1067-1080.

678 Pesole G, Allen JF, Lane N, Martin W, Rand DM, Schatz G, Saccone C. The
679 neglected genome. *EMBO Reports* 2012;13:473-474.

680 Peters SA, Huxley RR, Sattar N, Woodward M. Sex differences in the excess risk
681 of cardiovascular diseases associated with type 2 diabetes: potential
682 explanations and clinical implications. *Current Cardiovascular Risk Reports*,
683 2015.

684 Peters SA, Huxley RR, Woodward M. Comparison of the sex-specific associations
685 between systolic blood pressure and the risk of cardiovascular disease: a
686 systematic review and meta-analysis of 124 cohort studies, including 1.2
687 million individuals. *Stroke; a journal of cerebral circulation* 2013a; 44(9): 2394-
688 401.

689 Peters SA, van der Schouw YT, Woodward M, Huxley RR. Sex differences in
690 smoking-related risk of vascular disease and all-cause mortality. *Current*
691 *Cardiovascular Risk Reports* 2013b; 7(6): 473-79.

692 Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women
693 compared with men: a systematic review and meta-analysis of 81 cohorts,
694 including 3,980,359 individuals and 42,401 strokes. *Stroke; a journal of*
695 *cerebral circulation* 2013c; 44(10): 2821- 8.

696 Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women
697 compared with men: a systematic review and meta-analysis of 64 cohorts,
698 including 775,385 individuals and 12,539 strokes. *Lancet* 2014a; 383(9933):
699 1973-80.

700 Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary
701 heart disease in women compared with men: a systematic review and meta-
702 analysis of 64 cohorts including 858,507 individuals and 28,203 coronary
703 events. *Diabetologia* 2014b; 57(8): 1542-51.

704 Peto R, Lopez AD, Boreham J, Thun M, Heath C. "Mortality from tobacco in
705 developed countries: indirect estimation from national vital statistics." *The*
706 *Lancet* 1992;339(8804): 1268-1278.

707 Pirie K, Peto R, Reeves GK, Green J, Beral V, Million Women Study Collaborators.
708 The 21st century hazards of smoking and benefits of stopping: a prospective
709 study of one million women in the UK. *Lancet* 2013;381:133-141.

710 Praud D, Rota M, Rehm J, Shield K, Zatoński W, Hashibe M, La Vecchia C,
711 Boffetta P. Cancer incidence and mortality attributable to alcohol
712 consumption. *Int J Cancer* 2015 Oct 11. doi: 10.1002/ijc.29890.

713 Pressat R. Surmortalité biologique et surmortalité sociale. In: *Revue Francaise de*
714 *Sociologie* 1973;14 (numéro spécial): 103-110.

715 Radzvilavicius A, Blackstone N. Conflict and cooperation in eukaryogenesis:
716 implications for the timing of endosymbiosis and the evolution of sex. *J. R.*
717 *Soc. Interface* 2015 12: 20150584. <http://dx.doi.org/10.1098/rsif.2015.0584>

718 Raj A, Saggurthi N, Balaiah D and Silverman JG. Prevalence of child marriage and
719 its effect on fertility and fertility-control outcomes of young women in India: a
720 cross-sectional, observational study. *Lancet*. 2009;373:1883-9.

721 Sedgh G, Singh S, Shah IH, Ahman E, Henshaw SK, Bankole A. Induced
722 abortion: incidence and trends worldwide from 1995 to 2008. *Lancet* 2012;
723 379: 625-32.

724 Sen A. Missing women. *BMJ*. 1992;304(6827):587-8

725 Stöckl H, Devries K, Rotstein A, Abrahams N, Campbell J, Watts C, Garcia
726 Moreno C. The global prevalence of intimate partner homicide: a systematic
727 review. *Lancet* 2013;382:859-865.

728 Surgeon_General. Women and Smoking: A Report of the Surgeon General.
729 Atlanta, GA, USA, 2001.

730 Tabutin D. La surmortalité féminine en Europe avant 1940. *Population*
731 1978;33(1):121-148.

732 Thomsen M, Nordestgaard BG. Myocardial Infarction and Ischemic Heart Disease
733 in Overweight and Obesity With and Without Metabolic Syndrome. *JAMA*
734 *Intern Med* 2014;174:15-22.

735 Thun M, Peto R, Boreham J, Lopez AD. Stages of the cigarette epidemic on
736 entering its second century. *Tobacco Control* 2012;21:96-101.

