64° Congresso Nazionale SIGG

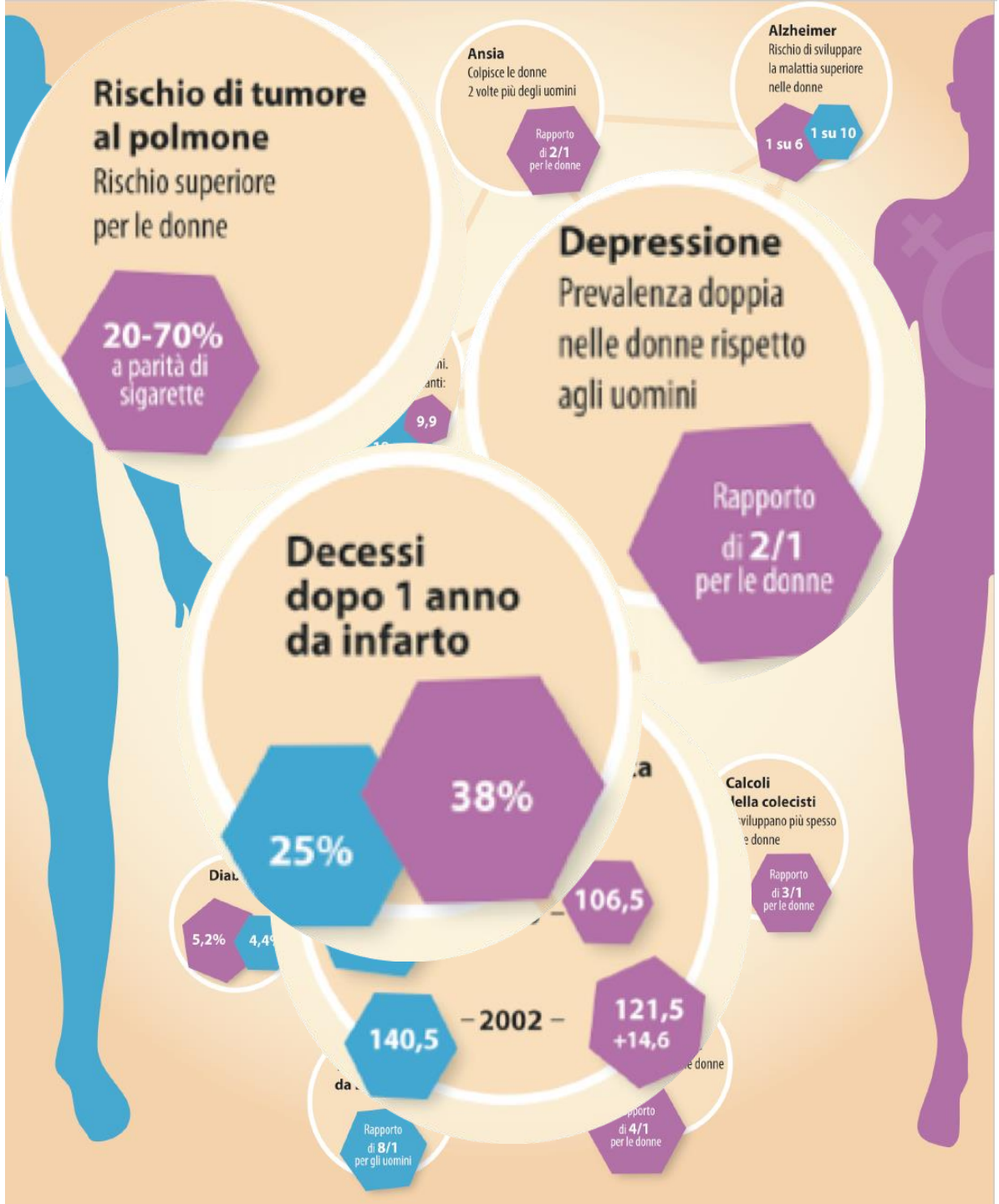
Continuità di affetti, continuità di cure

AUDITORIUM DELLA TECNICA - ROMA, 27/30 NOVEMBRE 2019

STRESS OSSIDATIVO, MALATTIE CRONICO-DEGENERATIVE E GENDER

Nicola Ferrara, MD
University of Naples "Federico II"
Department of Translational Medical Sciences, Naples, Italy
Past President of Italian Society of Gerontology and Geriatrics

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA


Rischio di tumore al polmone
Rischio superiore per le donne
20-70%
a parità di sigarette
Ansia
Colpisce le donne 2 volte più degli uomini
Rapporto di 2/1 per le donne
Alzheimer
Rischio di sviluppare la malattia superiore nelle donne
1 su 6
1 su 10
Depressione
Prevalenza doppia nelle donne rispetto agli uomini
Rapporto di 2/1 per le donne
9,9
Decessi dopo 1 anno da infarto
38%
25%
106,5
140,5
– 2002 –
121,5
+14,6
Rapporto di 8/1 per gli uomini
Rapporto di 4/1 per le donne
Calcoli
Rapporto di 3/1 per le donne
5,2%

STRESS OSSIDATIVO, MALATTIE CRONICO-DEGENERATIVE E GENDER

AGENDA

- GENDER: MEANINGS AND DEMOGRAPHIC DATA
- AGING AND OXIDATIVE STRESS
- GENDER AND OXIDATIVE STRESS
- GENDER AND DEMENTIA
- GENDER AND CARDIOVASCULAR DISEASES
- FRAILTY AND GENDER

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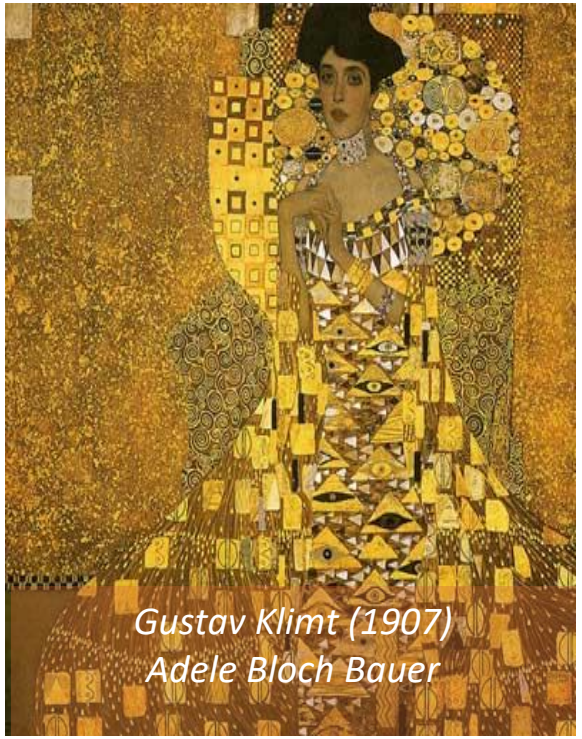
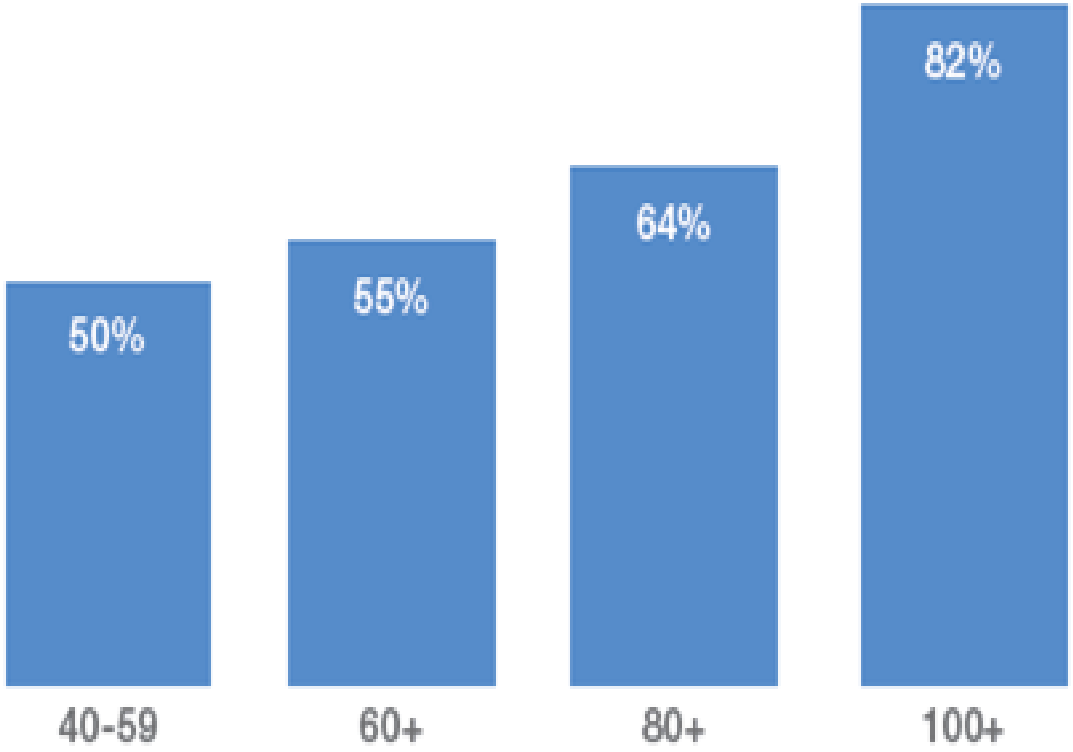
Con il termine “genere” (gender) si intende definire le categorie “uomo" e “donna”
non solo fondate su differenze biologiche, ma anche, condizionate da fattori ambientali, sociali e culturali, nonché dall’esperienza propria del singolo individuo

Ministero della Salute

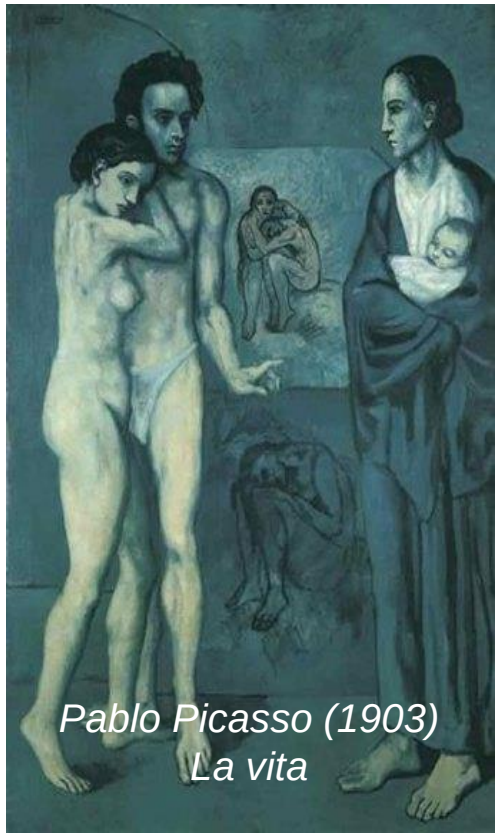


Gender is rooted in biology and
shaped by environment and experience.

