

LA RICERCA E LA MDG

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The human genome contains 23 chromosome pairs **and one pair determines the sex of an individual.**

Human genome between any **two men and any two women is 99.9% identical.** This means all of the phenotypic, environmental and hereditary differences between any two women or two men are accounted for by just 0.1% of their total genome.

The difference of men and women is 1.5% in genome thus 98.5% of female and male genome is identical, suggesting that there is a tremendous amount of genetic information in the sex chromosomes controlling the development and function of not only sex organs and sex hormones, but also a myriad of biological attributes at every level of the organism: macro, micro, cellular and molecular.

http://www.pharmaceutical-journal.com/opinion/comment/sex-bias-in-drug-research-a-call-for-change/20200727.article#fn_1

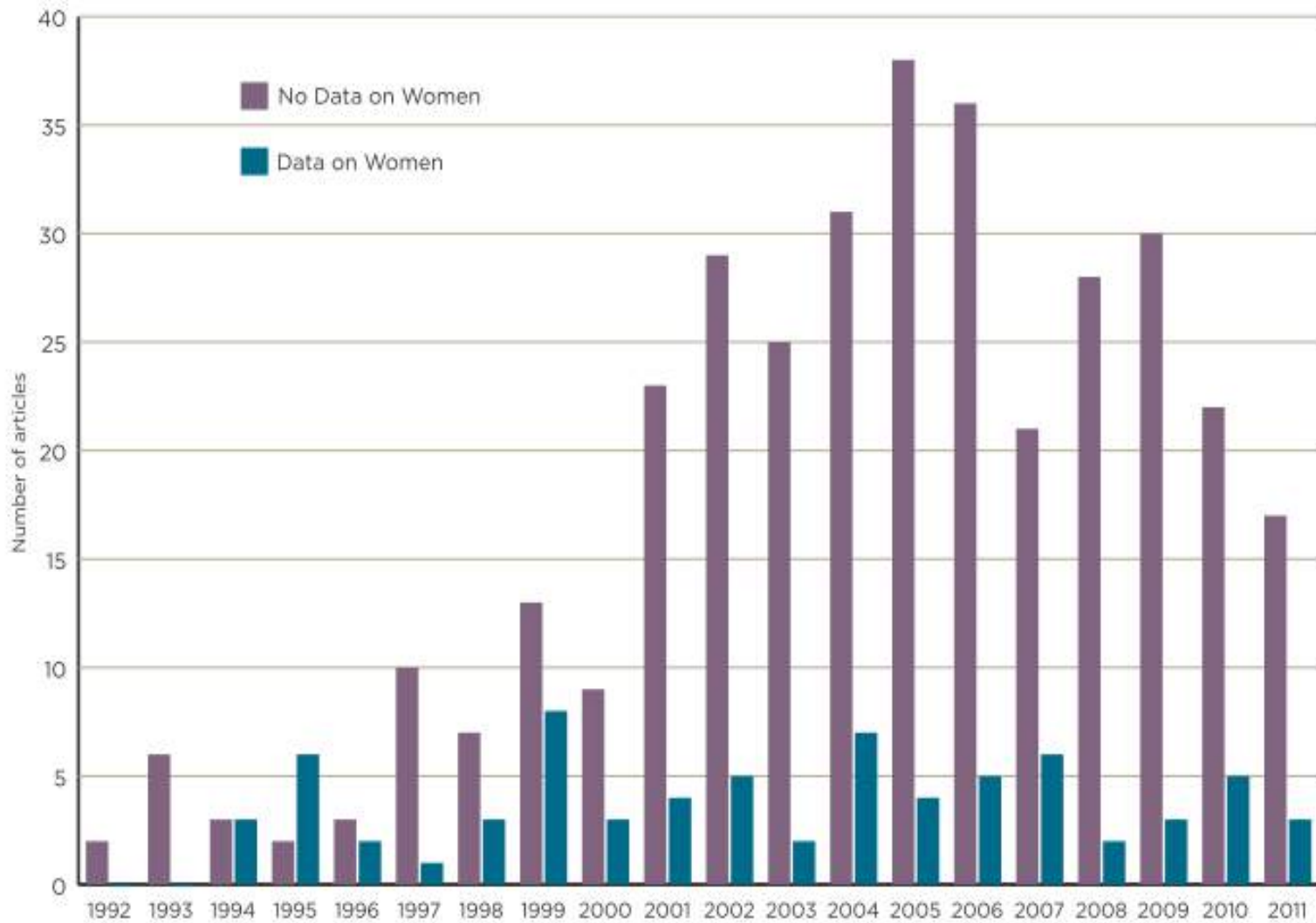




...“Uomini e donne non sono solo sé stessi: sono anche la regione dove sono nati, la casa o l'aia dove hanno imparato a camminare, i giochi con cui si sono divertiti da bambini, i racconti delle vecchie comari uditi di straforo, i cibi che mangiavano, le scuole che hanno frequentato, gli sport che l'interessavano, i poeti che leggevano, il dio in cui credevano. Tutte queste cose li hanno resi ciò che essi sono”.

W. Somerset Maugham. Il filo del rasoio. Gli Adelphi





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Source: Dolor, R. J., Melloni, C., Chatterjee, R., LaPointe, N. M. A., Williams, J. B., Coeytaux, R. R., et al., *Treatment Strategies for Women With Coronary Artery Disease*, Agency for Healthcare Research and Quality, August 2012.



Efficacy of Medications Approved for the Treatment of Alcohol Dependence and Alcohol Withdrawal Syndrome in Female Patients: A Descriptive Review

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Fig. 2. Rates of male and female patients recruited in randomised, placebo-controlled trials conducted to evaluate the efficacy of AWS medications.

