Journal Club
4 Marzo 2016

Specificità dell'invecchiamento al femminile

Bianca Faraci

Sommario

Gender medicine and specific-gender medicine

Gender gap: Longevity and Disability

Causes of gap

Diseases of women more than men

Specific attention for women

Future for women

Open Conclusions

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Le donne sono diverse dagli uomini:

La Medicina di genere non esiste. Esiste, invece, solo la Medicina genere-specifica.

Poiché nel momento in cui si insegna o si pratica una medicina a misura di uomo e di donna non vi può essere una via separata dal resto della medicina. Non si può insegnare la Medicina di genere come medicina parallela, o alternativa.

La medicina va insegnata e praticata in modo genere-specifico in tutte le sue specialità. Non può esistere un Corso di medicina di genere, un Congresso di medicina di genere, una specialità di medicina di genere, mentre tutte le branche della medicina vengono insegnate e applicate come se non esistessero le differenze di genere.

È incredibile, ma all'inizio del terzo millennio siamo chiamati a rifondare la medicina: dobbiamo completare le conoscenze, che sono davvero molto avanzate ma mai differenziate in base al genere, o meglio non sempre desunte da sperimentazioni condotte nei due generi; e dobbiamo applicare nella pratica quotidiana in tutte le specialità una Medicina genere-specifica.

Le più grandi riviste internazionali ci indirizzano in tal senso.

Il termine Medicina di genere sembra riferirsi a una medicina parallela, è fuorviante e va evitato. Noi tutti dobbiamo fondare e mettere in pratica una Medicina genere-specifica.

Giovannella Baggio. Dalla medicina di genere alla medicina genere-specifica. Italian Journal of Gender Specific Medicine, 11-2015

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Epidemiologic Reviews

Gender Gap in Longevity and Disability in Older Persons

Anne B. Newman[1,2] and Jennifer S. Brach[2,3]

INTRODUCTION

Women live longer than men, but older men have fewer disabilities than do older women. The purpose of this review is to examine the magnitude of the difference in longevity and disability that exists between older men and older women. Possible explanations for the differences in longevity and disability will be presented.

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Longevity gap

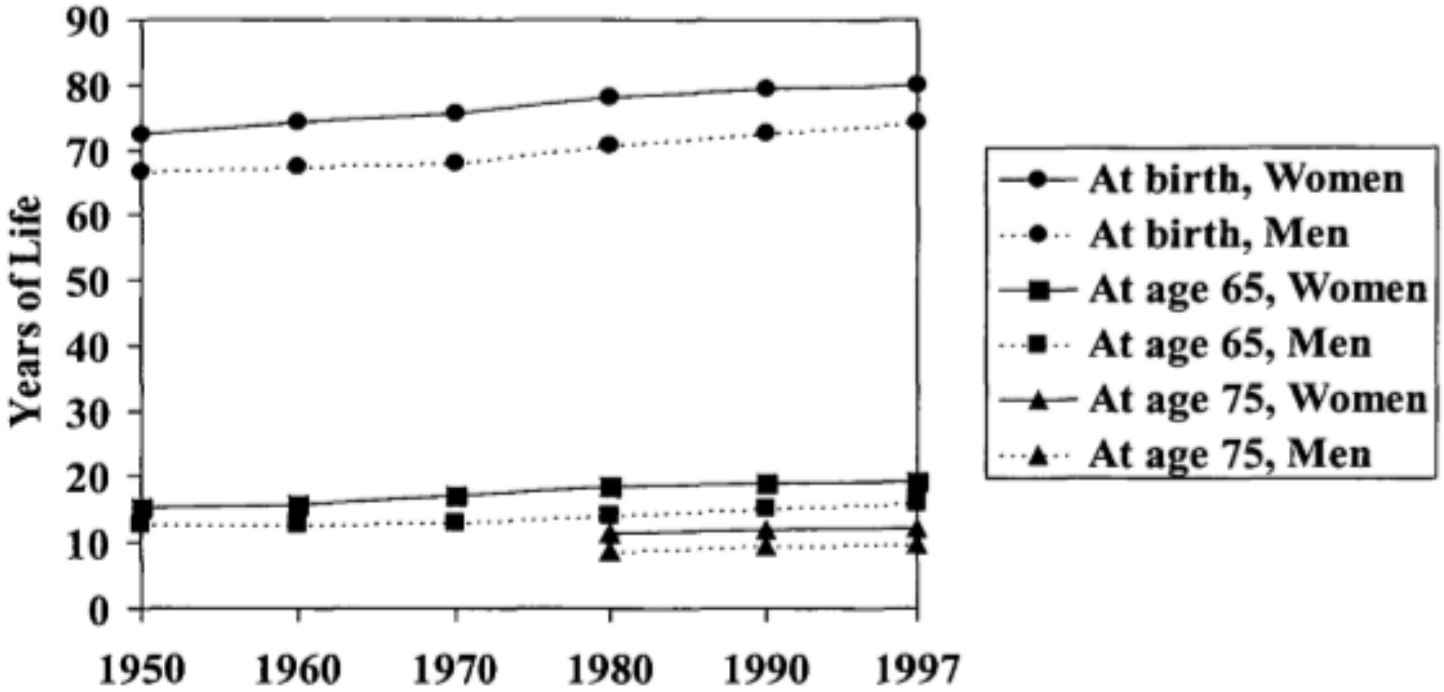


FIGURE 1. Life expectancy at birth, at age 65 years, and at age 75 years, by sex, United States, 1950–1997. (Source: National Center for Health Statistics, 1999 (1)).

Il divario tra uomini e donne è più grande in giovane età e diventa più piccolo all'aumentare dell'età. A tutte le età le donne hanno una sopravvivenza migliore rispetto agli uomini. Alla nascita il divario è di circa 6 anni ; a 65 anni si riduce a 3 anni e a 75 anni a 2.

Longevity gap

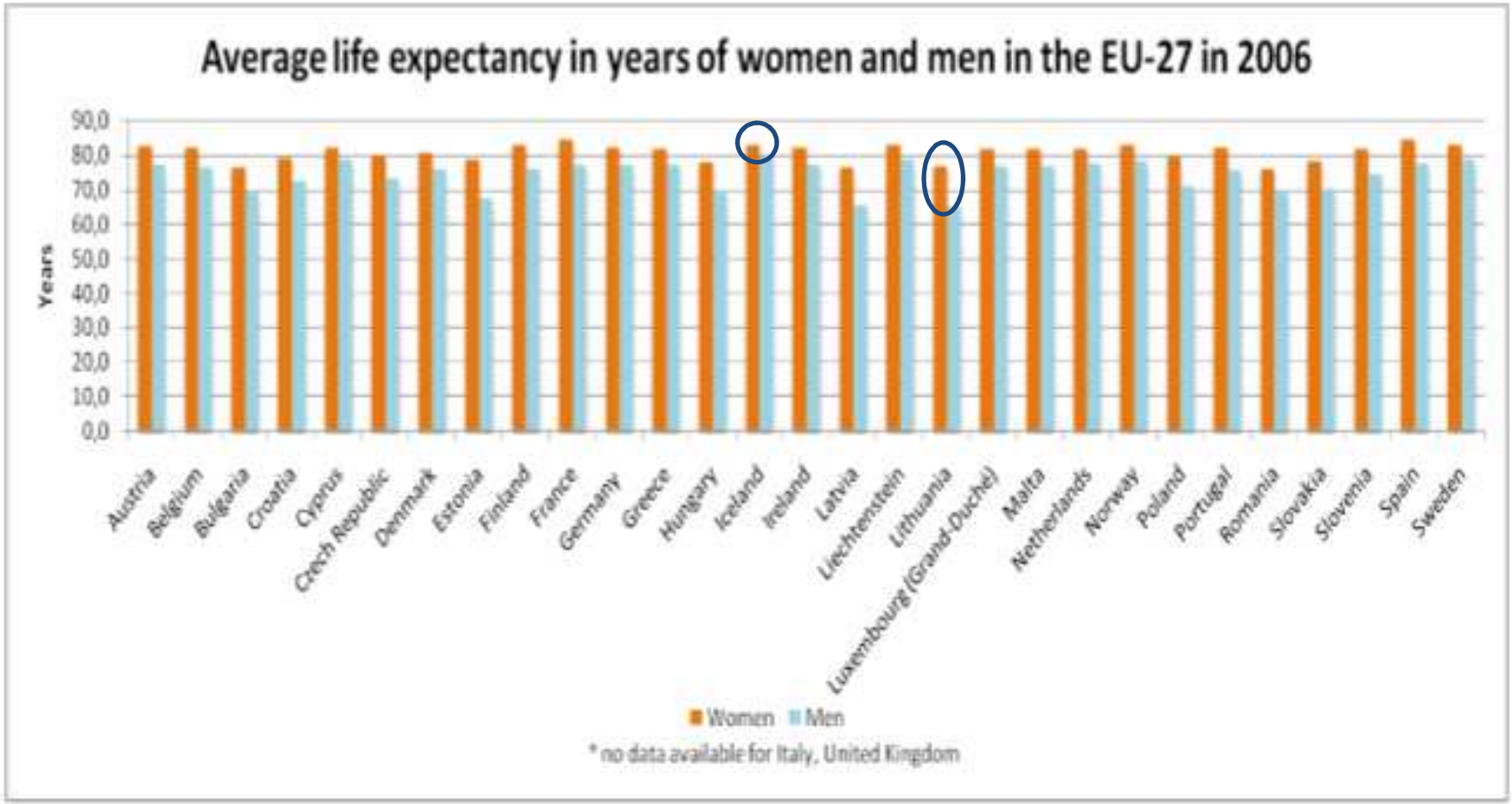
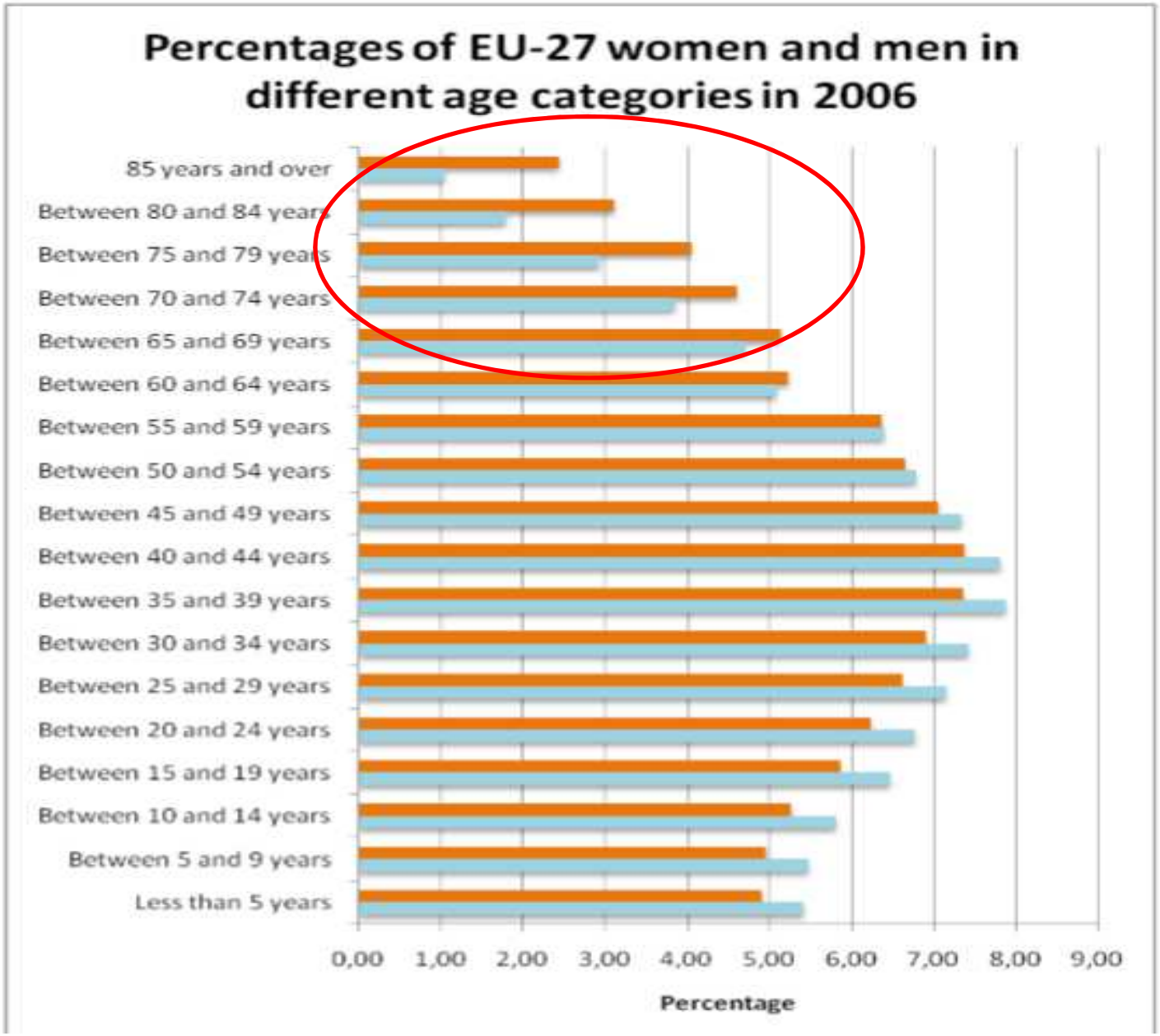