Percentuale di donne per età (world 2007)



Source: United Nations Department of Economic and Social Affairs, Population Division, "World Population Ageing 2007



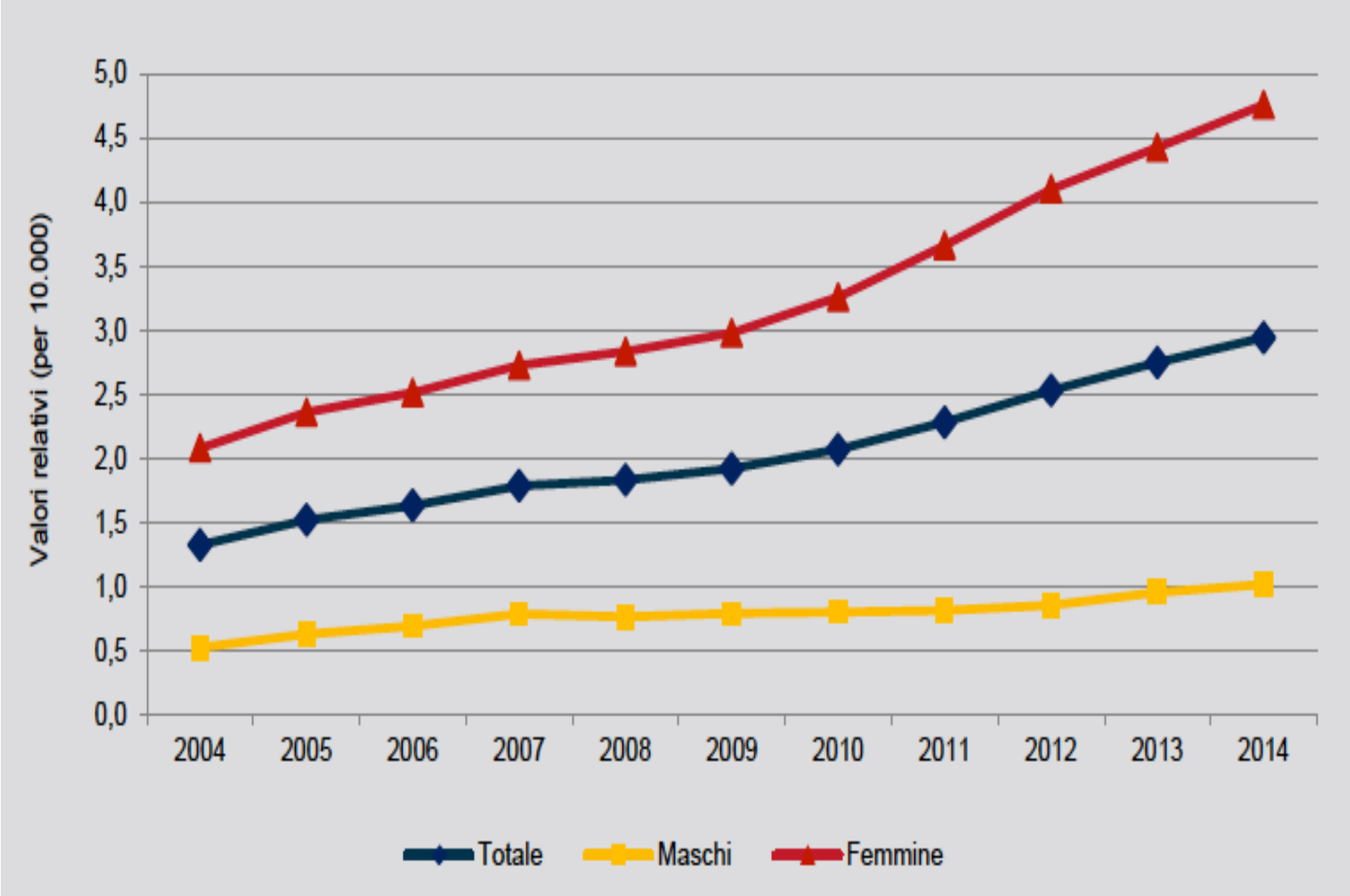
Pablo Picasso (1903)
La vita

	Men	Women
Africa	15	17
Asia	19	22
Latin America & Caribbean	17	20
North America	20	24
Europe	18	22

Source: United Nations Population Division, 2009. Population Ageing 2009.

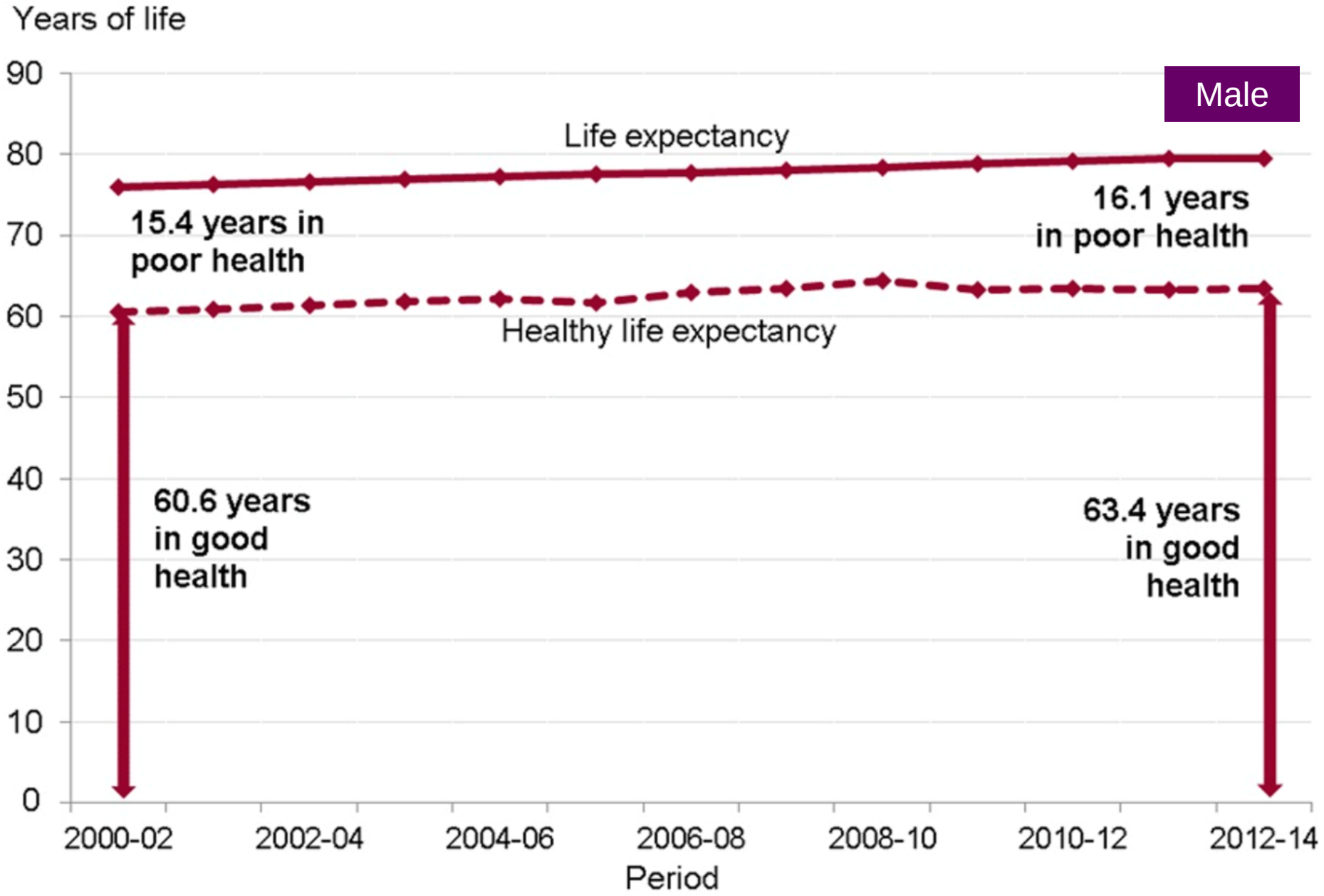
Popolazione ultracentenaria per sesso.

Anni 2004-2014 (valori relativi per 10.000 residenti)



ISTAT 2016

Life expectancy, healthy life expectancy and years spent in poor health from birth, males 2000 to 2002 up to 2012 to 2014



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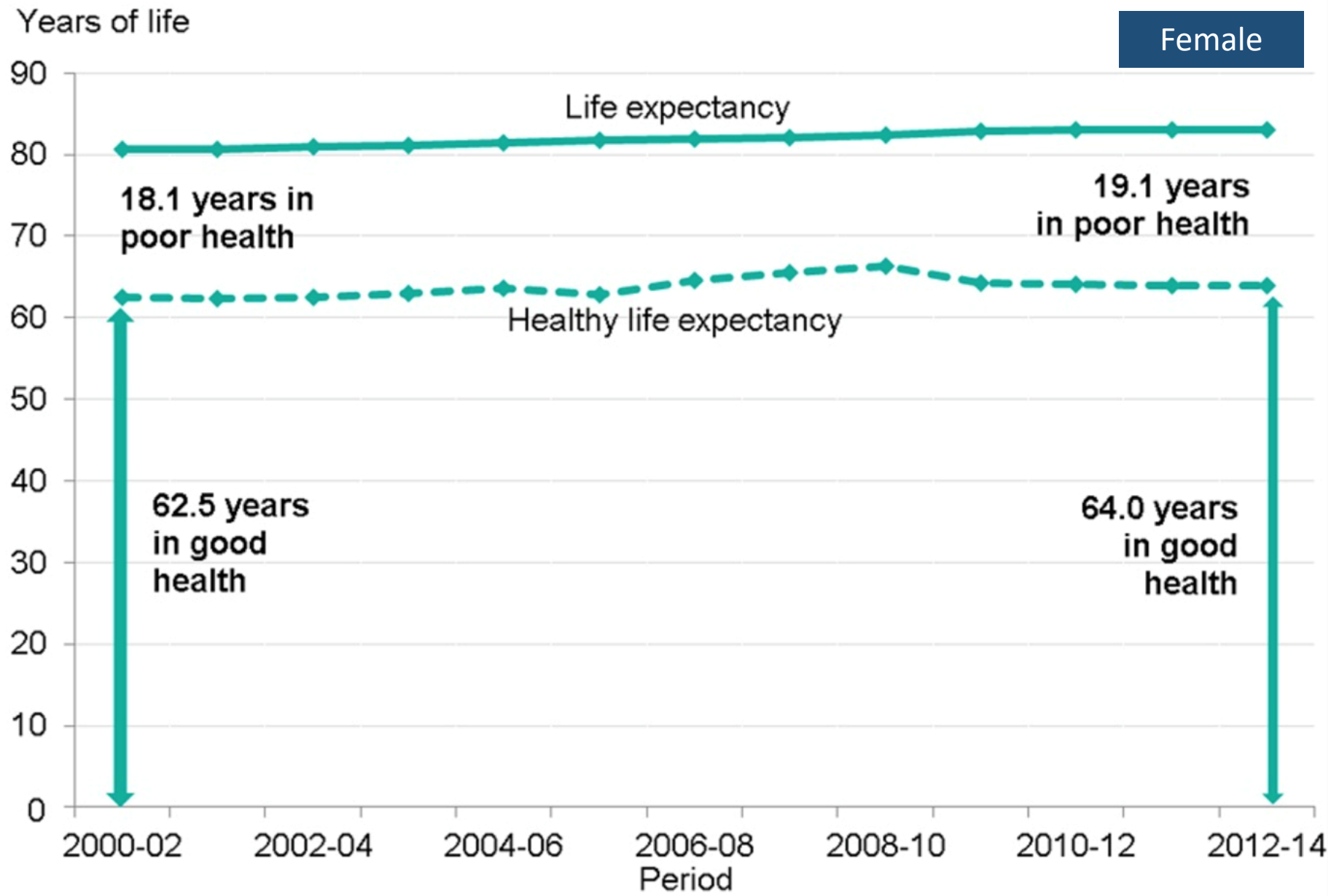
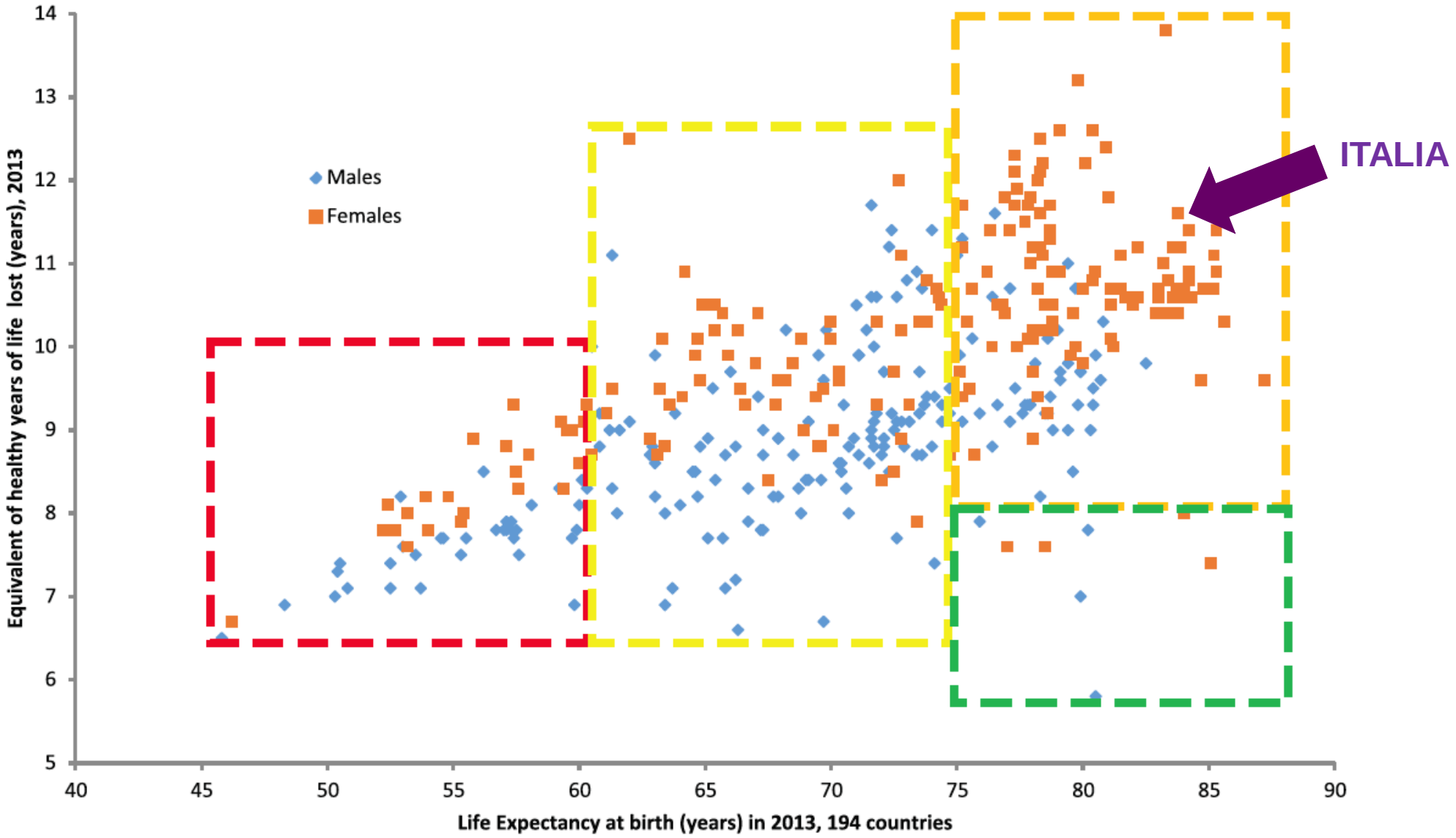