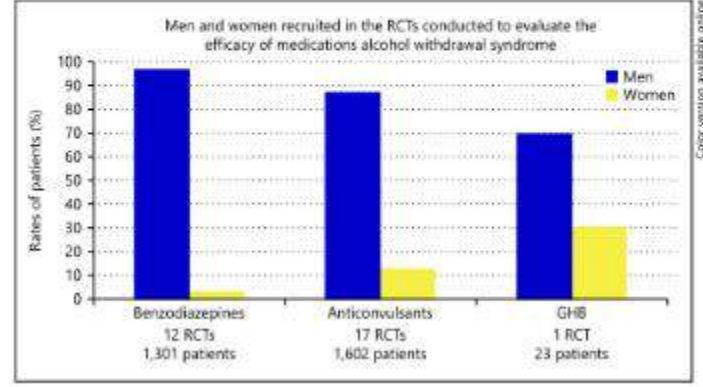
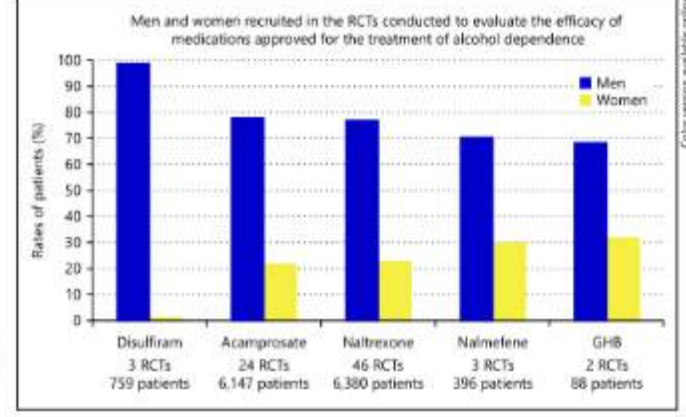
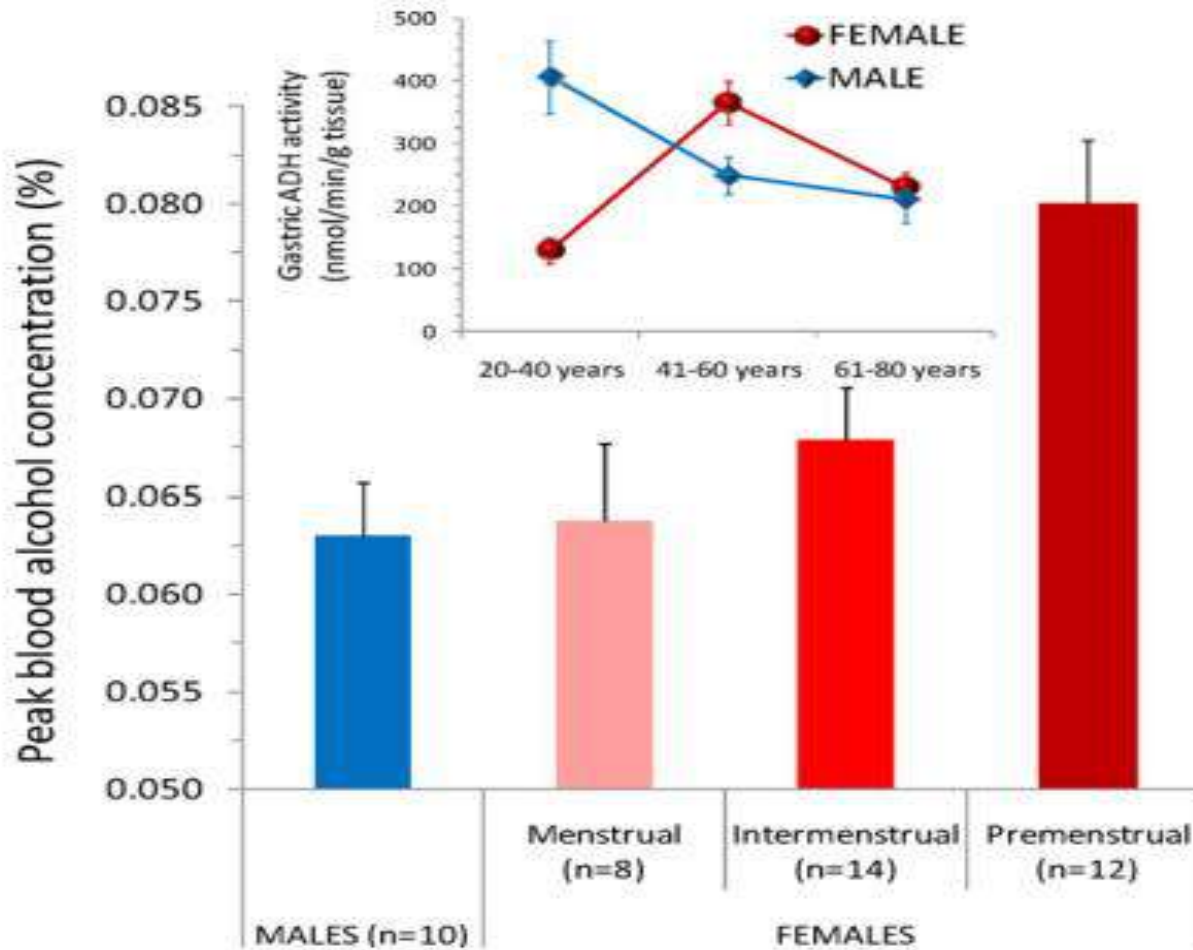


Fig. 1. Rates of male and female patients recruited in randomised, placebo-controlled trials conducted to evaluate the efficacy of AD medications.





Freire AC et al
Int J
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s;415:15,
2011.

Fig. 7. Mean (\pm SE) peak blood alcohol levels for males and females tested at different times in the menstrual cycle. Figure redrawn from Jones and Jones (1976). The inset shows the gastric alcohol dehydrogenase enzyme activity (Mean \pm SD) in gastric biopsies from 111 subjects (Figure redrawn from Parlesak et al., 2002).



SEX – GENDER EFFECTS IN EARLY LIFE

Indomethacin prevents intraventricular hemorrhage in preterm infants halving them and this reduction is associated with higher verbal scores at 3 to 8 years in boys. (Ment LR et al J Pediatr. 2004;145:832-4).

Early-life antibiotic exposure is associated with increased childhood BMI in boys, but not in girls (Murphy R et al, Int J Obes (Lond) doi: 10.1038/ijo.2013.218. 2013)

Effect of epidural anaesthesia (bupivacaine and fentanyl) during labor in male and female (Babies Bell A F et al JOGNN, 39, 178-190; 2010).



Figure 2. Mean (+95% CI) nutritive sucking pressure (mm Hg) by gender. Girl's group $n = 19$, boy's group $n = 29$. $t = 2.09$, $p = .042$.