Fig. 3: Average life expectancy in years of women and men in the EU-27 in 2006. (EUROSTAT 2009)



15% donne in più in età compresa tra 65 e 69 anni e quasi il doppio in età superiore agli 80

Disability gap

TABLE 2. Percentage of men and women with limitations in functional activities, activities of daily living, and instrumental activities of daily living, United States, 1997*

	Age group (years)					
	Men			Women		
	65–74	75–84	≥85	65–74	75–84	≥85
Functional activities	23.9	37.0	50.0	30.9	46.2	65.6
ADL†	4.5	10.6	21.0	5.8	13.5	29.2
IADL†	12.4	21.9	42.1	18.1	32.3	57.9

* Source: 1994 National Health Interview Survey disability supplement (28).
† ADL, activity of daily living; IADL, instrumental activity of daily living.

Epidemiol Rev Vol. 23, No. 2, 2001

TABLE 3. Total life expectancy, active-life expectancy, and disabled-life expectancy at ages 65, 75, and 85 years, according to sex, United States, 1997*

	Total life expectancy (years)								
	At age 65 years			At age 75 years			At age 85 years		
	Total	Active	Disabled	Total	Active	Disabled	Total	Active	Disabled
Men	12.6	11.2	1.4	7.1	5.7	1.5	3.6	2.1	1.5
Women	18.6	16.0	2.7	11.8	9.0	2.8	6.9	3.9	3.0

* Source: Guralnik et al. (30).

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Disability gap

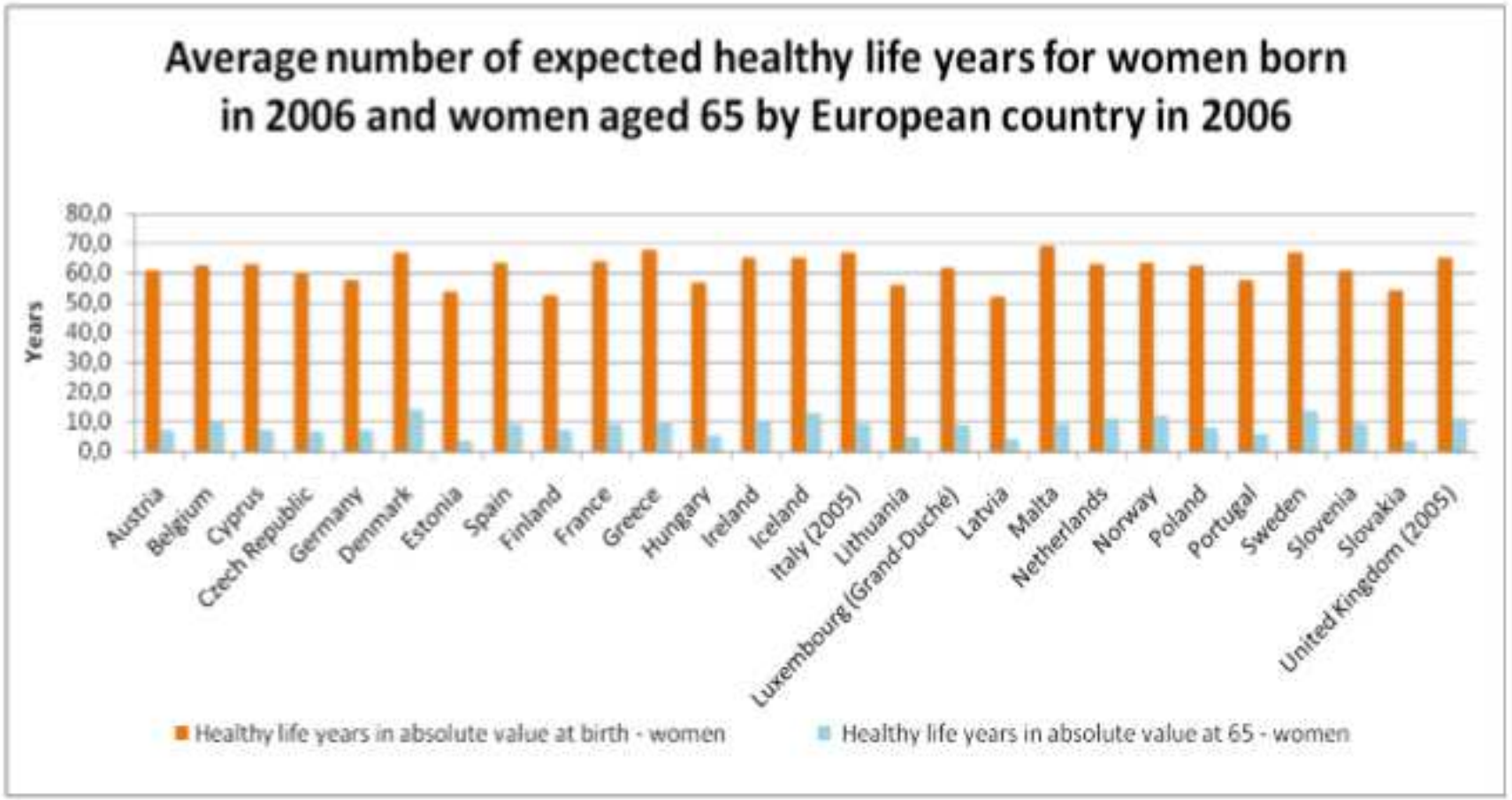

Fig. 4: Average number of expected healthy life years for women born in 2006 and women aged 65 by European country in 2006. (EUROSTAT 2009)

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TABLE 1. Age-adjusted death rates per 100,000 population, United States, 1997*

Cause of death	Men	Women
Heart disease	173.1	95.4
Cerebral vascular accident	27.9	24.2
Neoplasms	150.4	107.3
Lung cancer	52.8	27.5
Chronic obstructive pulmonary disease	26.1	17.7
Motor vehicle accident	21.7	10.2
Suicide	17.4	4.1
Homicide	12.5	3.3

* Source: National Center for Health Statistics, 1999 (1).

Alla base di questa differenza di genere vi è una complessa interazione di fattori ambientali, comportamentali e biologici.

Fattori comportamentali

- Incremento di K polmone, malattie cardiache e malattie polmonari croniche (fumo di sigaretta).
- Uomini vittime di incidenti automobilistici e omicidi («machismo», propensione al rischio e abitudini pericolose, alcool, sostanze d'abuso).
- Attività fisica irrilevante in entrambi i sessi.
- Minor utilizzo di servizi di assistenza sanitaria per prevenzione rispetto alle donne.
- Gli uomini ricercano cure in stadi più avanzati di malattia.

Research article

Open Access

Gender differences in the utilization of health-care services among the older adult population of Spain

Áurea Redondo-Sendino, Pilar Guallar-Castillón, José Ramón Banegas and Fernando Rodríguez-Artalejo*

Abstract

Background: Compared to men, women report greater morbidity and make greater use of health-care services. This study examines potential determinants of gender differences in the utilization of health-care services among the elderly.

Methods: Cross-sectional study covering 3030 subjects, representative of the non-institutionalized Spanish population aged 60 years and over. Potential determinants of gender differences in the utilization of health services were classified into predisposing factors (age and head-of-family status), need factors (lifestyles, chronic diseases, functional status, cognitive deficit and health-related quality of life (HRQL)) and enabling factors (educational level, marital status, head-of-family employment status and social network). Relative differences in the use of each service between women and men were summarized using odds ratios (OR), obtained from logistic regression. The contribution of the variables of interest to the gender differences in the use of such services was evaluated by comparing the OR before and after adjustment for such variables.

Results: As compared to men, a higher percentage of women visited a medical practitioner (OR: 1.24; 95% confidence limits (CL): 1.07–1.44), received home medical visits (OR: 1.67; 95% CL: 1.34–2.10) and took ≥3 medications (OR: 1.54; 95% CL: 1.34–1.79), but there were no gender differences in hospital admission or influenza vaccination. Adjustment for need or enabling factors led to a reduction in the OR of women compared to men for utilization of a number of services studied. On adjusting for the number of chronic diseases, the OR (95% CL) of women versus men for ingestion of ≥3 medications was 1.24 (1.06–1.45). After adjustment for HRQL, the OR was 1.03 (0.89–1.21) for visits to medical practitioners, 1.24 (0.98–1.58) for home medical visits, 0.71 (0.58–0.87) for hospitalization, and 1.14 (0.97–1.33) for intake of ≥3 medications. After adjustment for the number of chronic diseases and HRQL, the OR of hospitalization among women versus men was 0.68 (0.56–0.84).