Life expectancy at birth, plotted against equivalent of healthy years of life lost since birth, males and females

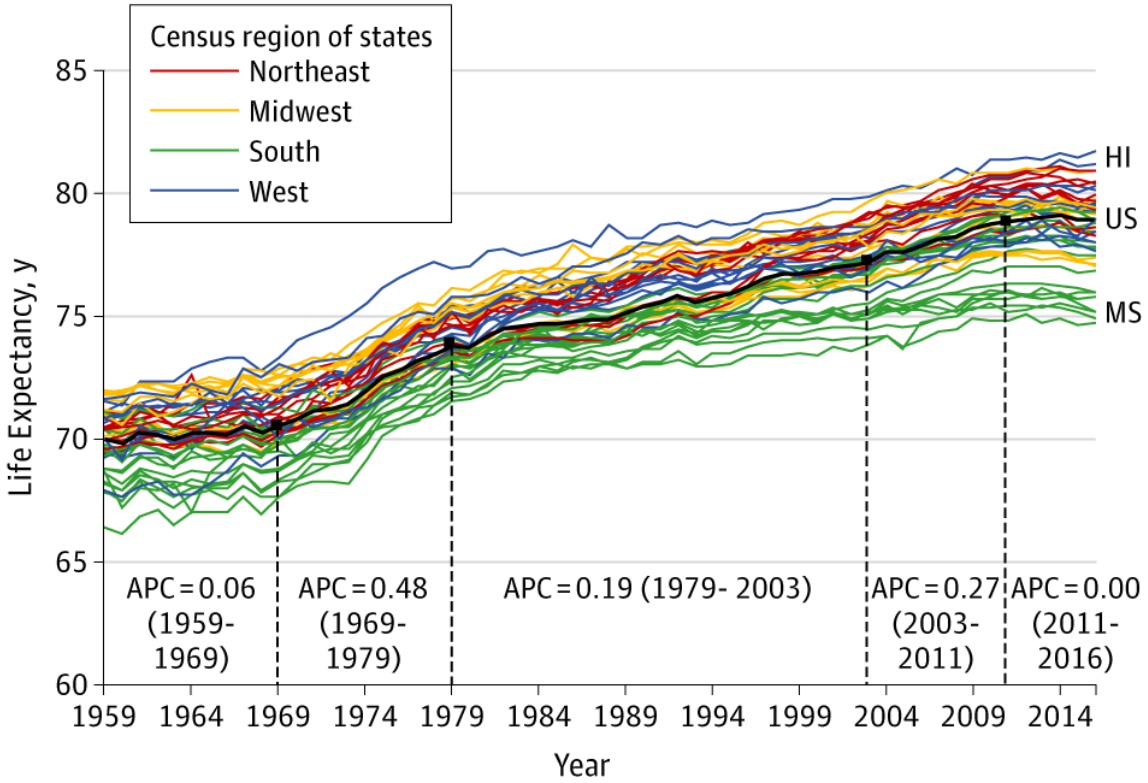


Gerontologist, 2016;56:S2, S178–S193 doi:10.1093/geront/gnw034

JAMA Network™

From: **Life Expectancy and Mortality Rates in the United States, 1959-2017**

JAMA. 2019;322(20):1996-2016. doi:10.1001/jama.2019.16932



Steven H. Woolf & Heidi Schoomaker JAMA. 2019;322(20):1996-2016.

Date of download: 11/27/2019

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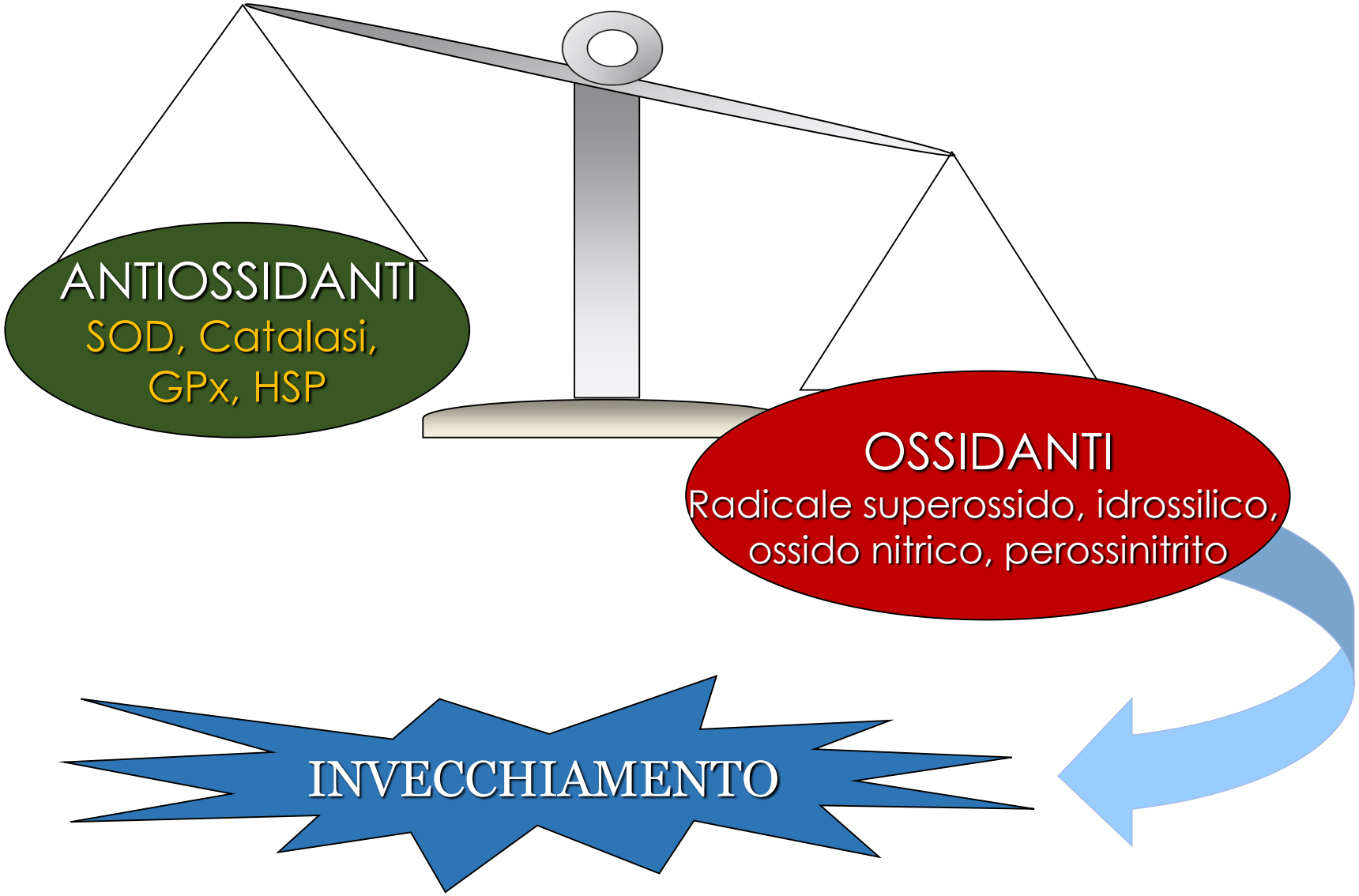
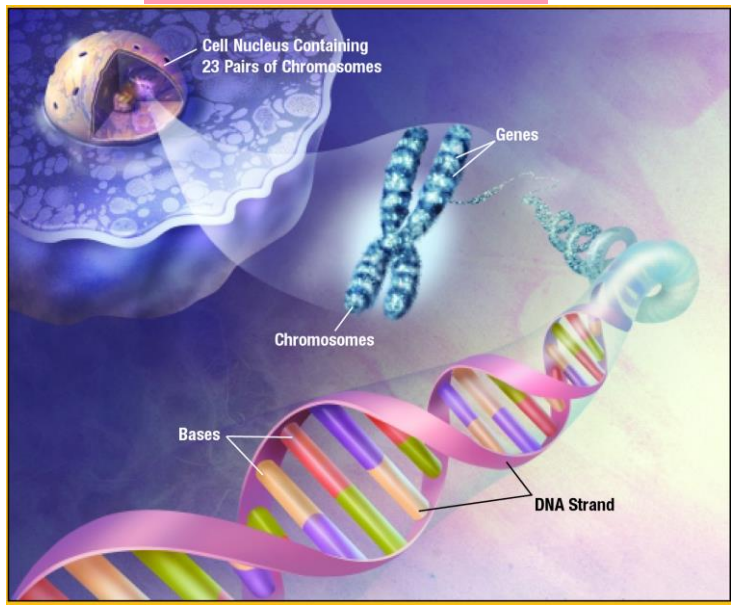
Invecchiamento e stress ossidativo

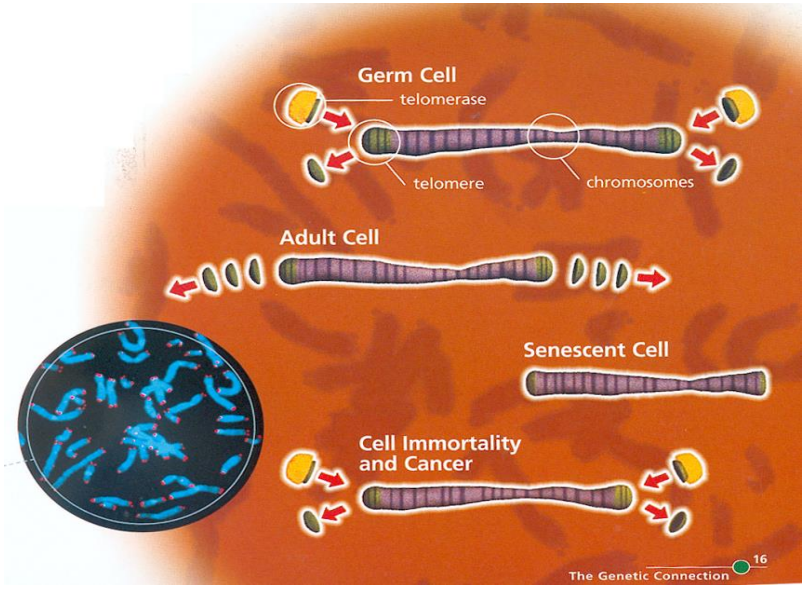


Why do we age?