737 Trovato F, Lalu NM. Narrowing sex differentials in life expectancy in the
738 industrialized world: early 1970's to early 1990's. *Soc Biol* 1996;43(1-2):20-
739 37.

740 Turkish Penal Code, Law No. 5237. Republic of Turkey; 2004

741 Turner N, Robker RL. Developmental programming of obesity and insulin
742 resistance: Does mitochondrial dysfunction in oocytes play a role? *Molec Hum*
743 *Reprod* 2015;21:23-30.

744 UN Demographic and Health Survey, 2000-2010.

745 UNFPA: Sex Imbalances at Birth. Current trends, Consequences and policy
746 implications. UNFPA, Bangkok, 2012.

747 UNFPA. State of the world population 2000. New York: United Nations; 2000

748 UNICEF. Early marriage: a harmful traditional practice. A statistical exploration.
749 2005:43 pp.

750 UNICEF Innocenti Research Centre. Early marriage, child spouse. 2001:30 pp.

751 United Nations Committee on the Elimination of Discrimination against Women:
752 General Recommendation No. 19: Violence against women. New York (NY);
753 1992. (A/47/38)

754 United Nations, Declaration on the Elimination of Violence Against Women. New
755 York: United Nations; 1993. (General Assembly Resolution 48/104.

756 US Census bureau. International database world population by age and sex
757 <https://www.census.gov/population/international/data/idb/worldpop.php>

758 Van Blerkom J. Mitochondria in human oogenesis and preimplantation
759 embryogenesis: engines of metabolism, ionic regulation and developmental
760 competence. *Reproduction* 2004;128:269-280.

761 Waldron I, Johnston S. Why do women live longer than men? Part II. Journal of
762 Human Stress 1976;2(2):19-30.

763 Wiedemann, Angela; Wegner-Siegmundt, Christian; Luy, Marc, 2015: "Ursachen
764 und Trends der Geschlechterdifferenz in der Lebenserwartung in Deutschland"
765 [Causes and trends of the gender difference in life expectancy in Germany],
766 Zeitschrift für Allgemeinmedizin 91(12): 494-498.

767 World Health Organization/London School of Hygiene and Tropical Medicine.
768 Preventing intimate partner and sexual violence against women: taking action
769 and generating evidence. Geneva, World Health Organization, 2010.
770 (http://whqlibdoc.who.int/publications/2010/9789241564007_eng.pdf,
771 accessed 9 June 2015).

772 World Health Organization. Eliminating Female Genital Mutilation: An
773 Interagency Statement OHCHR, UNAIDS, UNDP, UNECA, UNESCO, UNFPA,
774 UNHCR, UNICEF, UNIFEM, WHO. Geneva, Switzerland: WHO Press; 2008.
775 [http://www.unifem.org/
776 attachments/products/fgm_statement_2008_eng.pdf](http://www.unifem.org/attachments/products/fgm_statement_2008_eng.pdf).

777 World Health Organization. Trends in maternal mortality: 1990 to 2013.
778 Estimates by WHO, UNICEF, UNFPA, the World Bank and the United Nations
779 Population Division. World Health Organization, Geneva, 2014.

780 Wu, LL, Russell DL, Wong SL, Chen M, Tsai T-S, St John JC, Norman RJ,
781 Febbraio MA, Carroll J, Robker RL. Mitochondrial dysfunction in oocytes of
782 obese mothers: transmission to offspring and reversal by pharmacological
783 endoplasmic reticulum stress inhibitors. Development 2015;142:681-691.

784 Yaffe MP. The machinery of mitochondrial inheritance and behavior. Science
785 1999;283:1493-1497.

786 Zaridze D, Lewington S, Boroda A, Scelo G, Karpov R, Lazarev A, *et al.*. Alcohol
787 and mortality in Russia: prospective observational study of 151,000 adults.
788 *Lancet* 2014;**383**: 1465-1473.

789
790
791

792
793
794
795
796

Table I. Clinical characteristics of the most common X-linked diseases (Online Mendelian inheritance in men (OMIM). A knowledgebase of human gene and genetic disorders: <http://www.mcj.nlm.nih.gov/omim>. 2015; Orphanet the portal for rare disorders: <http://www.orpha.net>).

	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.	
--	--	---------------------------------------------------------------	--

797

798

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	<i>ref.</i>	<i>ref.</i>
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)

801

802

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)

806

807

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

809

810

811

812 Cancer

813

814

815

816 Oral cavity and pharynx

817 Esophagus SCC

818 Colon and rectum

819 Liver

820 Gallbladder

821 Pancreas

822 Larynx

823 Breast

824

825 TOTAL CANCER

826

Cancer	Men		Women	
	Fraction %	Cases	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

827 SCC: squamous cell carcinoma. NA: not applicable

828 *Denominator comprises all cancer.