Conclusion: The factors that best explain the greater utilization of health-care services by elderly women versus men are the number of chronic diseases and HRQL. For equal need, certain inequality was observed in hospital admission, in that it proved less frequent among women.

Gender differences in the utilization of health-care services among the older adult population of Spain

The percentage of women using health-care services was significantly higher than that of men in terms of visits to medical practitioners, home medical visits, number of medications and overall utilization (Table 2). No significant gender differences ($p > 0.05$) were observed in the percentage of subjects that were admitted to hospitals or received influenza vaccination.

Table 2
Utilization of health-care services by gender.

Health service	% women	% men	p
Visit to medical practitioner ≥once per month	41.97	36.85	0.004
Home visit ≥once per year	15.07	9.58	<0.0001
Hospital admission in the preceding year	17.34	18.12	0.573
Influenza vaccination in the most recent campaign	54.75	56.14	0.443
Current intake of ≥3medications	52.19	41.40	<0.0001
Overall utilisation (≥1 of the above health-care services)	84.83	79.49	<0.0001

Comportamenti sanitari

Nella maggior parte degli studi è riportato che le femmine utilizzano i servizi sanitari più frequentemente dei maschi (specialmente le cure primarie) (Mustard et al, 1998). Non tutti i report raggiungono però le stesse conclusioni: i dati di un recente studio condotto nei paesi scandinavi indicano, ad esempio, che, in Norvegia, le donne anziane sono visitate da un medico di medicina generale più frequentemente dei maschi (specialmente nella classe di età che va dai 65 ai 69 anni), ma meno frequentemente da uno specialista o spedalizzate; diversamente, in Finlandia le donne anziane sono visitate dal medico di famiglia o da uno specialista con una frequenza maggiore dei maschi; le differenze di genere non sono associate allo stato di salute auto-valutato, né al tipo di patologia cronica di cui soffre il paziente, né a specifiche caratteristiche socio-demografiche.

Comportamenti sanitari

Tra le interpretazioni psicosociali del fenomeno vi è quella che afferma che le donne con più facilità accettano e assumono il ruolo di malate; esse tenderebbero a riconoscere e a sperimentare, più dei maschi, i problemi di salute (per una donna è inoltre socialmente e culturalmente più accettabile essere ammalata e ricercare un aiuto medico). Il tasso di visite più elevato nelle donne rifletterebbe la loro maggior coscienza, e attenzione rispetto ai problemi di salute, la loro maggior sensibilità alla sintomatologia somatica (Gijsbers van Wijk e al, 1999; Cecile e al, 1999; Suominen-Taipale e al, 2006).

Negli ultrasessantacinquenni i tassi più elevati di visite mediche, rispetto ai giovani, sono dovuti alla percezione della compromissione dello stato di salute e di una potenziale maggior gravità della condizione clinica (Dearborn e al, 2006).

Comportamenti sanitari

Altre spiegazioni suggeriscono che i maschi anziani sono visitati più frequentemente dagli specialisti o più frequentemente spedalizzati delle femmine per la maggior complessità della patologia dei maschi (ad es. cardiovascolare e respiratoria). Il fatto che le donne anziane dichiarino una peggior condizione economica dei maschi, cerchino più frequentemente una visita dal medico di famiglia, ma vadano meno frequentemente dallo specialista potrebbe suggerire che le donne sono più sane dei maschi, ma percepiscono una peggior condizione di salute.

Fattori geografici

- Fumo non ancora diffuso nella popolazione femminile nei paesi sottosviluppati.
- Differenti patologie (Es. TBC, mal. Infettive e parassitarie, tracoma nei paesi sottosviluppati).
- Differenze nell'alimentazione (Es. problemi economici, scarsa introduzione di alimenti essenziali in alcuni paesi).
- Istruzione e alfabetizzazione.
- Ruoli sociali (carriera lavorativa, caregiver, impegno in casa e in famiglia).

Fattori biologici

ISSN 0006-2979, Biochemistry (Moscow), 2015, Vol. 80, No. 12, pp. 1560-1570. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © V. A. Popkov, E. Yu. Plotnikov, D. N. Silachev, L. D. Zorova, I. B. Pevzner, S. S. Jankauskas, S. D. Zorov, V. A. Babenko, D. B. Zorov, 2015, published in Biokhimiya, 2015, Vol. 80, No. 12, pp. 1817-1829.

REVIEW

Diseases and Aging: Gender Matters

V. A. Popkov[1], E. Yu. Plotnikov[1]*, D. N. Silachev[1], L. D. Zorova[2], I. B. Pevzner[1], S. S. Jankauskas[1], S. D. Zorov[3], V. A. Babenko[3], and D. B. Zorov[1]*

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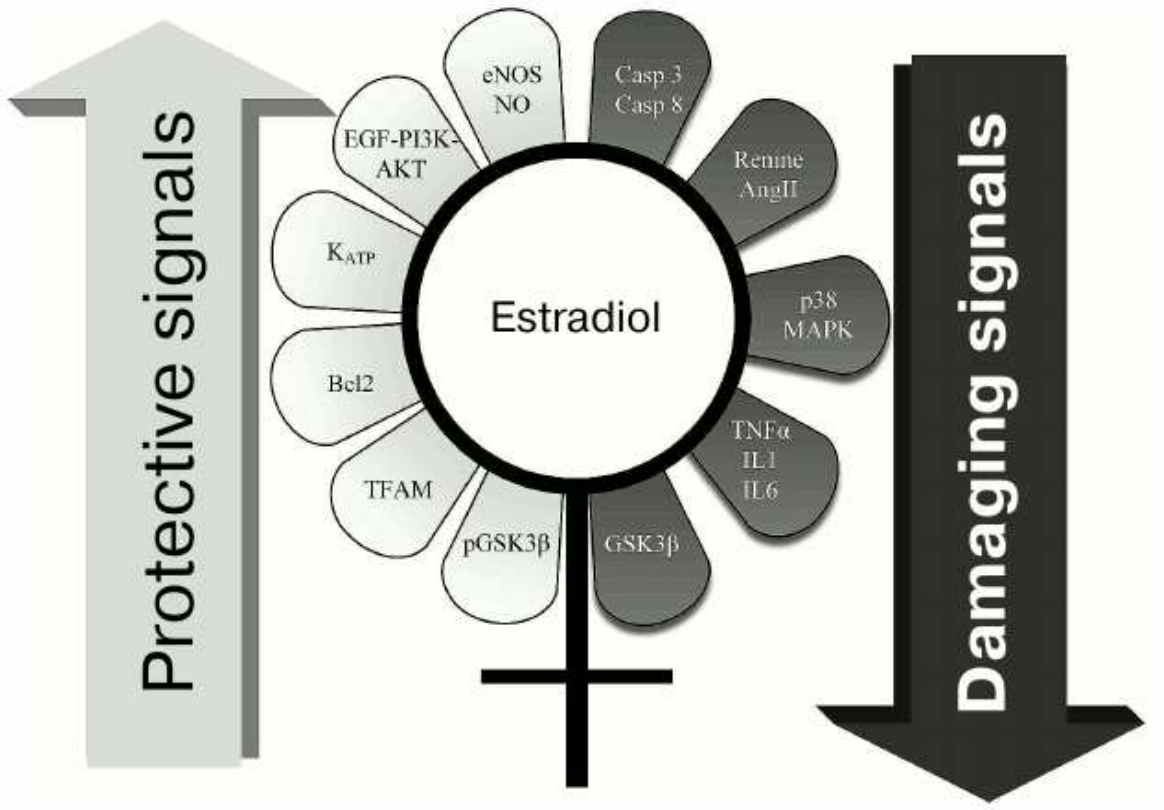
- **It is commonly believed that it is estrogen (as a major female hormone) that provides resistance to diseases in women, whereas testosterone (as the major male hormone), in contrast, accounts for severe manifestation of diseases in men. Female mice more easily overcome myocardial infarction, and administration of testosterone worsens outcome, whereas in males administration of estrogen affords protective effect . Androgens elevate blood pressure in males, whereas castration decreases it .**

Fattori biologici

- **Castration of male rats lowers renal injury during ischemia, whereas excision of ovaries in females aggravates the injury. Testosterone administered to males and females lacking reproductive glands potentiates injuries, whereas estrogen attenuates injury in ovariectomized females. Treatment of postmenopausal women with estrogen ameliorates the manifestation of some types of renal failure.**
- **Estradiol displayed remarkable cardioprotective effects in a model of cardiac trauma in rats, which are also mediated by the influence of the hormone on mitochondrial transcription factor A (TFAM), ATP metabolism, and mitochondrial functioning. It is believed that estrogen and testosterone regulate activity of NADPH oxidase, which in females and males results in downregulated and upregulated production of ROS, respectively.**

Fattori biologici



Females contained glycogen synthase kinase 3β (GSK3β) inactivated via phosphorylation, which is a key enzyme in signaling mechanisms in ischemic injury and anti-ischemic defense. Also, the p38 MAPK signaling pathway is more inactivated in females, and they have lower levels of proinflammatory cytokines TNFα, IL-1, IL-6 . On the contrary, endothelial NO synthase is activated in females. Altogether, these changes are related to defense of various tissues against ischemic injuries.

Fattori biologici

Testosterone raises low density lipoproteins and lowers high density lipoproteins, while estrogen does just the opposite. Estrogen also protects the vascular endothelium, and these effects may persist well after the menopause. After menopause, there is a shift in lipid levels that parallels the increase in cardiovascular disease risk postmenopausally. Although the mortality risk for a women comes closer to that of a man, it never catches up . Older women always remain somewhat more protected from heart disease. The risk of death from heart disease for women aged 75 years lags about 10 years behind that of men, but even at advanced age, the risk remains lower than the risk for older men. Since most of these women never took postmenopausal estrogen, estrogen cannot be the only factor in protecting women from mortality.