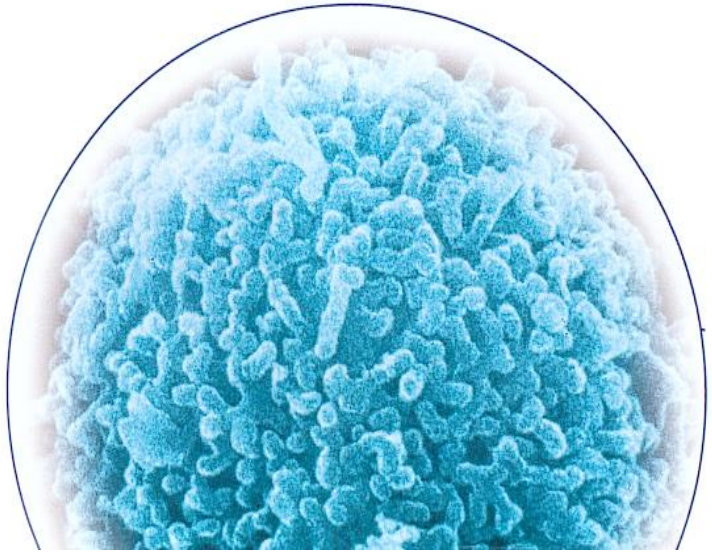
Genetic hypothesis



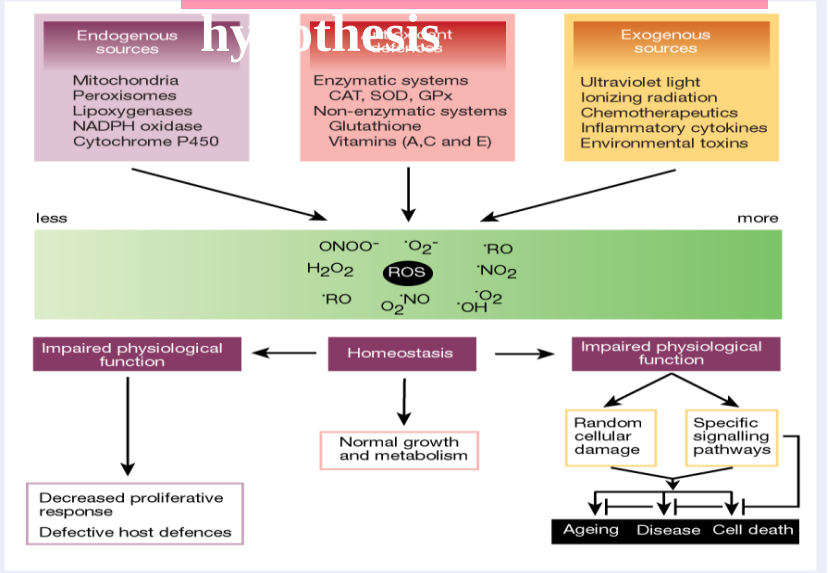
Telomeres



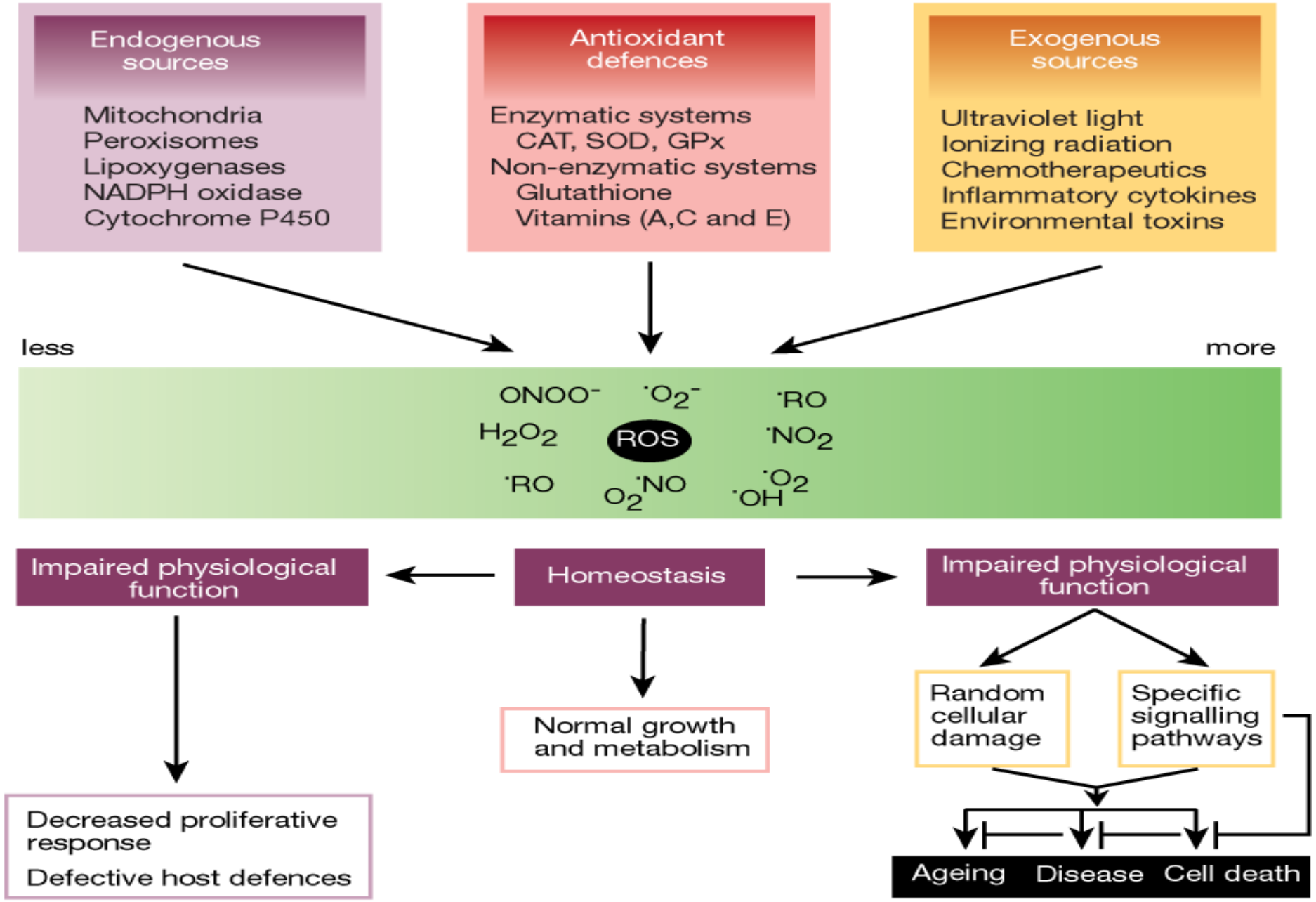
Inflammaging

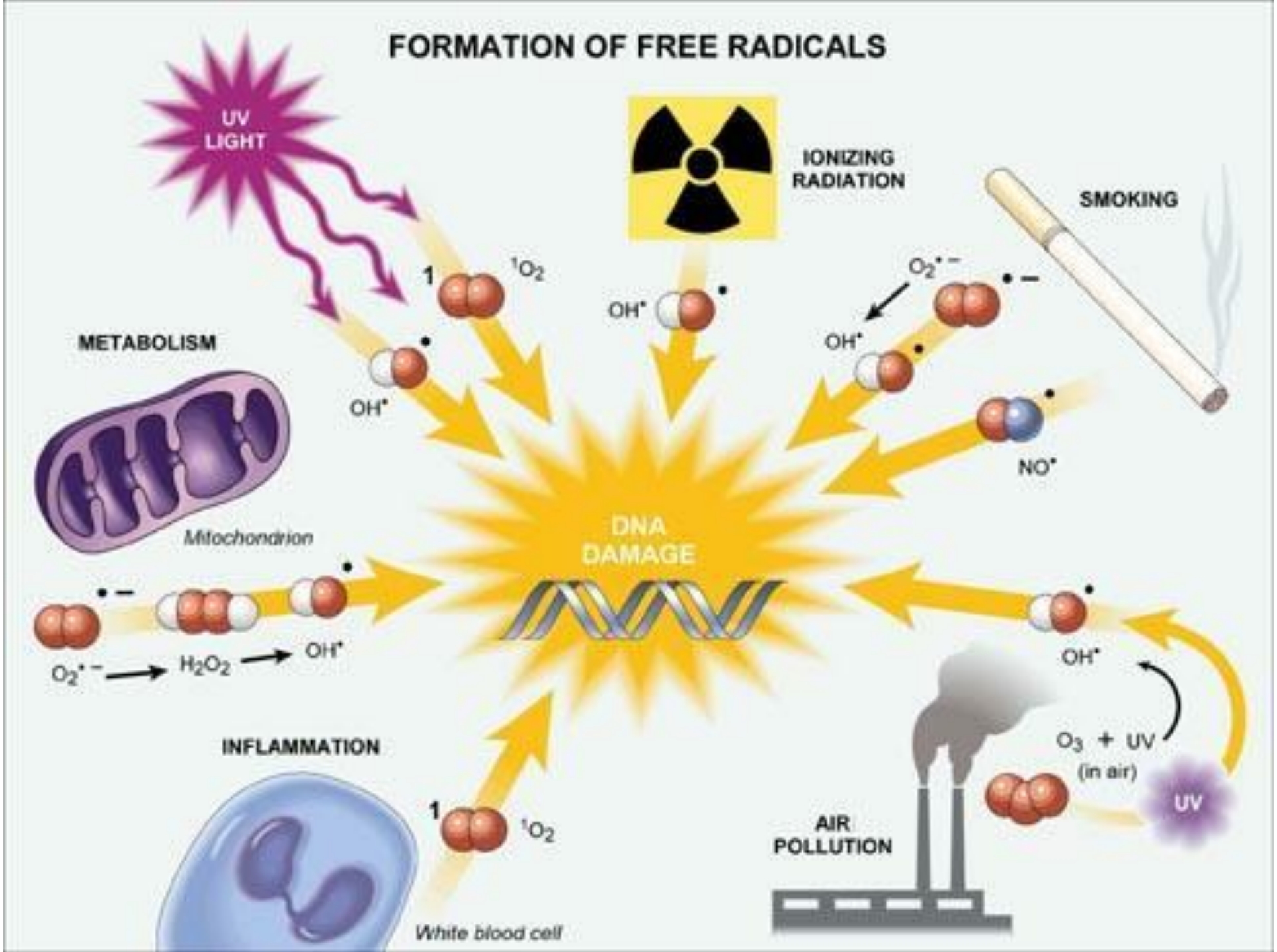


Free radicals hypothesis



Free radicals hypothesis




FORMATION OF FREE RADICALS
UV LIGHT
IONIZING RADIATION
SMOKING
METABOLISM
Mitochondrion
DNA DAMAGE
INFLAMMATION
White blood cell
AIR POLLUTION
(in air)
UV