Overall, ADRs are more frequent and severe in women than in men

(Hurwitz, 1969; Botinger, 1973; Domecq et al, 1980; Simpson et al, 1987; Lazarou et al, 1998; Martin et al, 1998; Makkar et al, 1993; Szarfman, 2000, Fattinger et al, 2000, Franconi et al, 2007, Montilla et al, 2008 and many others).

Older women are more vulnerable to ADRs because of multiple-drug regimens and age-associated changes in pharmacokinetics-and-dynamics and because more women than men have cognitive disturbs (Onder, et al J Am Geriatr Soc 50:1962–1968, 2002, Franceschi M et al Drug Safety 2008;31(6):545-56).

The manifestation of ADRs may vary between sexes Men had a significantly higher incidence of hiccups whereas women had significantly higher rates of vomiting and nausea when treated with cisplatin + dexamethazone. The cause of this differences is not known (Liaw CC et al Support Care Cancer (2001) 9:435–441). Cyclophosphamide –doxorubicin and etoposide-visplatin induces hematologic toxicity (anemia, leukopenia) in men whereas stomatitis and vomiting of all grades are more frequent in women than in men. Whereas toxic death rates do not diverge in men and women (**Singh S et al J Clin Oncol. 2005 Feb 1;23(4):850-6**).



The study include 969 adult psoriatic patients stratified: fertile women and corresponding age-matched men; postmenopausal women and corresponding age-matched men.

The frequency of ADE is significant different between fertile and postmenopausal women, but not between women and age-matched men.

The ADE seems to be influenced by hormonal levels.

FSH levels were significantly higher in postmenopausal women reporting no AEs, **DHEA** sulfate levels were about 10% higher in men with no AEs, compared to those reporting at least one AE.

Cortisol levels were slightly though significantly higher in postmenopausal women with no AE.



About 6.5% of hospital admissions depend on to adverse drug reactions (BMJ. 2004 Jul 3; 329(7456):15) which are about 15% in inpatients (Davies EC et al PLoS One. 2009; 4(2):e4439) up to 7000 deaths annually in the United States are the result of adverse drug reactions [L. T. Khon, "Organizing and Managing Care in a Changing Health System," Health Service Research, Vol. 35, No. 1, 2000, pp. 37-52.] The cost of ADE in USA ranges between 30 and \$130 billion per year, and results in more than 100,000 deaths (https://healthpolicy.duke.edu/sites/default/files/atoms/files/dg_5_16_16.pdf).

The decrease in Adrs in women must be a pivotal goal to reduce individual, social and economic costs



Sex and gender are well-documented linked to variability in drug response.

The proportion of individuals who respond beneficially to the first drug offered is estimated between 50–75% (Spear BB et al Trends Mol Med. 2001 May; 7(5):201-4.)

Evidently, individual variability is very elevated and produces social and economical costs therefore its prediction during drug development is a relevant concern for pharmaceutical industries, regulatory agencies and healthcare systems (Burroughs, V.J et al 2002. J Natio Med Ass, 94(10):1-26).

Sex and gender differences can depend on pharmacokinetics (man and women may differ in absorption, distribution, metabolism, and excretion of a drug by the body and pharmacodynamics and social factors (Franconi et al, 2014).

Till now the reductionist approach has prevailed. Actually, it is emerging that it is insufficient because it does not consider both the complexity of the interactions between a medication and the human body and the influence of environment (past and present) in drug response. Indeed, both factors shape the dynamic biological factors such as epigenome, transcriptome, proteome, metabolome, and tissues/organs (Turner et al Wiley Interdiscip Rev Syst Biol Med. 2015 Jul; 7(4): 221–241).



Gender and sex interact with racial and ethnic factors

In African American population, **hsCRP** is useful in identifying a subset of *nonobese* men with higher carotid intima–media thickness, but not in women. hsCRP, in fact, does not identify a subset of *obese* individuals with less subclinical atherosclerosis. (Arterioscler Thromb Vasc Biol. 2016;36:2431-2438)

In Caucasians, [Recombinant tissue plasminogen activator](#) have the same effects in men and women. In African men, there was a strong trend for improvement. Conversely, African women showed not different response versus controls (Stroke. 2013;44:1525-1531.)