Epidemiol Rev Vol. 23, No. 2, 2001

Sex Differences in the Gut Microbiome Drive Hormone-Dependent Regulation of Autoimmunity

Janet G. M. Markle[1,2], Daniel N. Frank[3], Steven Mortin-Toth[1], Charles E. Robertson[4], Leah M. Feazel[3], Ulrike Rolle-Kampczyk[5], Martin von Bergen[5,6,7], Kathy D. McCoy[8], Andrew J. Macpherson[8], Jayne S. Danska[1,2,9,*]

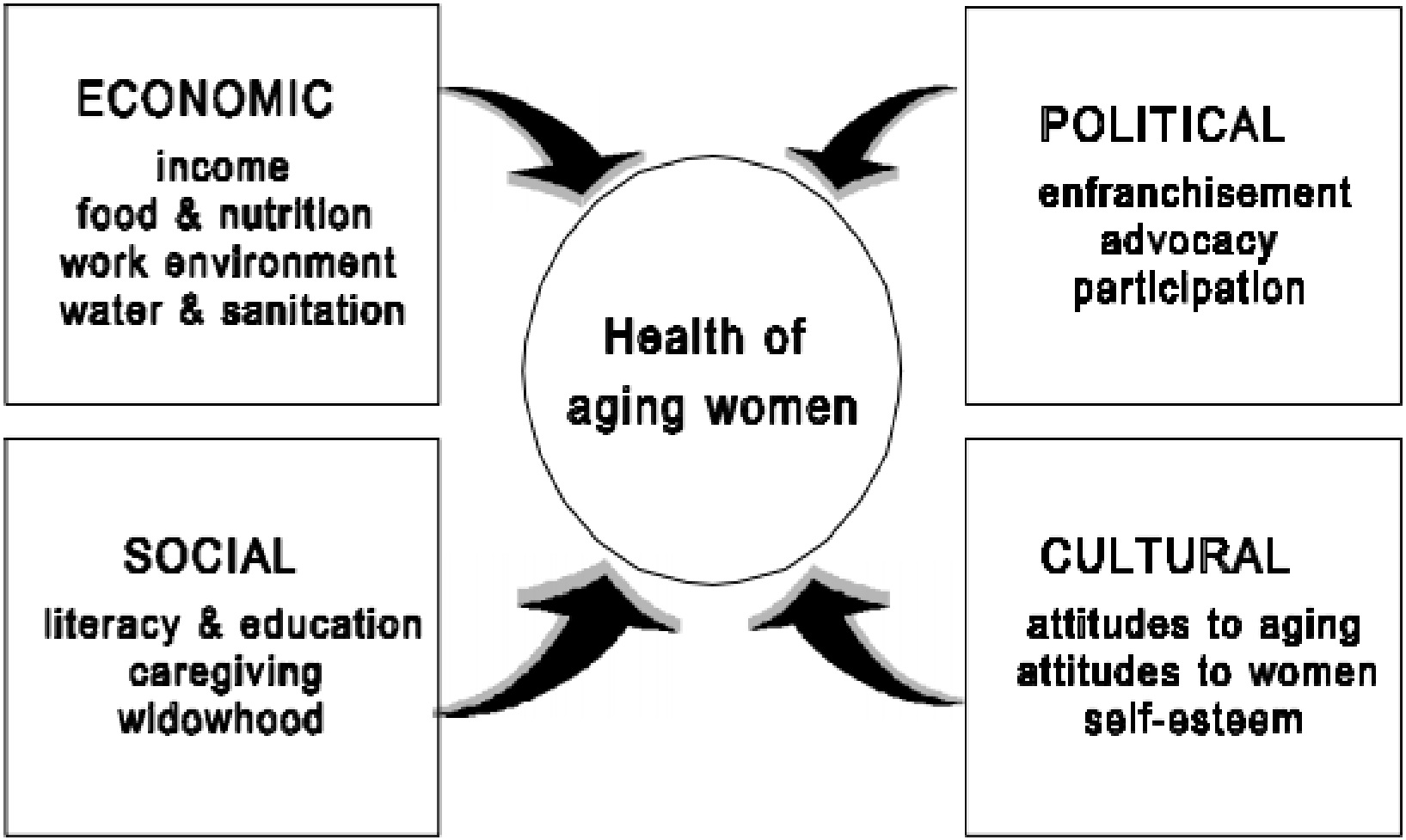
Microbial exposures and sex hormones exert potent effects on autoimmune diseases, many of which are more prevalent in women. We demonstrate that early-life microbial exposures determine sex hormone levels and modify progression to autoimmunity in the nonobese diabetic (NOD) mouse model of type 1 diabetes (T1D). Colonization by commensal microbes elevated serum testosterone and protected NOD males from T1D. Transfer of gut microbiota from adult males to immature females altered the recipient's microbiota, resulting in elevated testosterone and metabolomic changes, reduced islet inflammation and autoantibody production, and robust T1D protection. These effects were dependent on androgen receptor activity. Thus, the commensal microbial community alters sex hormone levels and regulates autoimmune disease fate in individuals with high genetic risk.

Science 1 March 2013:
Vol. 339 no. 6123 pp. 1084-1088

It was completely unexpected to find that the sex of an animal determines aspects of their gut microbe composition, that these microbes affect sex hormone levels, and that the hormones in turn regulate an immune-mediated disease. It's a pretty startling result which may impact how we think about a variety of autoimmune diseases in humans, from multiple sclerosis to rheumatoid arthritis. Like a lot of science, though, it generates nearly as many questions as it does answers, from the possible role of the microbiome in pubescent development to how the gut bacteria actually regulate testosterone. It also clearly underlines the fact that our microbiome isn't really "something we have" but is a part and parcel of who we are, helping defining each of us, both as an individual and an ecosystem.

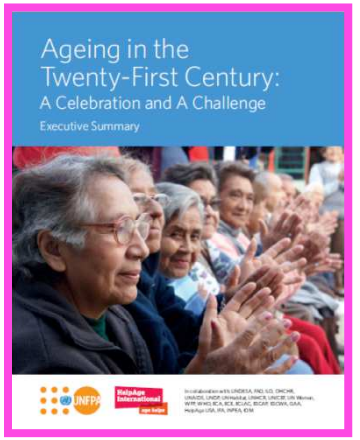
Science 1 March 2013:
Vol. 339 no. 6123 pp. 1084-1088

Figure 4.1
Social determinants of health



Fattori socio-culturali

Men and women experience old age differently. Older women tend to have stronger social networks than men and there is evidence that mothers are more likely than fathers to receive material and emotional support from their adult children. Older women are also more likely than older men to be caregivers of children or sick relatives, particularly in families affected by migration or illness. Men's greater economic role means that loss of earning power can have negative consequences for their roles in society after they have retired. Traditional roles in the household can result in older men becoming more isolated once they retire from their jobs.



Fattori socio-culturali

We are gaining a much deeper understanding of chronic disease. And we understand that it is not just about biological differences between women and men, although this is one piece of the picture. For example, we know that women and men tend to manage their chronic disease differently because of their gender roles. We also know that chronic disease can affect people differently according to their cultural background, where they live and how rich or poor they are. We are beginning to understand, too, that some of the major risk factors for chronic diseases – physical inactivity, inadequate fruit and vegetable intake, being overweight or obese, and smoking – are related in complex ways to sex, gender, income, education, geography, and a myriad of other factors.

Canadian Women's Health Network
Le Réseau canadien pour la santé des femmes

Fattori socio-culturali

The loss of a spouse can make women more vulnerable. Older women are more likely to be widowed than older men and are less likely to remarry than men who are widowed. As the status of women in many societies is linked to the status of their husbands, widows and unmarried older women can become particularly vulnerable to poverty and social exclusion.

Aging Clin. Exp. Res. 12: 77-84, 2000

Do men and women follow different trajectories to reach extreme longevity?

C. Franceschi[1,2], L. Motta[3], S. Valensin[1], R. Rapisarda[3], A. Franzone[3], M. Berardelli[3], M. Motta[3], D. Monti[4], M. Bonafè[1], L. Ferrucci[2], L. Deiana[5], G.M. Pes[5], C. Carru[5], M.S. Desole[5], C. Barbi[1], G. Sartoni[1], C. Gemelli[1], F. Lescai[1], F. Olivieri[2], F. Marchegiani[2], M. Cardelli[2], L. Cavallone[2], P. Gueresi[6], A. Cossarizza[7], L. Troiano[6], G. Pini[2], P. Sansoni[8], G. Passeri[8], R. Lisa[2], L. Spazzafumo[2], L. Amadio[2], S. Giunta[2], R. Stecconi[2], R. Morresi[2], C. Viticchi[2], R. Mattace[9], G. De Benedictis[10], G. Baggio[11], and the Italian Multicenter Study on Centenarians (IMUSCE)*

ABSTRACT. Gender accounts for important differences in the incidence and prevalence of a variety of age-related diseases. Considering people of far advanced age, demographic data document a clear-cut prevalence of females compared to males, suggesting that sex-specific mortality rates follow different trajectories during aging. In the present investigation, we report data from a nationwide study on Italian centenarians (a total of 1162 subjects), and from two studies on centenarians living in two distinct zones of Italy, i.e., the island of Sardinia (a total of 222 subjects) and the Mantova province (Northern Italy) (a total of 43 subjects). The female/male ratio was about 2:1 in Sardinia, 4:1 in the whole of Italy, and about 7:1 in the Mantova province. Thus, a complex interaction of environmental, historical and genetic factors, differently characterizing the various parts of Italy, likely plays an important role in determining the gender-specific probability of achieving longevity. Gender differences in the health status of centenarians are also reported, and an innovative score method to classify long-lived people in different health categories, according to clinical and functional parameters, is proposed. Our data indicate that not only is this selected group of people, as a whole, highly heterogeneous, but also that a marked gender difference exists, since male centenarians are less heterogeneous and more healthy than female centenarians. Immunological factors regarding the age-related increase in pro-inflammatory status, and the frequency of HLA ancestral haplotypes also show gender differences that likely contribute to the different strategies that men and women seem to follow to achieve longevity. Concerning the different impact of genetic factors on the probability of reaching the extreme limits of the human life-span, emerging evidence (regarding mtDNA haplogroups, Thyrosine Hydroxilase, and IL-6 genes) suggests that female longevity is less dependent on genetics than male longevity, and that female centenarians likely exploited a healthier life-style and more favorable environmental conditions, owing to gender-specific cultural and anthropological characteristics of the Italian society in the last 100 years.

(Aging Clin. Exp. Res. 12: 77-84, 2000)

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The “female paradox”:

1. women enjoy longer life expectancy than men, but they suffer from many chronic systemic diseases;
2. chronic drug assumption is elevated in female sex, but women are more prone to develop adverse drug reactions;
3. women need a higher number of medical interventions than men, but they are under-represented in most clinical trials.

Le donne sono diverse dagli uomini:

È necessario ristudiare le patologie che affliggono uomini e donne nel quotidiano: malattie cardiovascolari, tumori, malattie metaboliche, neurologiche, infettive e tutte le specialistiche anche chirurgiche. La Medicina di genere riguarda di fatto tutte le specialità del sapere medico.

Nei paesi occidentali le donne hanno un vantaggio in numero di anni di vita rispetto agli uomini. In Italia, ad esempio, la spettanza di vita alla nascita dell'uomo è 79,9 anni mentre quella della donna è 84,6 (ISTAT, 2014). Molte le teorie sui "perché" di questa differenza che spaziano dalla genetica alla cultura.

Tuttavia la spettanza di vita sana è identica nei due generi, quindi i 5 anni di vantaggio delle donne sono anni di vita ammalata e disabile, principalmente per le conseguenze delle malattie cardiovascolari, osteoarticolari e neurologiche (demenza e depressione).

Questo ha una enorme influenza sulla qualità della vita e sulla spesa sanitaria. Le donne, inoltre, soprattutto con età superiore ai 65 anni, sono molto più sole, hanno un livello culturale inferiore e una situazione economica molto più fragile.

Eppure, poco sappiamo sulla cura e sulla prevenzione delle malattie nel genere femminile.