L’invecchiamento e numerose patologie cronico-degenerative sono associate con lo stress ossidativo

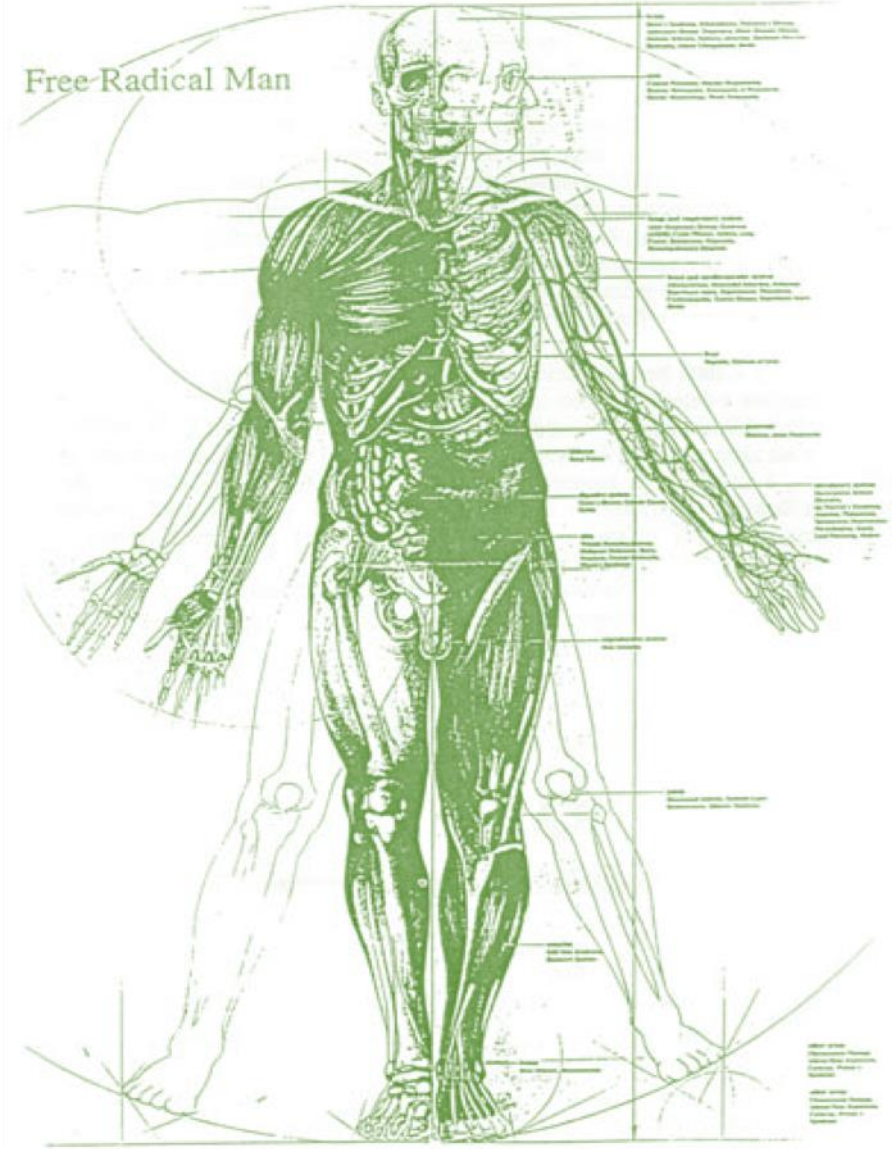
Infarto del miocardio

Pancreatite

Ipertensione

Stroke

Aterosclerosi



Parkinson

Alzheimer

Artrite reumatoide

Diabete

Cancro

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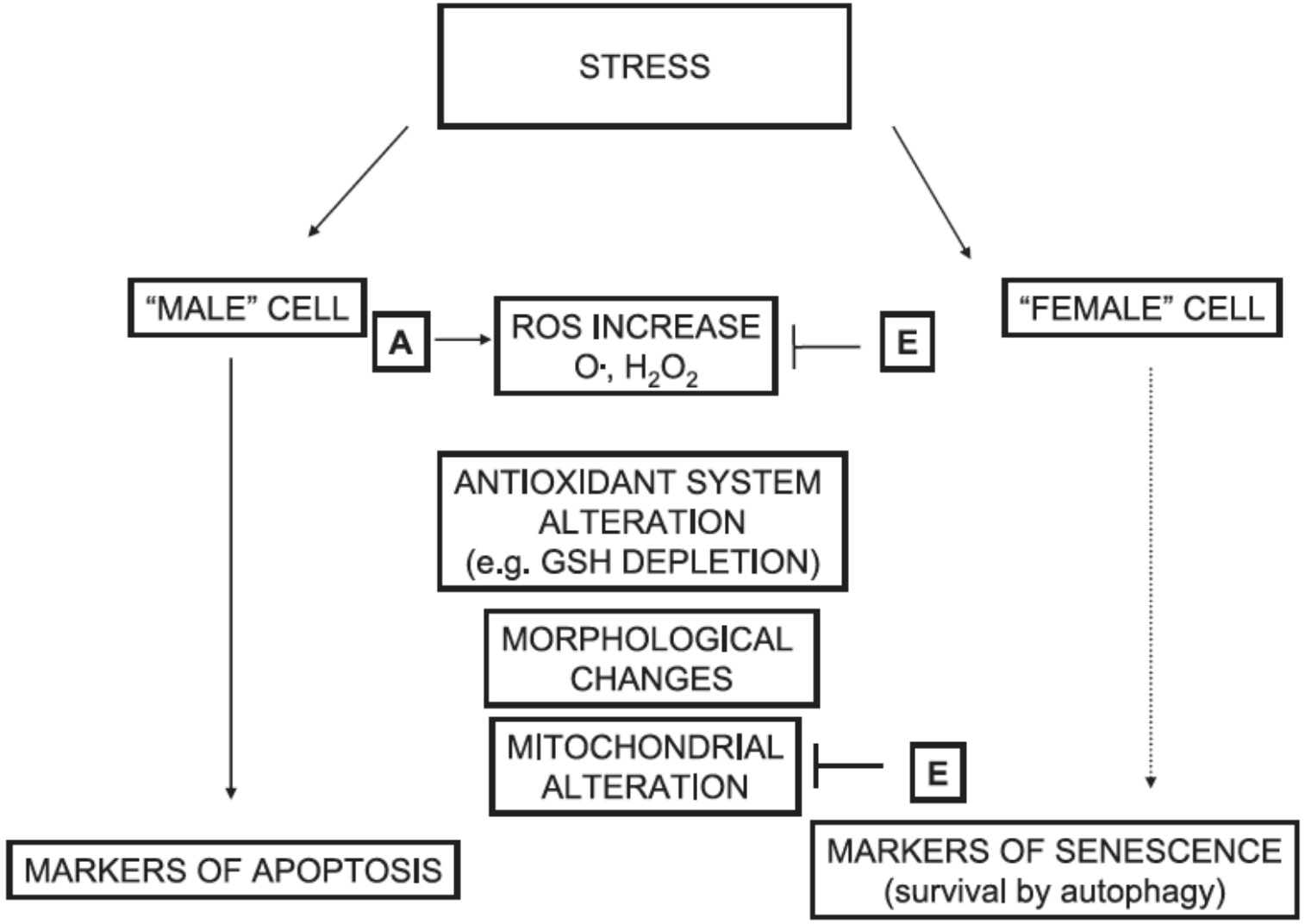
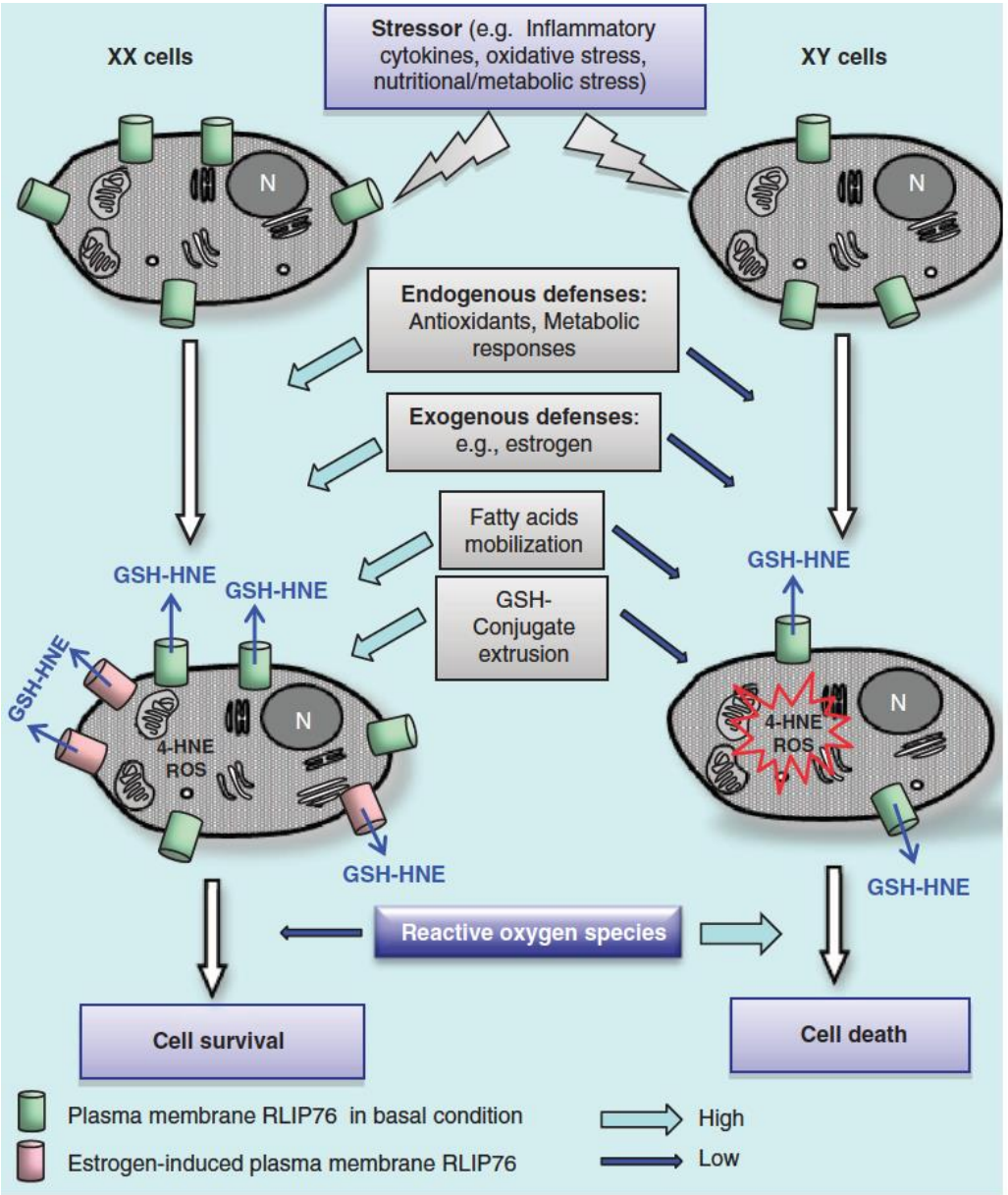
Main differences in freshly isolated cells in culture



FASEB J. 23, 978–984 (2009)

Taking into account the gender issue in cell death studies

E Ortona[1,2], P Matarrese[3,4] and W Malorni*[,2,3]