Social Factors

In the literature, behavioural risk factors explained 53% among men and 25% among women of the relative differences between low and high educated in IHD mortality 15 and smoking and physical inactivity were reported to be the most important health behaviours explaining educational differences in mortality (Laaksonen M, et al. Eur J Public Health 2008;18:38–43).

Finally, socioeconomic differences in access to health care and treatment should be taken into account. A poorer access to revascularization operations and a higher risk of coronary mortality after revascularization operation or cardiac surgery was observed in persons with lower socioeconomic status in Finland (De Henauw S et . J Epidemiol Community Health 1998;52:513–9)



SOCIAL AND PSYCHOLOGICAL FACTORS

Östlin and Paraje (unpublished data, 2004) scrutinized health-related scientific literature for the period 1992–2001.

They found that only 0.2% of the total of 3,361,298 health-related articles dealt with health and social connections.

Ignoring factors such as, race and gender leads to biases in both the content and process of research

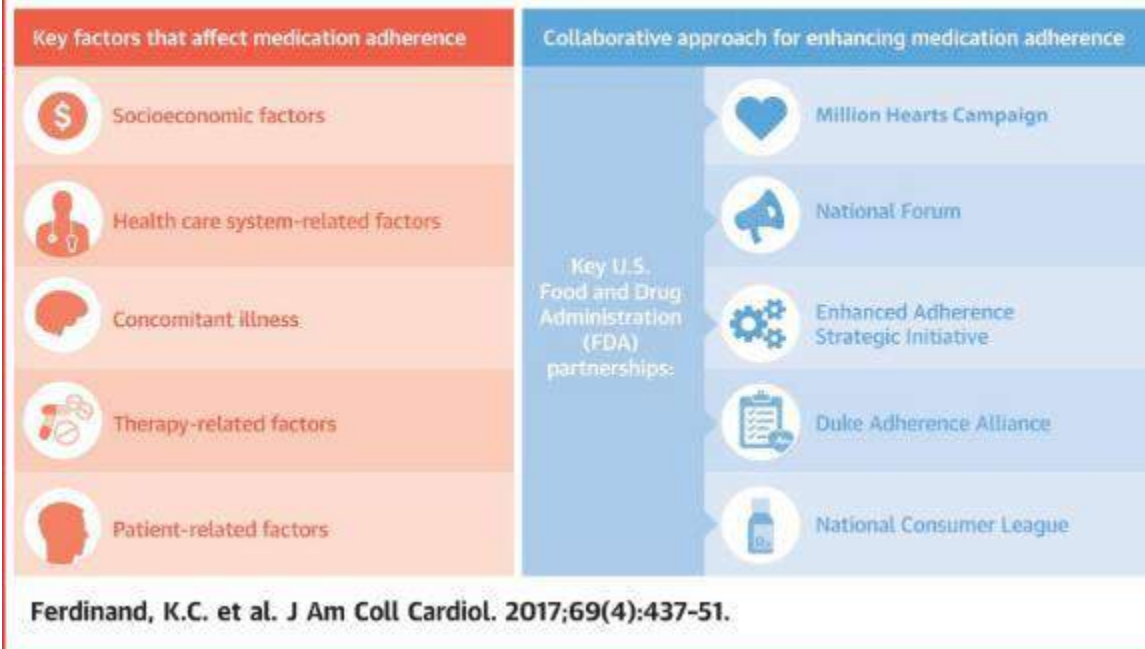
Clinical setting

Men have less pain when the nursery and doctor are women (Aslaksen PM et al Pain. 2007 129(3):260-8. 2006).