829

830

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

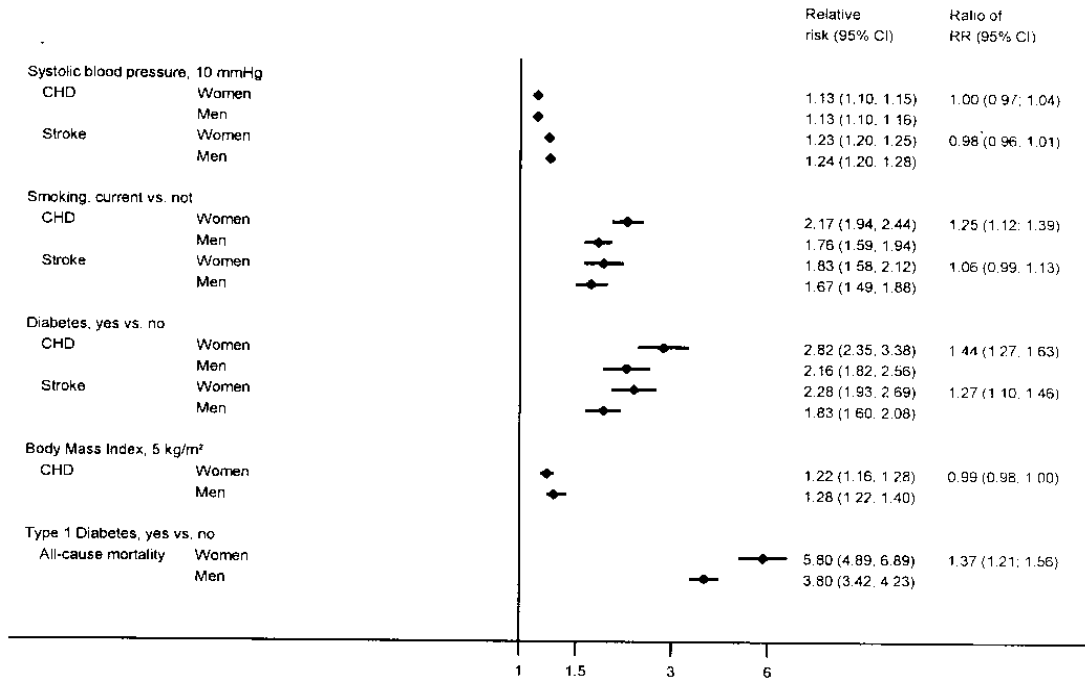
833

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

834

835

836 Figure 1. Summary results from meta-analyses of sex differences in the association
 837 between cardiovascular risk factors and following events (Appelman et
 838 al., 2015)
 839
 840
 841



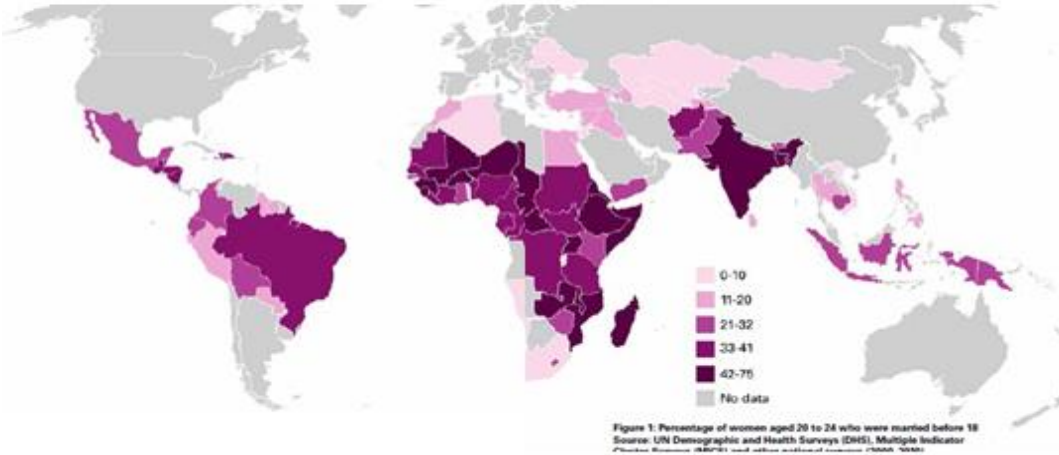
842
 843
 844 Boxes and bars represent relative risks and 95% confidence intervals for women
 845 and men. Ratio of RR represents the female:male ratio of relative risk for CHD,
 846 stroke, and all-cause mortality