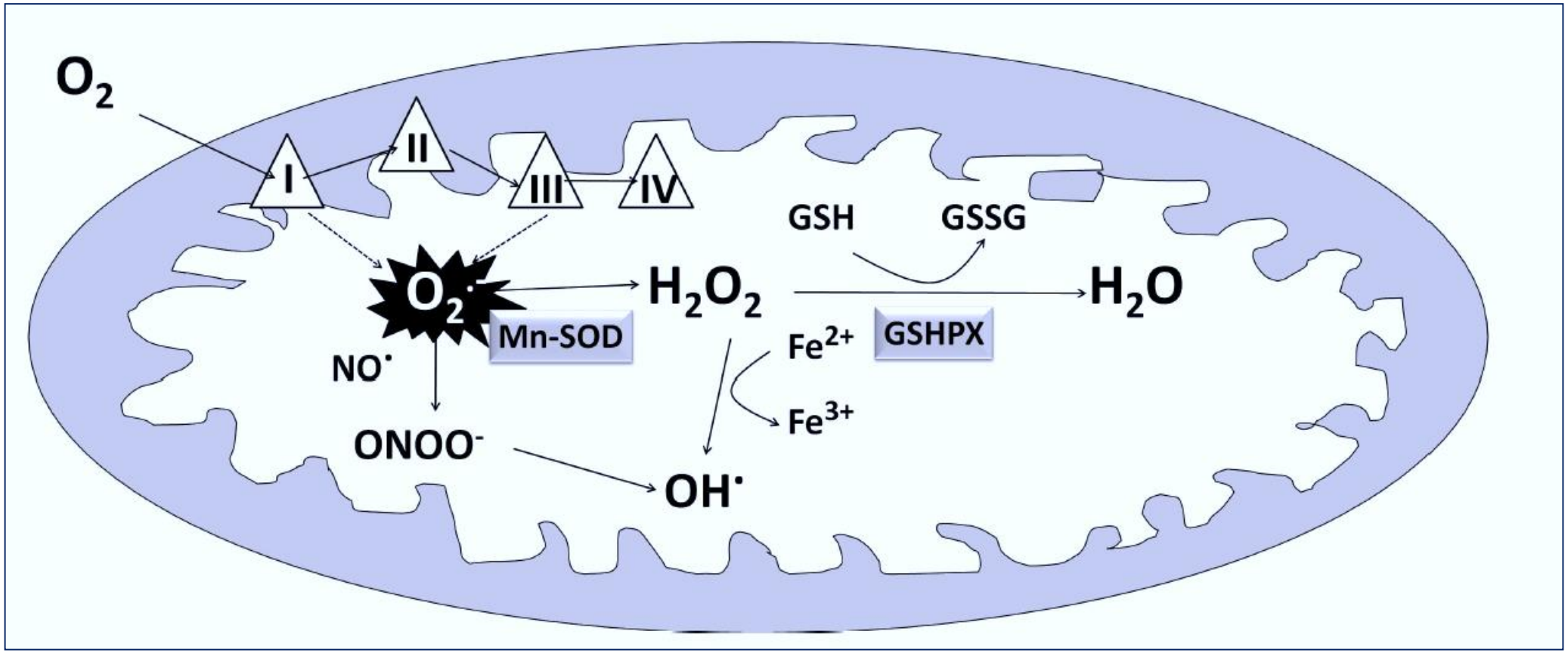
Cell Death and Disease (2014) **5**, e1121; doi:10.1038/cddis.2014.73; published online 13 March 2014

Current Pharmaceutical Design, 2011, *17*, 3959-3965

Females Live Longer than Males: Role of Oxidative Stress

Jose Viña*, Juan Gambini, Raul López-Grueso, Khira M. Abdelaziz, Mariona Jove[1] and Consuelo Borras

ROS and antioxidant system in cells.



Matarrese et al. *Cell Death and Disease* (2019)10:673
https://doi.org/10.1038/s41419-019-1888-3

Cell Death & Disease

ARTICLE Open Access

X-chromosome-linked miR548am-5p is a key regulator of sex disparity in the susceptibility to mitochondria-mediated apoptosis

Paola Matarrese[1], Paolo Tieri[2,3], Simona Anticoli[1], Barbara Ascione[1], Maria Conte[4,5], Claudio Franceschi[6,7], Walter Malorni[1,8], Stefano Salvioli[4,5] and Anna Ruggieri[1]

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Abstract

Sex dimorphism in cell response to stress has previously been investigated by different research groups. This dimorphism could be at least in part accounted for by sex-biased expression of regulatory elements such as microRNAs (miRs). In order to spot previously unknown miR expression differences we took advantage of prior knowledge on specialized databases to identify X chromosome-encoded miRs potentially escaping X chromosome inactivation (XCI). MiR-548am-5p emerged as potentially XCI escaper and was experimentally verified to be significantly up-regulated in human XX primary dermal fibroblasts (DFs) compared to XY ones. Accordingly, miR-548am-5p target mRNAs, e.g. the transcript for Bax, was differently modulated in XX and XY DFs. Functional analyses indicated that XY DFs were more prone to mitochondria-mediated apoptosis than XX ones. Experimentally induced overexpression of miR548am-5p in XY cells by lentivirus vector transduction decreased apoptosis susceptibility, whereas its down-regulation in XX cells enhanced apoptosis susceptibility. These data indicate that this approach could be used to identify previously unreported sex-biased differences in miR expression and that a miR identified with this approach, miR548am-5p, can account for sex-dependent differences observed in the susceptibility to mitochondrial apoptosis of human DFs.

Matarrese et al. *Cell Death and Disease* (2019)10:673
https://doi.org/10.1038/s41419-019-1888-3

Cell Death & Disease

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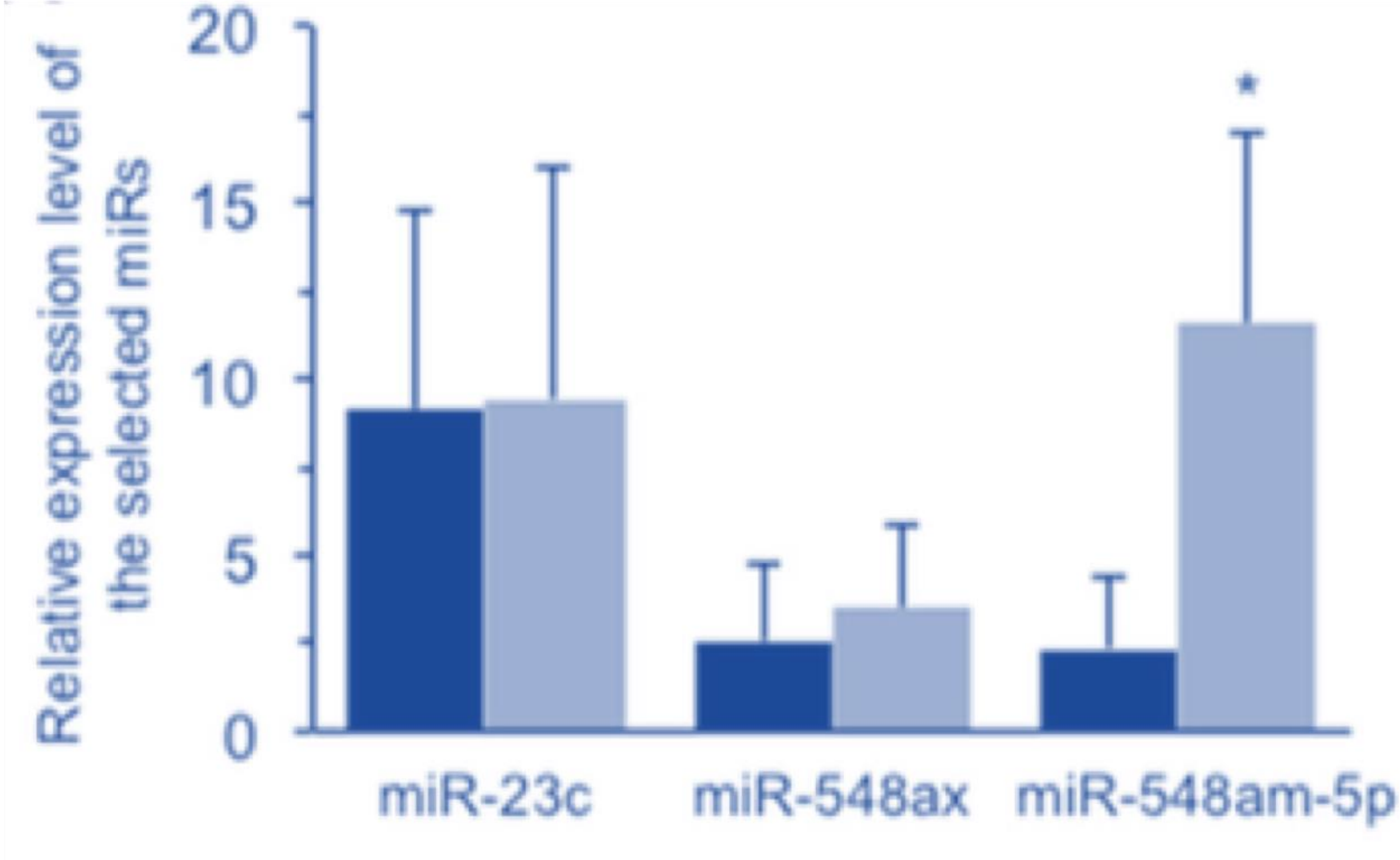

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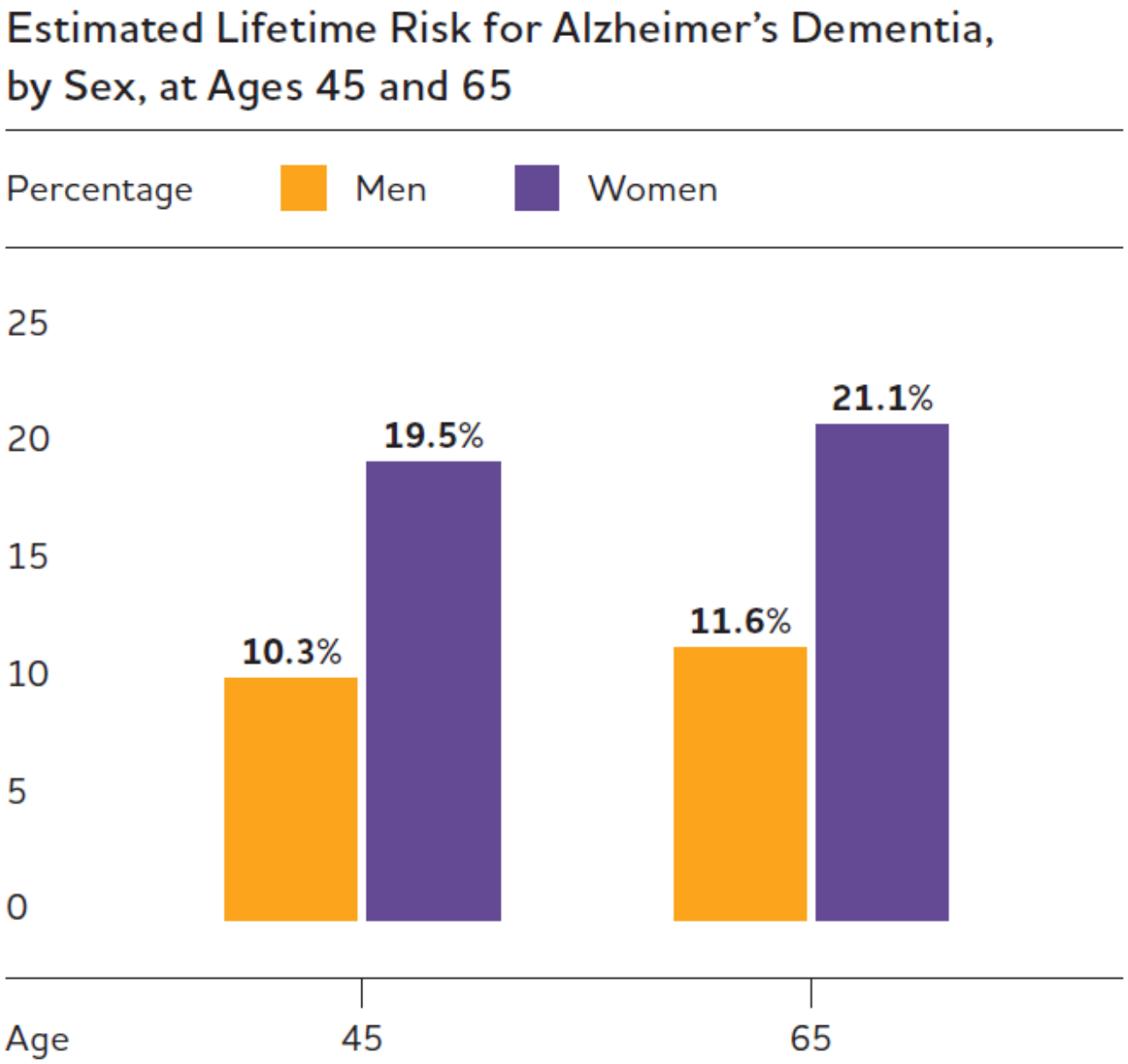
Gender-gap nelle demenze: epidemiologia