Please note the importance of social context in drug response



CENTRAL ILLUSTRATION: Multifactorial Approach to Influence Medication Adherence



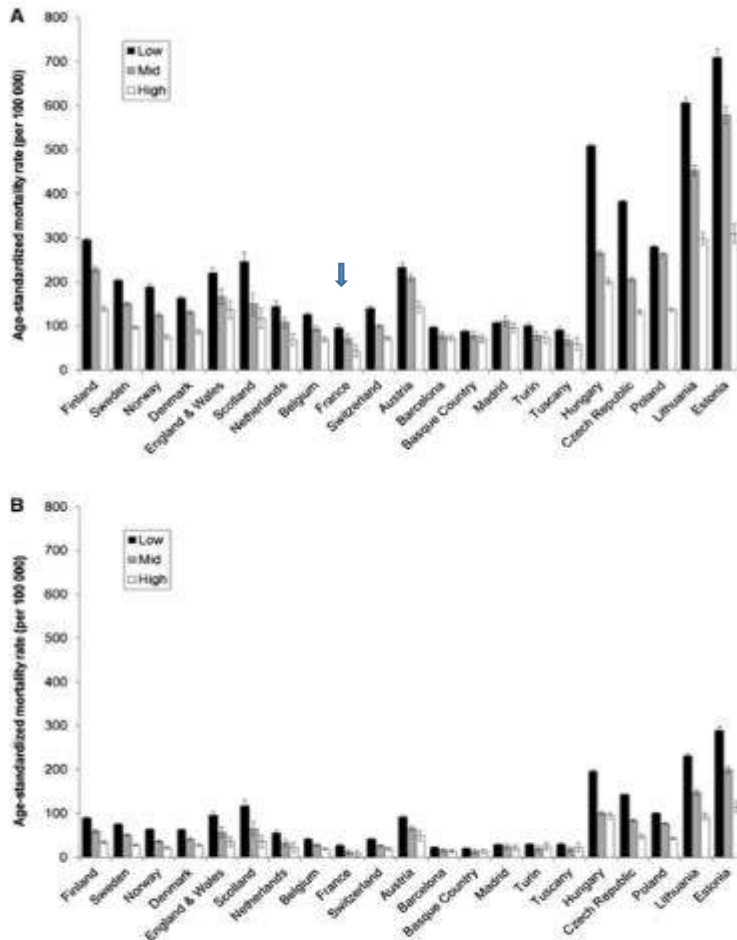


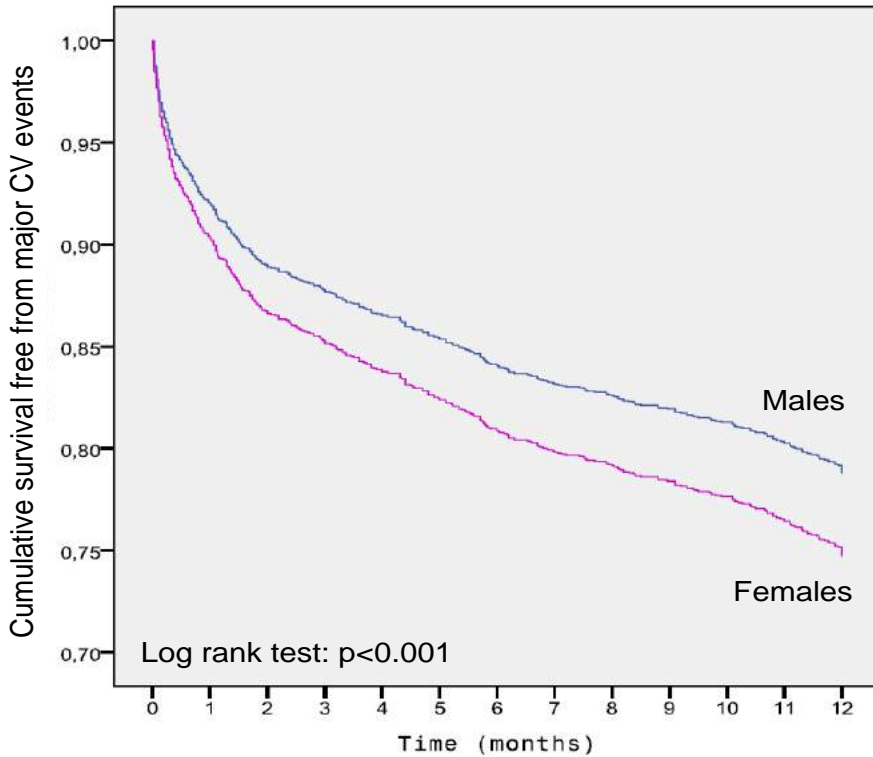
Figure 1. Age-standardized mortality rates (per 100 000 person-years) from IHD by education, country and sex, with corresponding 95% CI. 21 European populations, 30–79 years. (A) men, (B) women