847
 848

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



Early marriage worldwide

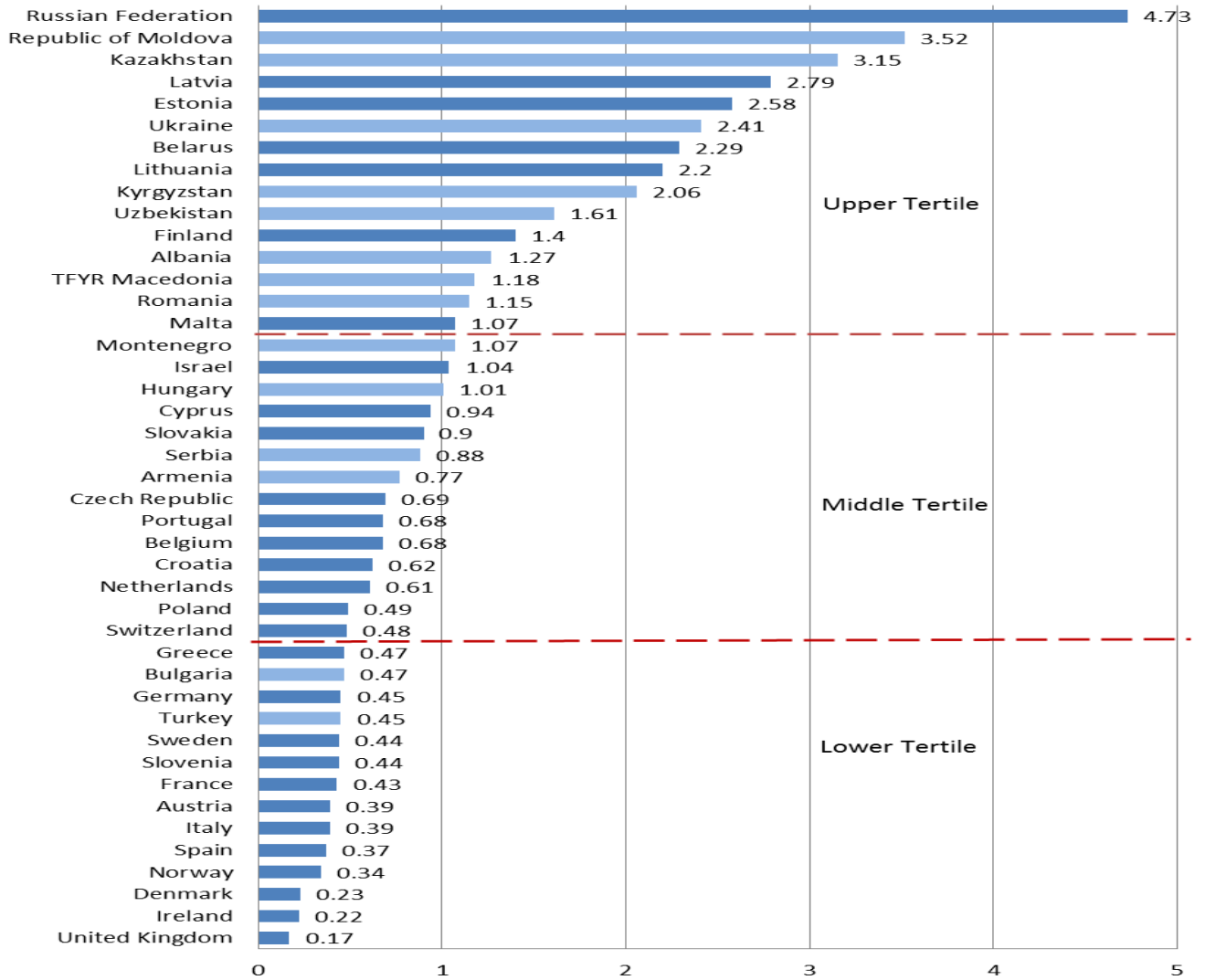


851

852

853

854 Figure 3. Mortality rates in women aged 15-69 years due to assault in the European
 855 Region by country income level per 100 000 population (REFERENCE
 856 - Sethi).
 857
 858



859
 860
 861 ■ HIC
 862
 863 ■ LMIC
 864
 865
 866