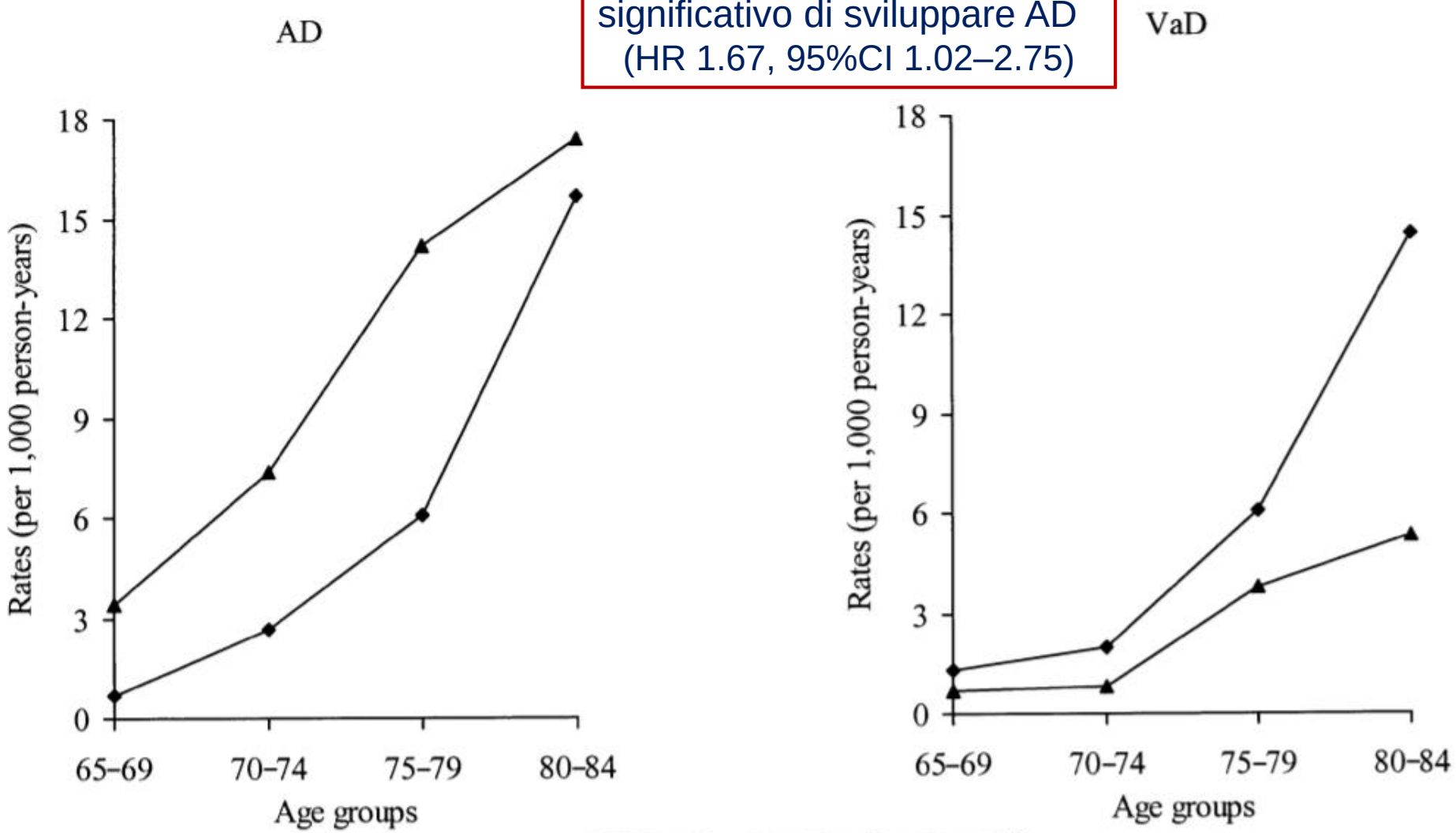


- Circa 2/3 dei pazienti con Alzheimer negli US sono donne
- Dei 5.6 milioni di ultra 65enni statunitensi con Alzheimer, 3.5 milioni sono donne e 2.1 milioni sono uomini

Alzheimer's disease facts and figures 2018

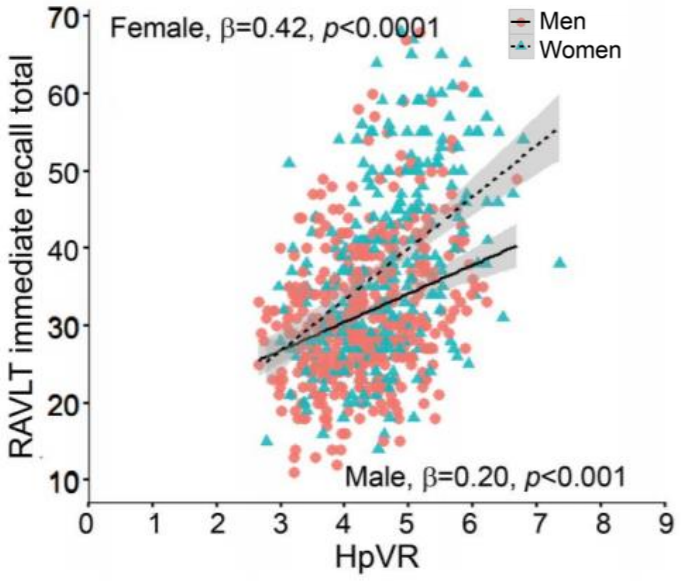
Gender-gap nelle demenze: epidemiologia

In Italia (dati ILSA)
Le donne hanno un rischio significativo di sviluppare AD
(HR 1.67, 95%CI 1.02–2.75)



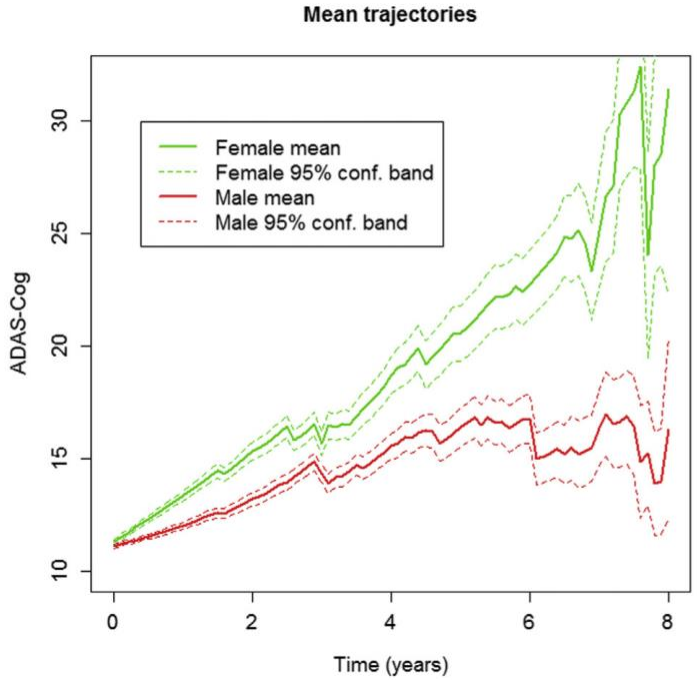
Di Carlo A et al, J Am Geriatr Soc. 2002

Differenze di performance cognitiva



La memoria verbale e' preservata nelle donne con aMCI rispetto agli uomini con la stessa diagnosi e un grado simile di atrofia dell'ippocampo

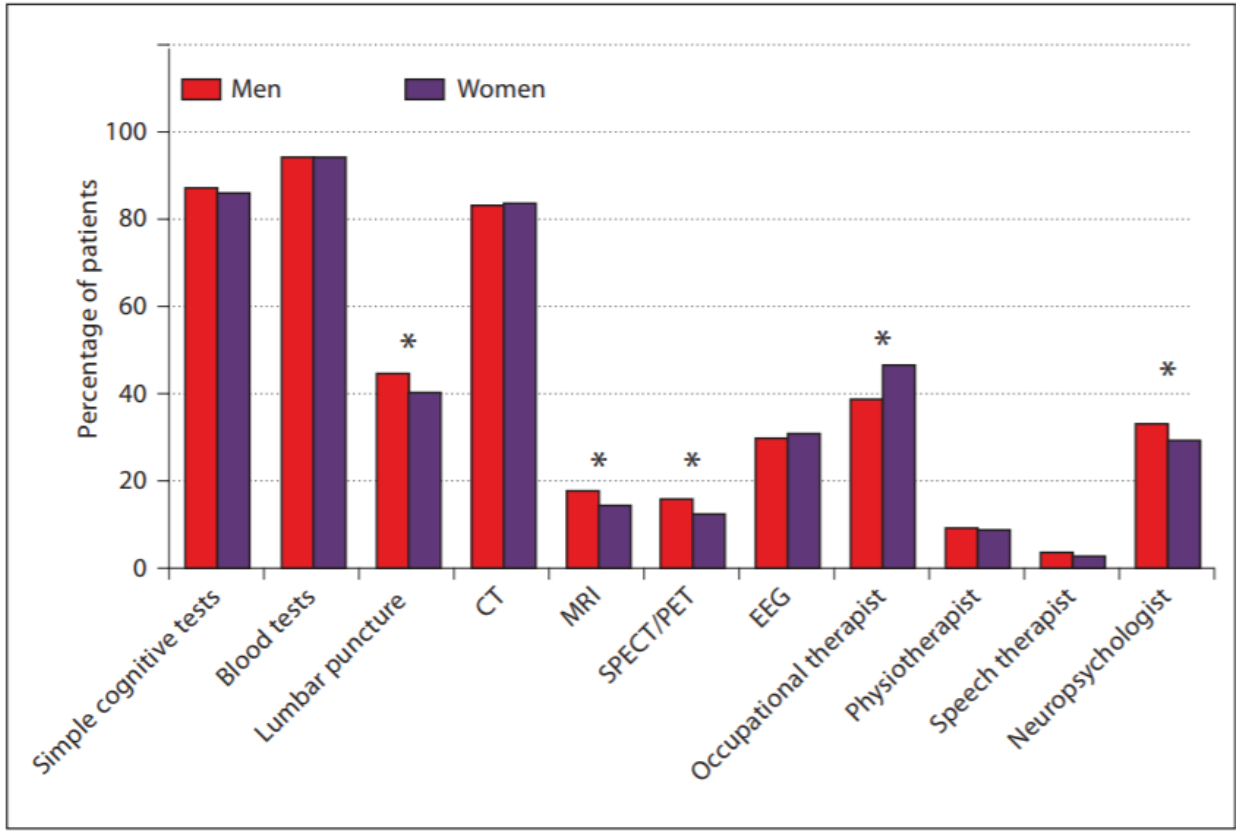
Sundermann EE et al, Neurology 2016



La progressione del deterioramento cognitive in un follow-up di 8 anni e' maggiore nelle donne con MCI che negli uomini

Lin KA et al, Alzheimers Dement (N Y) 2015

Differenze nel management



Le donne avevano una probabilita' inferiore una puntura lombare o una MRI, un effetto principalmente attribuibile alla eta' piu' avanzata delle donne in tale coorte