- 1) These findings revealed important **country-specific** and **gender-specific** patterns IHD. Being the women less sensible to variations induced by SES such as South European country.
- 2) The impact of **smoking** on IHD mortality and on **educational differences** in IHD mortality was larger in the North, West and East and was present in men only
- 3) The impact of **overweight/obesity** was larger in the South of Europe, especially among women.
- 4) **physical inactivity** has only small impact in most European countries

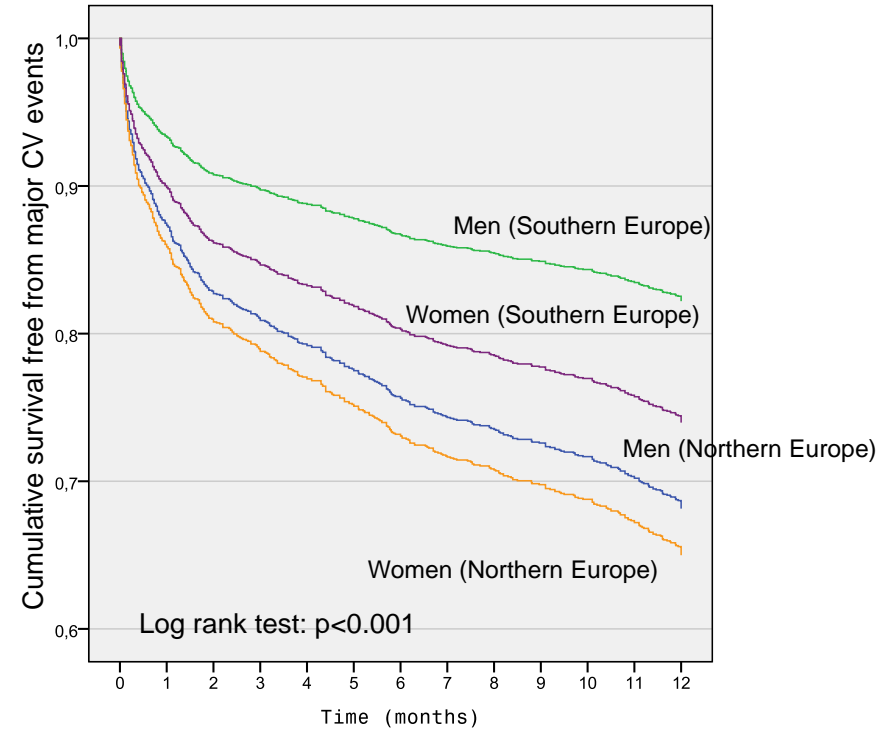
Kulhanova I et al, [Eur J Public Health](#). 2016 Aug 12



All patients (n=3630)



All patients (n=3630)



Kaplan-Meier cumulative survival curves during 1-year of follow-up in men and women enrolled in the SMILE Programme

Citation: Franconi F, Omboni S, Ambrosioni E, Reggiardo G, Campesi I, et al. (2014) Effects of Treatment with Zofenopril in Men and Women with Acute Myocardial Infarction: Gender Analysis of the SMILE Program. PLoS ONE 9(11): e111558. doi:10.1371/journal.pone.0111558



Access to care:

Sex-gender is important for access to healthcare, including treatments and individual use of the healthcare system .

For example:

Women receive less total joint arthroplasty than men, despite the fact that they have more osteoarthritis, and they undergo surgical procedures at a more advanced stage of disease compared with men.

Although not univocally reported, several studies from the USA, UK and other European countries [54–66] have indicated that access to primary therapy is more difficult for female patients with cardiovascular diseases than men.

Diabetic women are less treated for many cardiovascular risk factors than diabetic men

The significance of sex-gender on access to care and treatment cannot be neglected because the lack of awareness leads to inequality in the care of males and females.