Dalla medicina di genere alla medicina genere-specifica

Giovannella Baggio, Italian Journal of Gender specific Medicine, 11-2015

Le donne sono diverse dagli uomini:

Desidero fare un esempio proprio in campo cardiologico. L'infarto è la prima causa di morte delle donne. Negli ultimi 40 anni la mortalità per malattie cardiovascolari (infarto del miocardio, ictus) è diminuita fortemente nell'uomo e in modo molto meno significativo nelle donne, non è diminuita affatto nelle donne diabetiche.

Ancor oggi sia le donne sia il mondo medico pensano che queste malattie siano prevalentemente maschili.

Questo ha fatto sì che il genere femminile quasi non esista nei trial epidemiologici che hanno descritto i fattori di rischio e la prevenzione, i sintomi e la terapia dell'infarto.

Le donne, oggi lo sappiamo, possono avere sintomi molto diversi quando sono colpite da un infarto del miocardio, tanto che si parla di sintomatologia atipica: spesso non hanno il dolore precordiale, ma al collo, al dorso oppure non hanno alcun dolore ma solo irrequietezza, ansia, lieve dispnea; per tale motivo possono non essere ricoverate, essere soccorse in ritardo o non essere indirizzate in area "rossa" del Pronto Soccorso.

Di conseguenza la mortalità delle donne in fase acuta e in periodo ospedaliero, dopo un infarto, è sempre superiore rispetto agli uomini. Ma anche la mortalità a 6 mesi da un infarto è superiore nelle donne e anche a distanza di 6 anni da un intervento di bypass. Nelle donne, inoltre, si ammalano facilmente le piccole arterie del cuore (il microcircolo) piuttosto che le grandi arterie, di conseguenza la diagnostica è più complessa e deve seguire percorsi differenti. La coronarografia, ad esempio, può non evidenziare gravi alterazioni delle coronarie epicardiche. Ci sono serie patologie cardiovascolari come la rottura di cuore, la dissezione coronarica, la Sindrome di tako-tsubo che si reperiscono quasi esclusivamente nelle donne.

Ma poco si è fatto in questi anni di grandi ricerche e scoperte per capire il perché di tali diversità.

Giovannella Baggio. Dalla medicina di genere alla medicina genere-specifica. Italian Journal of Gender Specific Medicine, 11-2015

Redberg RF. Don't assume women are the same as men: include them in the trial. Arch Intern Med 2012;172: 921.

Putting Gender on the agenda. Nature 2010; 7299: 665.

Schiebinger L. Scientific research must take gender into account. Nature 2014; 507: 9.

Prevalence of AD and other dementias in women and men

More women than men have AD and other dementias. Almost two-thirds of Americans with AD are women. Of the 5 million people age 65 years and older with AD in the United States, 3.2 million are women and 1.8 million are men. Based on estimates from ADAMS, 16% of women age 71 years and older have AD and other dementias compared with 11% of men. The larger proportion of older women who have AD and other dementias is explained primarily by the fact that women live longer, on average, than men. Many studies of the age-specific incidence (development of new cases) of AD or any dementia have found no significant difference by sex. Thus, women are not more likely than men to develop dementia at any given age.

William Thies, Ph.D., and Laura Bleiler.

Alzheimer's & Dementia 9 (2013) 208–245

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REVIEW

Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences

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Abstract: With the aging of the population, the burden of Alzheimer's disease (AD) is rapidly expanding. More than 5 million people in the US alone are affected with AD and this number is expected to triple by 2050. While men may have a higher risk of mild cognitive impairment (MCI), an intermediate stage between normal aging and dementia, women are disproportionally affected with AD. One explanation is that men may die of competing causes of death earlier in life, so that only the most resilient men may survive to older ages. However, many other factors should also be considered to explain the sex differences. In this review, we discuss the differences observed in men versus women in the incidence and prevalence of MCI and AD, in the structure and function of the brain, and in the sex-specific and gender-specific risk and protective factors for AD. In medical research, sex refers to biological differences such as chromosomal differences (eg, XX versus XY chromosomes), gonadal differences, or hormonal differences. In contrast, gender refers to psychosocial and cultural differences between men and women (eg, access to education and occupation). Both factors play an important role in the development and progression of diseases, including AD. Understanding both sex- and gender-specific risk and protective factors for AD is critical for developing individualized interventions for the prevention and treatment of AD.

Keywords: Alzheimer's disease, dementia, sex, gender, risk factors, dimorphic medicine

Sex and Gender differences in AD

In medical research, sex refers to biological differences such as chromosomal (eg, XX versus XY chromosomes), gonadal, or hormonal differences. In contrast, gender refers to psychosocial and cultural differences between men and women (eg, access to education and occupation). Both factors play an important role in the development and progression of diseases, including AD.

Clinical Epidemiology 2014:6 37–48

Sex and Gender differences in AD

Gender refers to the cultural and psychosocial factors that impact our identity and modify our risk of disease via health perception, risk behavior, social and work-related stressors, personal and societal perceptions of men's and women's role, patient– doctor relationships, and adherence to therapy. Specific factors related to gender identity that may contribute to the risk of AD include education, occupation, diet and exercise, and smoking and drinking behaviors. Gender is also strongly linked with the concept of cognitive reserve such that a higher education/occupation and greater engagement in cognitive activities provides higher reserve against disease and results in varying cognitive aging trajectories among individuals.

Clinical Epidemiology 2014:6 37–48

Sex and Gender differences in AD

Low education and low occupational history (eg, unskilled versus skilled worker) have repeatedly been associated with either a higher prevalence or incidence of AD. Cognitive activities have been shown to reduce the risk of dementia in the elderly. In the past century men have had more opportunities for higher education and higher occupational attainment than women. This is particularly true for individuals aged 70 and older who are now at greatest risk of developing AD, suggesting a higher education/occupation related reserve in men.

Clinical Epidemiology 2014:6 37–48

Sex and Gender differences in AD

At the most recent census, the educational attainment in the US was higher in women than men, and there also has been a dramatic shift in occupational engagement due to changing gender roles. For example, men and women have experienced different access to education and occupation in North America compared to Europe and Asia in the early part of this century. These gender-related differences may explain the observed geographic differences in the prevalence and incidence of AD that are described above. Indeed, it is possible that with greater educational and occupational attainment in women, the sex differences will diminish. The changing trends of intellectual lifestyles in men and women may contribute to changing epidemiologic patterns for AD and dementia across countries and over time.

Clinical Epidemiology 2014:6 37–48

Sex and Gender differences in AD

The most striking difference between the brain anatomy of men and women is the larger head size and cerebral brain volume in men (~10%). Therefore, one would expect men to be able to withstand more pathology compared to women. This hypothesis was supported by an autopsy study that found that women had significantly higher odds of a clinical diagnosis of AD at the same level of pathology. While overall larger head sizes may suggest larger brain reserve in men, studies have consistently shown faster age-associated brain volume decline in men compared to women in cognitively normal individuals.

Clinical Epidemiology 2014:6 37–48

Sex and Gender differences in AD

Functional imaging measures such as F-fluorodeoxyglucose positron emission tomography (FDG-PET) for measuring metabolism and resting state functional magnetic resonance imaging for measuring brain connectivity have shown significant differences between men and women. Typically, cerebral blood flow and connectivity have been found to be higher in women in the parietal association cortices and higher for men in the visual and motor cortices, providing evidence for brain function and behavior differences between the sexes.

Clinical Epidemiology 2014:6 37–48

Sex and Gender differences in AD

Observational studies show that the use of HRT, when initiated around the time of menopause but not years after, reduces the risk of AD. In the Cache County Study, women who initiated HRT within 5 years of menopause had a 30% lower risk of AD compared to women who reported no use of HRT. However, women who began hormone therapy more than 5 years after menopause did not have a lowered risk. In fact, those who started hormone use when they were 65 years or older had almost a two-fold increased risk.

Clinical Epidemiology 2014:6 37–48

Menopause Management — Getting Clinical Care Back on Track

JoAnn E. Manson, M.D., Dr.P.H., and Andrew M. Kaunitz, M.D.

N ENGL J MED 374;9 NEJM.ORG MARCH 3, 2016

Physicians become familiar with treatment options for menopausal symptoms through appropriate clinical training. However, most primary care residency programs in the United States don't provide adequate education in women's health in general or in menopause management in particular.

For instance, a 2009 survey of 100 U.S. internal medicine residents showed a clear mismatch between trainees' needs. Although more than three quarters of respondents considered care of menopausal women to be a "very important" area that should be addressed as a core component of their training in internal medicine, half reported a low comfort level managing menopausal symptoms, more than three quarters indicated that training opportunities in this area were limited, and more than one third indicated that they had no clinical experience managing menopausal symptoms in the previous 6 months.

Menopause Management — Getting Clinical Care Back on Track

JoAnn E. Manson, M.D., Dr.P.H., and Andrew M. Kaunitz, M.D.

N ENGL J MED 374;9 NEJM.ORG MARCH 3, 2016

Reluctance to treat menopausal symptoms has derailed and fragmented the clinical care of midlife women, creating a large and unnecessary burden of suffering.

Clinicians who stay current regarding hormonal and nonhormonal treatments can put menopause management back on track by helping women make informed treatment choices.

In addition, we must train and equip the next generation of health care providers with the skills to address the current and future needs of this patient population.

The North American Menopause Society provides a free mobile app called MenoPro to facilitate the individualized risk assessment required for counseling menopausal women regarding hormone therapy.
This decision support tool — which has a mode for clinicians and one for patients — also includes nonhormonal options for managing menopausal symptoms and genitourinary syndrome of menopause.

Osteoporosis and hip fracture

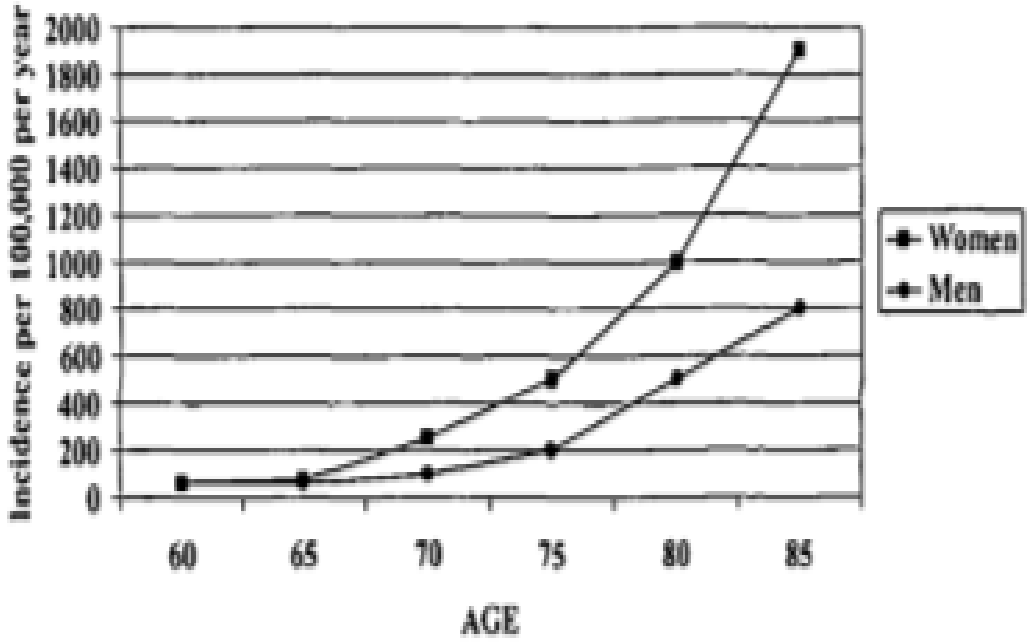

FIGURE 2. Age-specific incidence rates of hip fracture by sex, United States, 1950–1997. (Source: Lauritzen et al., 1993 (52)).

The prevalence of age-related osteoporotic (osteoporosis occurring in individuals over age 50) is higher in women than in men because of increased bone loss and related to menopause. The result is an increase in the incidence of fractures, particularly of hip fractures.

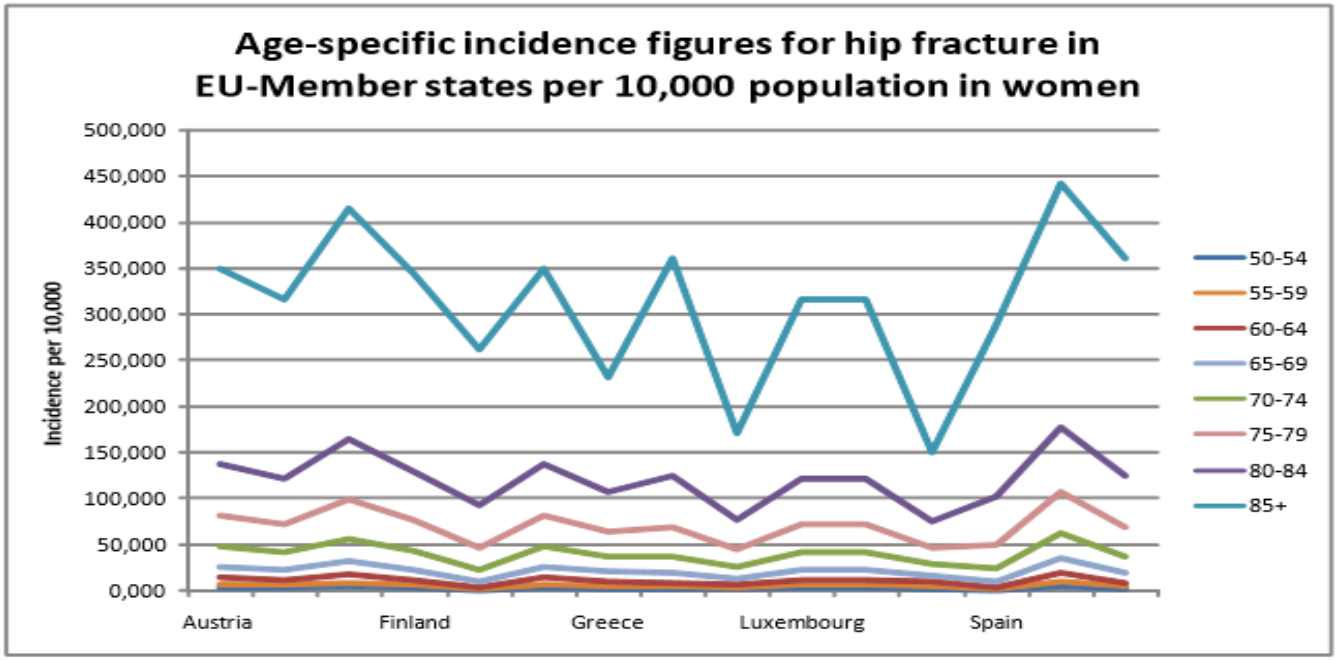

Fig. 14: Age-specific incidence for hip fracture in EU-Member States (per 10,000 populations) in women. (European Commission 2008b)

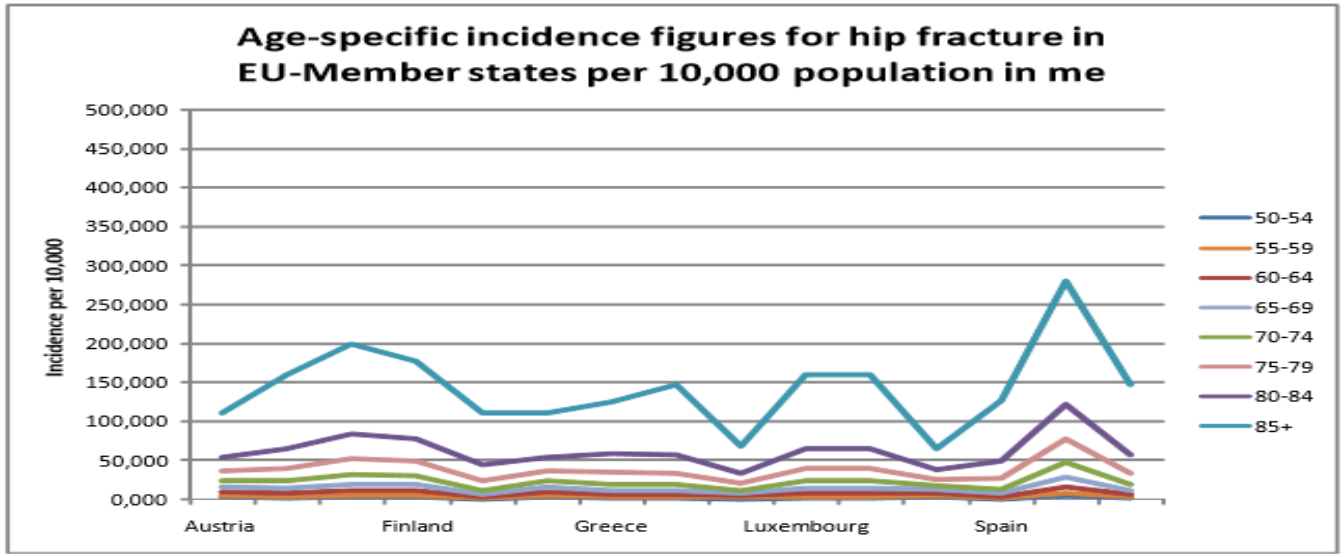

Fig.15: Age-specific incidence for hip fracture in EU-Member States (per 10,000 populations) in men. (European Commission 2008b)

Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival

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Abstract

Introduction: osteoporosis is a common disease, and the incidence of osteoporotic fractures is expected to rise with the growing elderly population. Immediately following, and probably several years after a hip fracture, patients, both men and women, have a higher risk of dying compared to the general population regardless of age. The aim of this study was to assess excess mortality following hip fracture and, if possible, identify reasons for the difference between mortality for the two genders.
Methods: this is a nationwide register-based cohort study presenting data from the National Hospital Discharge Register on mortality, comorbidity and medication for all Danish patients (more than 41,000 persons) experiencing a hip fracture between 1 January 1999 and 31 December 2002. Follow-up period was until 31 December 2005.
Results: we found a substantially higher mortality among male hip fracture patients than female hip fracture patients despite men being 4 years younger at the time of fracture. Both male and female hip fracture patients were found to have an excess mortality rate compared to the general population. The cumulative mortality at 12 months among hip fracture patients compared to the general population was 37.1% (9.9%) in men and 26.4% (9.3%) in women. In the first year, the risk of death significantly increased for women with increasing age (hazard ratio, HR: 1.06, 95% confidence interval, CI: 1.06–1.07), the number of comedications (HR 1.04, 95% CI 1.03–1.05) and the presence of specific Charlson index components and medications described below. For men, age (HR 1.07, 95% CI 1.07–1.08), number of comedications (HR 1.06, 95% CI 1.04–1.07) and presence of different specific Charlson index components and medications increased the risk. Long-term survival analyses revealed that excess mortality for men compared with women remained strongly significant (HR 1.70, 95% CI 1.65–1.75, $P < 0.001$), even when controlled for age, fracture site, the number of medications, exposure to drug classes A, C, D, G, J, M, N, P, S and for chronic comorbidities.

Age and Ageing 2010; **39:** 203–209

Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival

Table 1
Demographics and comorbidities for patients born in 1945 or earlier with incident hip fracture in Denmark 1999–2002

	Women (*N*=30,755)	Men (*N*=11,321)	*P*
Age	81.7 ± 8.9	78.1 ± 10.0	<0.001
Mortality			
3 months	15.3%	23.9%	<0.001
12 months	26.4%	37.1%	<0.001
36 months	46.3%	57.1%	<0.001

Cumulative mortality was significantly lower for women: 15.3% at 3 months, 26.4% at 12 months and 46.3% at 36 months. Corresponding numbers for men were 23.9%, 37.1% and 57.1%, resulting in a male/female risk ratio of 1.6, 1.4 and 1.2 after 3, 12 and 36 months, respectively. In patients aged >75 years, men had higher mortality than women only in the first year following fracture. For both genders, absolute mortality rates were highest in the older subset of patients.

Age and Ageing 2010; **39:** 203–209

Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival

Table 1
Demographics and comorbidities for patients born in 1945 or earlier with incident hip fracture in Denmark 1999–2002

Hospital-treated chronic comorbidity in the last 3 years (Charlson index components)	Women (*N*=30,755)	Men (*N*=11,321)	*P*
Cerebrovascular disease	2,650 (8.6%)	1,347 (11.9%)	<0.001
Any malignancy	1,860 (6.0%)	1,021(9.0%)	<0.001
Metastatic solid tumour	232 (0.8%)	126 (1.1%)	<0.01
Congestive heart failure	1,793 (5.8%)	903 (8.0%)	<0.001
COPD	1,692 (5.5%)	933 (8.2%)	<0.001
Dementia	1,309 (4.3%)	506 (4.5%)	0.34
DM w/o complications	1,018 (3.3%)	477 (4.2%)	<0.001
DM with complications	327 (1.1%)	265 (2.3%)	<0.001
Ulcer disease	951 (3.1%)	356 (3.1%)	0.78
Peripheral vascular disease	800 (2.6%)	530 (4.7%)	<0.001
Myocardial infarction	710 (2.3%)	424 (3.7%)	<0.001
Connective tissue diseases	635 (2.1%)	104 (0.9%)	<0.001
Moderate or severe renal disease	160 (0.5%)	135 (1.2%)	<0.001
Hemiplegia	61 (0.2%)	31 (0.3%)	0.16
Moderate or severe liver disease	32 (0.1%)	29 (0.3%)	<0.001
AIDS	0 (0.0%)	2 (0.0%)	0.07

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.