(Franconi F and Campesi I Expert Rev. Clin. Pharmacol. Early online, 1–17 (2014)



Access to care

Alcoholism: women receive less treatment than men. This seems to depend on childcare responsibilities, transportation, financial status, and social stigma [Greenfield et Drug and alcohol dependence, 2007, 86, 1]. There data that suggest that AUD women should receive medical treatment in special services dedicated to female patients.

Heart failure access to ACEI is less (30%) in Swedish women than men (Ohlsson A et alJ Epidemiol Community Health.2016;7:97). Adjusting for ARB dispensation did not explain the sex difference, in accordance with a previous Swedish investigation

Heart failure access to statins: Women at discharge receive less statin than men, which is associate with inadequate dosing (ballo et al)

Premature acute coronary syndrome. Less Women receive electrocardiography or fibrinolysis in benchmark times (Pelletier R et al, CMAJ 2014; 186: 497). Women with STEMI receive less reperfusion therapy (Pelletier R et al, CMAJ 2014; 186: 497; Seghieri C et al politiche sanitarie 2016), and women with non-ST-segment elevation MI or unstable angina are less likely to undergo nonprimary percutaneous coronary intervention (Pelletier R et al, CMAJ 2014; 186: 497).



Access to care

Osteoarthritis Women receive less total joint arthroplasty than men, despite the fact that they have more osteoarthritis, and they undergo surgical procedures at a more advanced stage of disease compared with men (Franconi F and Campesi I Expert Rev. Clin. Pharmacol. Early online, 1–17 (2014)

Diabetes mellitus Diabetic women are less treated for many cardiovascular risk factors than diabetic men (Franconi F and Campesi I Expert Rev. Clin. Pharmacol. Early online, 1–17 (2014)

The significance of sex-gender on access to care and treatment cannot be neglected because the lack of awareness leads to inequality in the care of males and females.



The question is
Is Placebo effect affect by sex and gender ?



Placebo

placebo effects are genuine psychobiological phenomenon attributable to the overall therapeutic context, and it can be robust in both laboratory and clinical settings.

Placebo effects can exist in clinical practice, even if no placebo is given.

Mainstream interest in placebo effects only began with the widespread adoption of the placebo controlled randomized controlled trial (RCT) Henry Beecher in his famous proto-meta-analysis suggest that about 35% of patients responded positively to placebo treatment (6).

This psychosocial context surrounding the patient can be comprised of both individual patient and clinician factors, and the interaction between the patient, clinician and treatment environment.



The gender of researchers and care provider on outcomes of research and clinical practice (Dyades)

Hadjistavropoulos and co-workers [Psychol Health. 1996;11:411-208] examining patients with low back pain, showed that an observer is significantly influenced by patient gender and by the patients' physical attractiveness

Experimental pain in humans is better tolerated when the researcher is of the opposite sex of the examined subject (Kallai I et al Pain 112 (2004) 142). Men report lower pain to female experimenters than to male experimenters in the absence of significant changes in automatic response (heart rate and skin conductance), suggesting that the effect of the experimenter's sex-gender is due to psychosocial factors [Aslaksen PM et al Pain 129 (2007) 260].

Diabetic women are more treated if their cardiologist is a women (Victor BM et al Am J Cardiol 2014;113:1611 e 1615)

Rats and mice responses to pain depend on the sex of researchers [Sorge R.E et al Nat. Methods 11 (2014) 629].

Male and female researchers focus on different aspects of behaviour and interpret the very same results in different ways [PA Gowaty (Ed.), Feminism and Evolutionary Biology, Chapman & Hall, New York, 1997 M.E. Robinson, E.A. Wise, Gender bias in the observation of experimental pain, Pain 104 (2003) 259].



Grazie per l'attenzione

Inserire e-mail Relatore



Scientists studied 234 traits in >50,000 mice, across 10 centres

In control mice, sex had an effect on:



quantitative traits



qualitative traits

In mutant mice, sex modified the effect on:



quantitative traits



qualitative traits

Source: Natasha Karp et al. (2017) Prevalence of sexual dimorphism in mammalian phenotypic traits. *Nature Communications*



Women make an average of 4.6 doctor visits per year.

Pro-capite average cost for health care are \$5,246 in women compared to \$4,125 for men.

<http://www.womenshealthadvocate.org/articles/sex-differences-in-clinical-trials-another-example-of-inequality/>