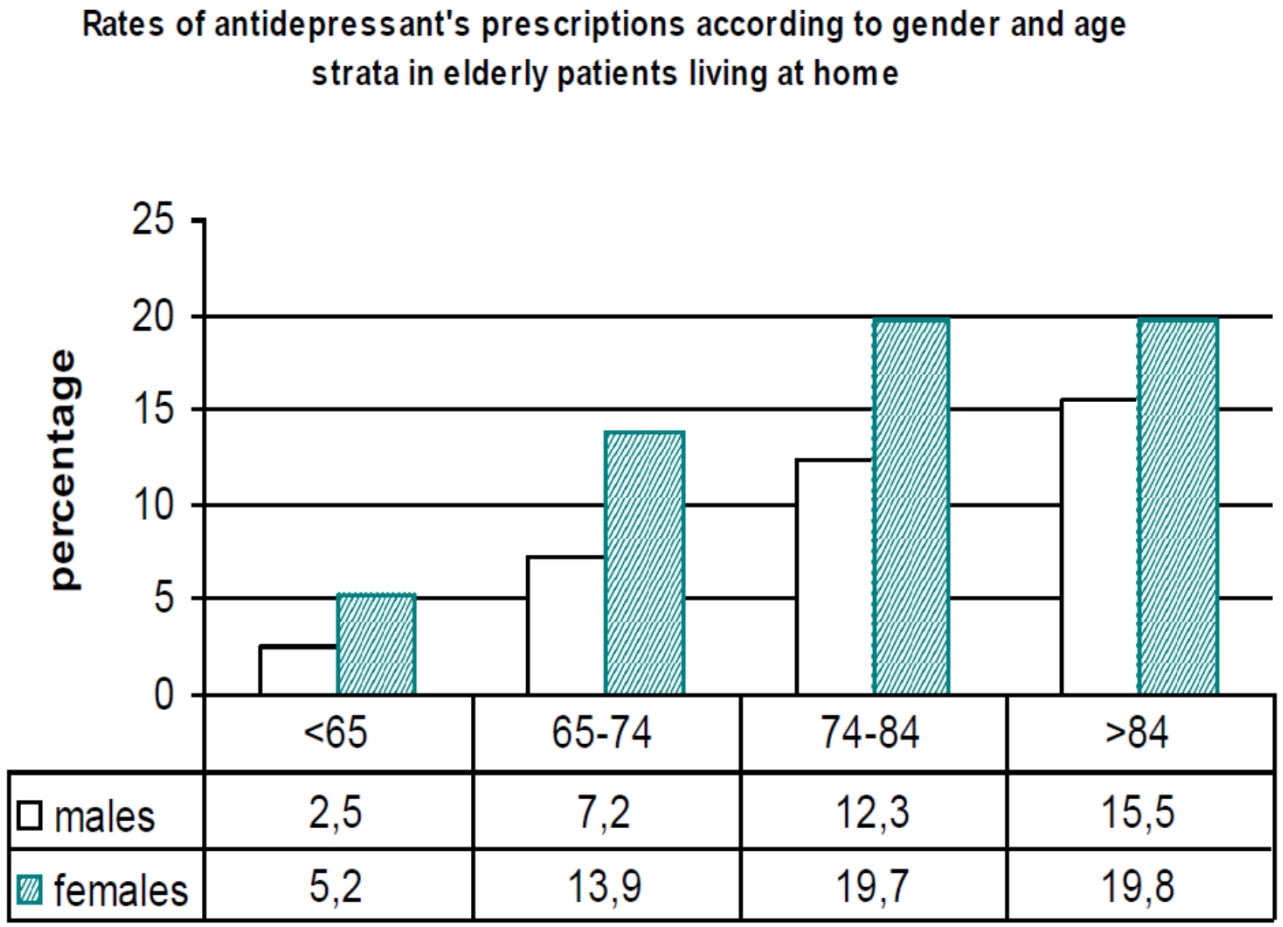
Men with hip fracture were significantly more likely to suffer from most comorbidities included in the Charlson index .This was especially pronounced for malignancy, cardiac heart failure, chronic obstructive pulmonary disease (COPD) and all forms of arterial disease. Women outnumbered men in collagen disorders.

Age and Ageing 2010; **39:** 203–209

In conclusion, using national health register data, this study confirms that mortality post-hip fracture is substantially higher in men than in women, despite men being on average 4 years younger at the time of fracture. This excess mortality is not explained by the slightly higher prevalence of chronic comorbidities in male fracture patients, nor by differences in comedications. The greatest difference between mortality in the two genders was observed in the first weeks following fracture. This study further emphasises the need for particular rigorous acute diagnostic evaluation of the male hip fracture patient more prone to acute postoperative complications and risk of mortality.

Age and Ageing 2010; **39:** 203–209

Rates of antidepressant prescriptions according to gender and age in elderly patients living at home *(Rozzini et al. Int J Geriatr Psychiatry, 2008)*



International Journal of Geriatric Psychiatry

GDS items and mortality in Italian elderly persons living at home

More interestingly, when measuring the relationship with mortality in males and females, we found that in elderly men only the GDS item "Are you basically satisfied with your life?" (n=21 answered no) is independently associated with an increased 5 year mortality risk (13 subjects died)(RR: 1.9 95% CI 1.0-3.6), while in the female group two GDS items were independently associated with mortality, i.e. "Have you dropped many of your activities and interests?" (n=152 answered yes, 52 subjects died during the 5 year follow-up period) (RR: 2.8 95% CI 1.6-4.6) and "Do you feel that your life is empty?" (n=111 answered yes and 35 died) (RR: 1.6 95% CI 1.1-2.7).

Rozzini & Trabucchi JAGS, 2012

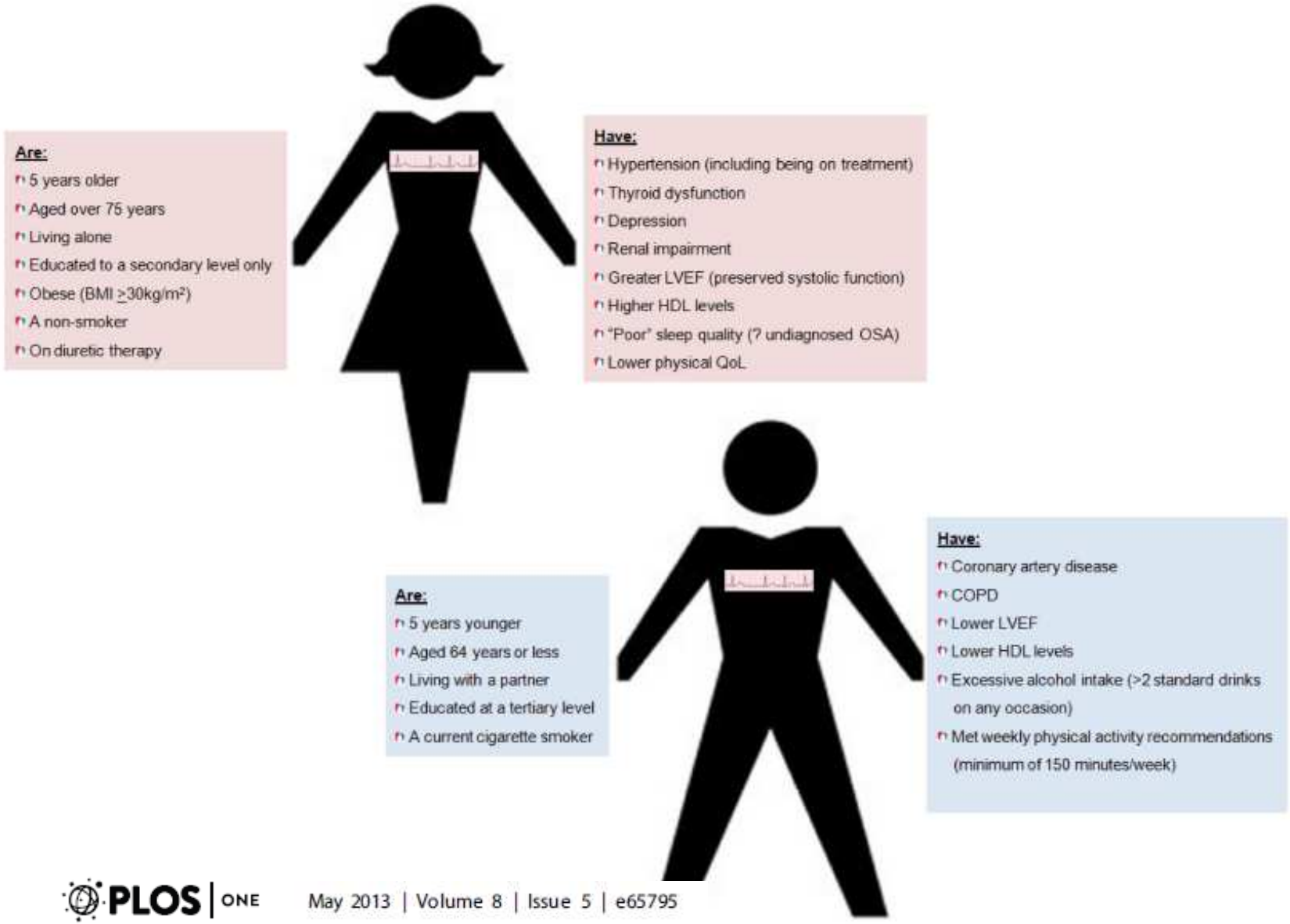
GDS items and mortality in Italian elderly persons living at home

These differences suggest that for males a life long pervasive condition characterized by unsatisfaction, exerts its negative consequence on survival. On the contrary, in females the association with survival is related to the negative interpretation of life in old age (loss of interest and activities and a feeling of emptiness) indicating that, in women, life's conditions "hic et nunc" exert deeper effects.

These gender differences should be taken into consideration when examining an elderly person with a mood problem. Indeed a different therapeutic approach may be necessary in old age when discomfort refers to a previous condition or to more recent events. This topic is also important from a pathogenic point of view. Depressive conditions in males and females may be of different origin and thus have specific biological mechanisms and a gender-related effect on survival.

Rozzini & Trabucchi JAGS, 2012

Women Versus Men with Chronic Atrial Fibrillation: Insights from the Standard Versus Atrial Fibrillation spEcific managemenT studY (SAFETY)



Lo scompenso cardiaco nell'anziano e nell'adulto

	ADULTO	ANZIANO
Prevalenza	< 1%	Circa 10 %
Sesso	M > F	**F > M**
Eziologia	Ischemica	Ipertensiva
Caratteristiche cliniche	Tipiche	Atipiche
LVEF	Ridotta	Normale
Comorbilità	Poche	Multiple
Trials clinici randomizzati	Numerosi	Pochi
Terapia	Evidence-based	Clinico-ragionata
Medico	Cardiologo	Medico di famiglia, Geriatra

Rich MW, American Journal of Medicine, 118:342, 2005

Gender differences and health status in old and very old patients.

Rozzini R, Sleiman I, Maggi S, Noale M, Trabucchi M

OBJECTIVES: To examine gender differences according to health status, social support, and DRG reimbursement in a population of elderly patients admitted to a hospital geriatric ward in Italy and also to examine the patterns of these differences across old age strata. **DESIGN:** Observational study. **PARTICIPANTS:** A total of 2171 patients, 70 years and older (females = 1088), consecutively admitted for acute care to a geriatric ward in a general hospital during a 30-month period were included. Patients were stratified into 3 age groups: 70 to 79 (n = 1038, females = 521), 80 to 89 (n = 948, females = 476), and 90+ (n = 185, females = 91). **MEASUREMENTS:** Demographics, main reason for hospitalization, Charlson Index, APACHE II score, APACHE II-APS subscore, serum albumin, number of currently administered drugs, cognitive status, depression, functional status, length of stay, Diagnoses Related Group (DRG) weight, in-hospital, and 3-month mortality were recorded. Differences were evaluated according to gender across old age strata. **RESULTS:** In the group of 70- to 79-year-old patients, significant differences were found regarding number of comorbidities, biological and clinical markers of clinical severity (ie, serum albumin, APS, delirium), and functional status on admission (ie, the greater impairment was found in male patients, with a higher in-hospital and 3-month mortality). Moreover, females had less social support and more often live alone. DRG weight parallels clinical complexity, whereas length of stay is comparable. Gender differences were less evident in the 80-89 year-old patients and almost absent in those 90+. **CONCLUSIONS:** Data indicate that on hospital admission gender differences are significant in young old patients, but not in old and very old, suggesting a poor survivorship of males with increasing age.

Perché le donne vivono di più?

Le donne conservano il loro potere legato ai rapporti familiari più che a quelli sociali. Inoltre, sono più abituate ai cambiamenti, sanno stare sole, sono più abituate alla solitudine e allo stesso tempo (forse proprio per questo) sanno tessere ragnatele di rapporti.

Le doti "naturali" femminili non vanno difatti intese come un fatto biologico, ma come frutto dell'esperienza di migliaia di anni di lavoro riproduttivo, intendendo per "lavoro riproduttivo" non solo il fare figli, ma l'accudire sotto molteplici aspetti (tanto materiali che psicologici) tutti i membri della famiglia ed in particolare i più deboli e bisognosi d'aiuto, come i bambini e gli anziani.

Le donne vivono più a lungo, Cristina Gamba

Perché le donne vivono di più?

Curare la propria casa, i corpi dei bambini, i corpi dei vecchi, insegna molte cose: in questo senso la vita stessa delle donne, nella spicciola quotidianità, è un immenso pozzo di saperi, conoscenza, saggezza, spiritualità. La relazione è centrale nella vita delle donne, e costituisce spesso l'unico mezzo per conoscere se stesse. Le donne sono legate più visceralmente alla vita, prima come madri e poi come nonne, in un continuo gioco di insegnamenti, trasmettendo i loro valori culturali a figli e nipoti e ricevendo in cambio stimoli che le aiutano a sentirsi vive.

Le donne vivono più a lungo, Cristina Gamba

Perché le donne vivono di più?

Il ciclo esistenziale di una donna può essere una serie continua di carriere che giungono a termine, seguite da nuove carriere; le gravidanze e la cura dei figli costringono le donne a considerare e riconsiderare nuovi inizi, ed il costante coinvolgimento con una famiglia che continuamente muta è un continuo stimolo ad ampliare gli orizzonti.

La cultura femminile è fatta principalmente di attenzione alle piccole cose, alla quotidianità, che porta come conseguenza anche una maggiore sensibilità a cogliere i segnali di malessere che possono provenire da se stesse e dagli altri. Ed è proprio l'elemento del quotidiano a fare la differenza, la conoscenza che nasce dalle piccole cose di ogni giorno.

Le donne vivono più a lungo, Cristina Gamba

Sommario

Gender medicine and specific-gender medicine

Gender gap: Longevity and Disability

Causes of gap

Diseases of women more than men

Specific attention for women

Future for women

Open Conclusions

Le donne :

- Sono più longeve
- Sono più disabili
- Sono più sole
- Sono più povere e meno istruite
- Utilizzano maggiormente i servizi di assistenza sanitaria
- Assumono più farmaci
- Hanno più ADR (politerapia, sovradosaggio, carenza di studi clinici)

Sommario

Gender medicine and specific-gender medicine

Gender gap: Longevity and Disability

Causes of gap

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Specific attention for women

Future for women

Open Conclusions

Test della troponina cardiaca ad alta sensibilità: potrebbe migliorare la diagnosi di infarto del miocardio nelle donne

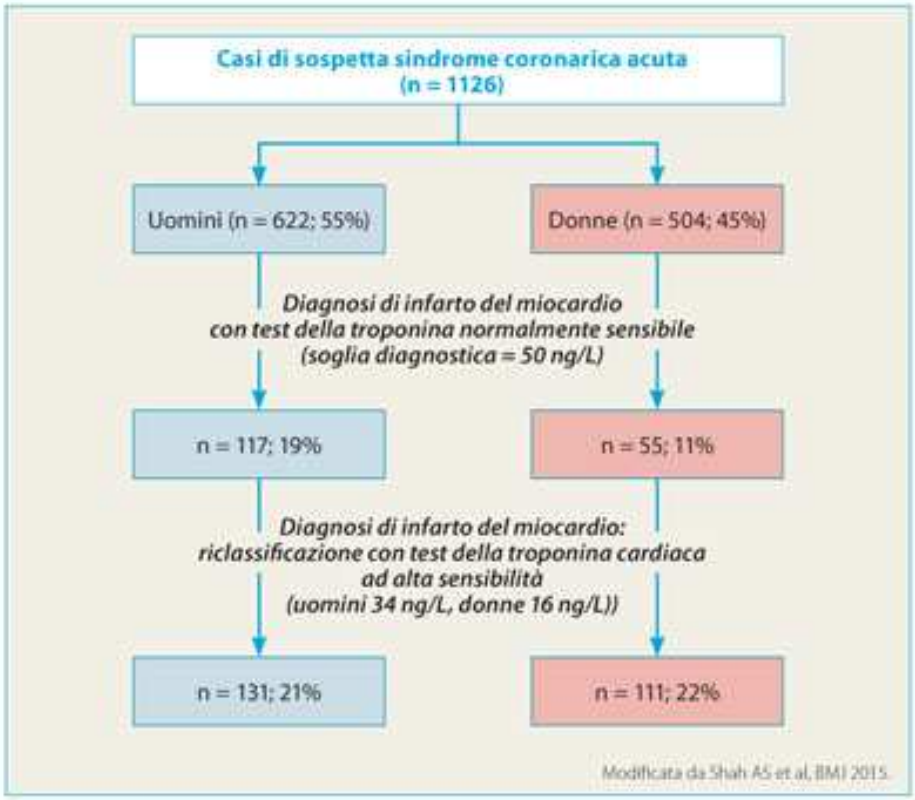

Figura 1. Diagnosi di infarto del miocardio in uomini e donne con il test della troponina cardiaca.

• Shah AS, Griffiths M, Lee KK et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. BMJ 2015;350:g7873.
• Ryan Radecki. Should men and women use different troponin cut-offs? Emergency Medicine Literature of Note, January 26, 2015.

Il NIH per una ricerca preclinica genere-specifica

Circa la metà di soggetti inclusi nelle ricerche cliniche sostenute dai National Institutes of Health (NIH) statunitensi è ormai composta da persone di sesso femminile. Tuttavia "nella ricerca su cellule e animali non c'è stata una analoga rivoluzione" scrivono su Nature (maggio 2014) Janine A Clayton (Office of Research on Women's Health, NIH) e Francis S Collins (NIH). "Fare troppo riferimento a cellule e animali di sesso maschile nella ricerca preclinica oscura differenze sessuali chiave che potrebbero guidare gli studi clinici. E questo potrebbe essere pericoloso" avvertono Clayton e Collins, "nelle donne infatti si registrano percentuali superiori di reazioni avverse ai farmaci rispetto agli uomini". Tutto ciò, inoltre, contribuisce al preoccupante aumento dell'irriproducibilità della ricerca biomedica preclinica.


NIH to balance sex in cell and animal studies

Una situazione destinata a cambiare: a partire dal 25 gennaio 2016 i NIH finanzieranno solo ricerche in cui il sesso, come variante biologica, sia considerato nel disegno delle ricerche e nelle analisi dei dati in tutti gli studi su vertebrati o umani. Qualora non lo sia, sarà necessario esplicitare le motivazioni di tale scelta.

Sulla pagina "Studying Sex to Strengthen Science" (S4) (NIH Office of Research on Women's Health) sono accessibili numerose risorse per una ricerca medica che includa la dimensione del genere. Altri utili strumenti anche sul sito "Gendered Innovations" alla pagina "Methods of Sex and Gender Analysis".

- Clayton JA, Collins FS. NIH to balance sex in cell and animal studies. Nature 2014; 509: 282-3.
- Collins FS, Tabak LA. Policy: NIH plans to enhance reproducibility. Nature 2014; 505 (7485): 612-3.
- NIH: Consideration of Sex as a Biological Variable in NIH-funded Research, Notice Number: NOT-OD-15-102, June 9, 2015.

Conclusioni

Gli uomini di oggi sono più disposti che in passato a farsi carico di compiti domestici, ma non hanno assunto allo stesso modo ruoli familiari così come le donne hanno preso su di sé ruoli lavorativi. Bisognerà aspettare la vecchiaia delle attuali generazioni di ventenni e trentenni per verificare se i nuovi atteggiamenti sociali, che inducono molti uomini ora a prendersi cura dei figli e a dare maggior spazio ed importanza alle relazioni, agli affetti, alle emozioni, influiranno sulla longevità maschile.

Le donne si stanno «mascolinizzando?»

Tra 30 anni ci sarà ancora un gap?

Conclusioni

Sex/Gender, differenze biologiche o sociali.

Cosa incide di più sulla salute?

Necessità di ulteriori approfondimenti.

Importanza di un approccio «multidimensionale», che tenga conto di tutti i fattori determinanti lo stato di salute (fattori sociali, culturali, economici, ambientali, comportamentali, biologici).

La visione di Linnea (86)

Gli uomini non parlano d'altro che dei fatti loro. Se sono soldati parlano di truppe ed armi, se poeti di prosodia, se sono medici di malattie orribili e pontificano sulle loro terapie, come se le piaghe mortali che affliggono l'umanità fossero un argomento di interesse universale…eppure ascoltando, avere imparato molte nozioni complesse…

Linnea rifletté a cosa comprare per souvenir…era veramente difficile…(il suo amico medico, 85) aveva tutto nel suo appartamento. Sembrava inoltre uno spreco comprare qualcosa di molto prezioso e duraturo a un uomo che poteva morire di vecchiaia di lì a poco.

Alla fine si decise per un fermacarte di marmo…Per sé scelse una camicia da notte di seta.

I veleni della dolce Linnea, Paasilinna A, Iperborea 2015