Religa D et al, Dement Geriatr Cogn Disord 2012

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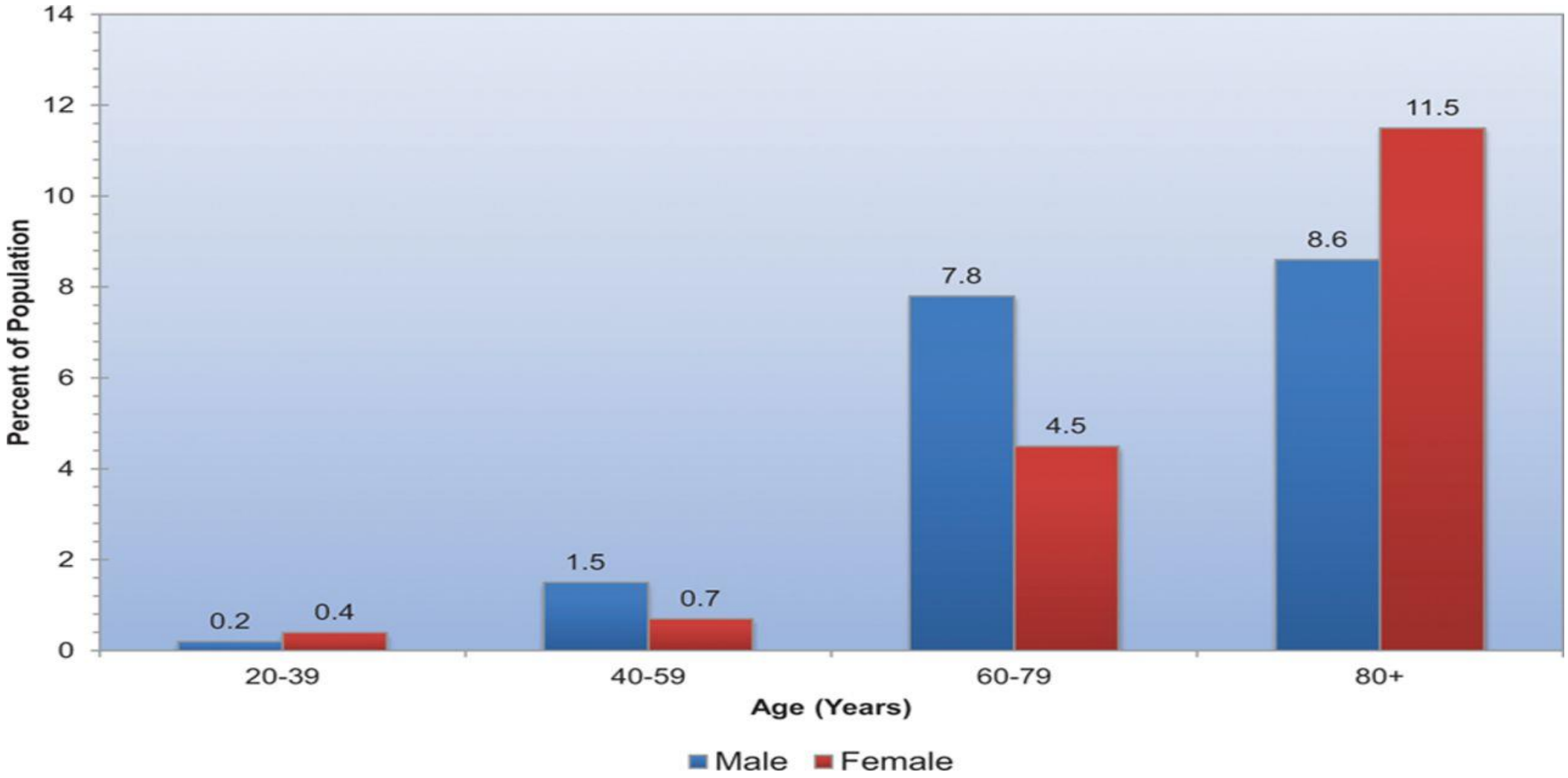
Prevalence of heart failure by sex and age

(National Health and Nutrition Examination Survey: 2007–2010).



American Heart Association

Go A S et al. Circulation. 2014;129:e28-e292

Circulation

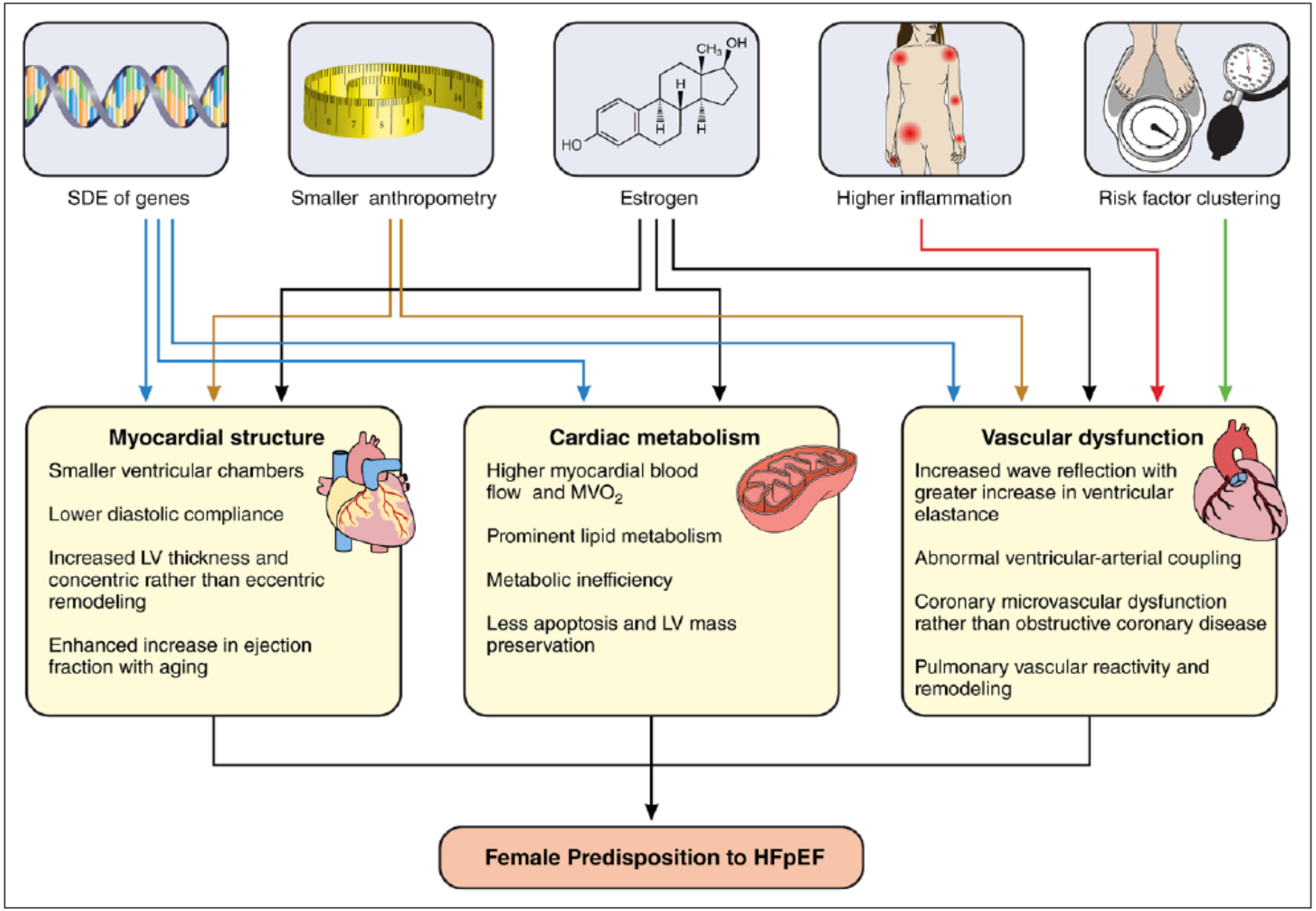
PRIMER

Sex Differences in Cardiovascular Pathophysiology

Why Women Are Overrepresented in Heart Failure With Preserved Ejection Fraction

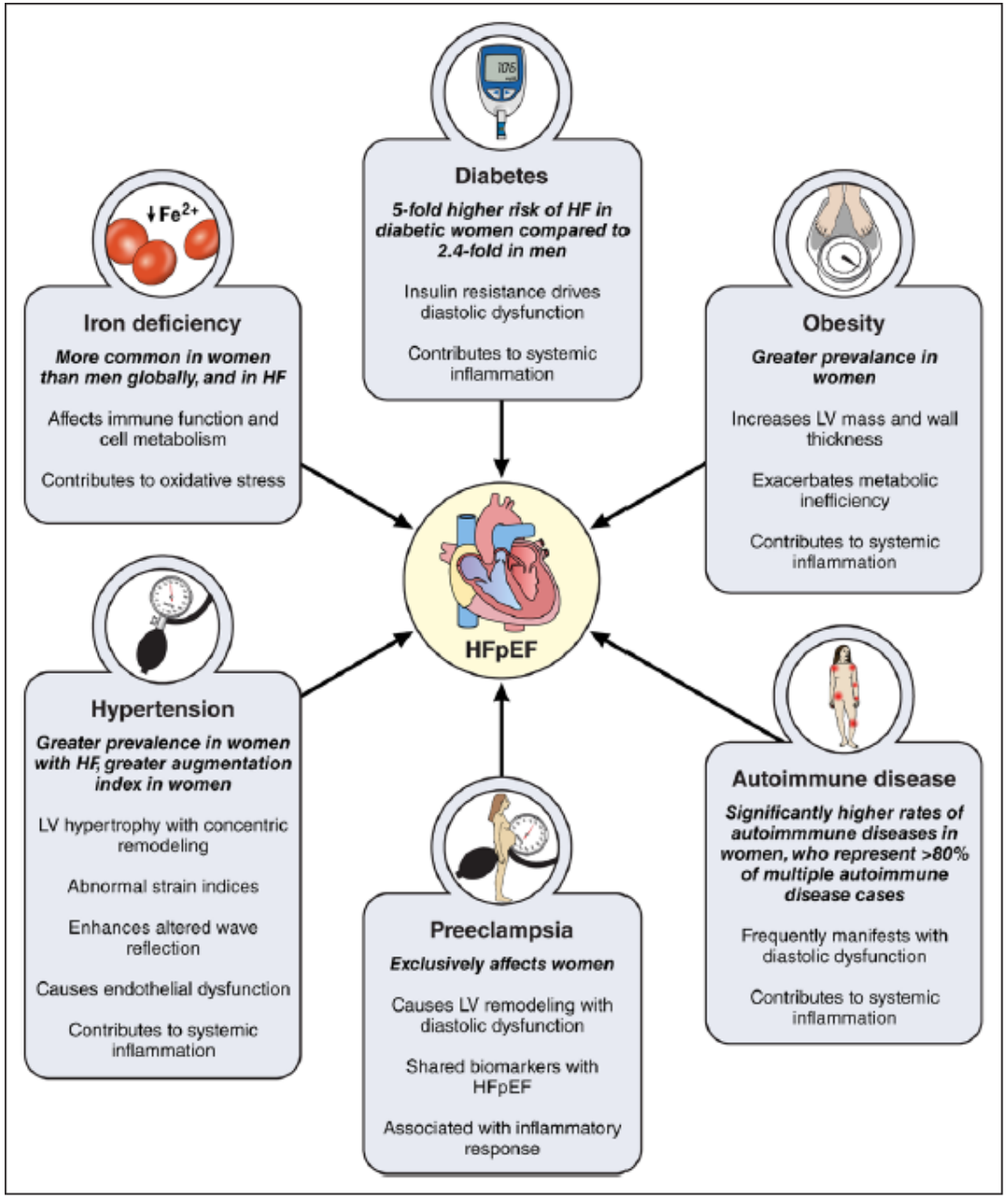
Circulation. 2018;138:198–205. DOI: 10.1161/CIRCULATIONAHA.118.034271

Fundamental sex differences that predispose women to the development of HFpEF.



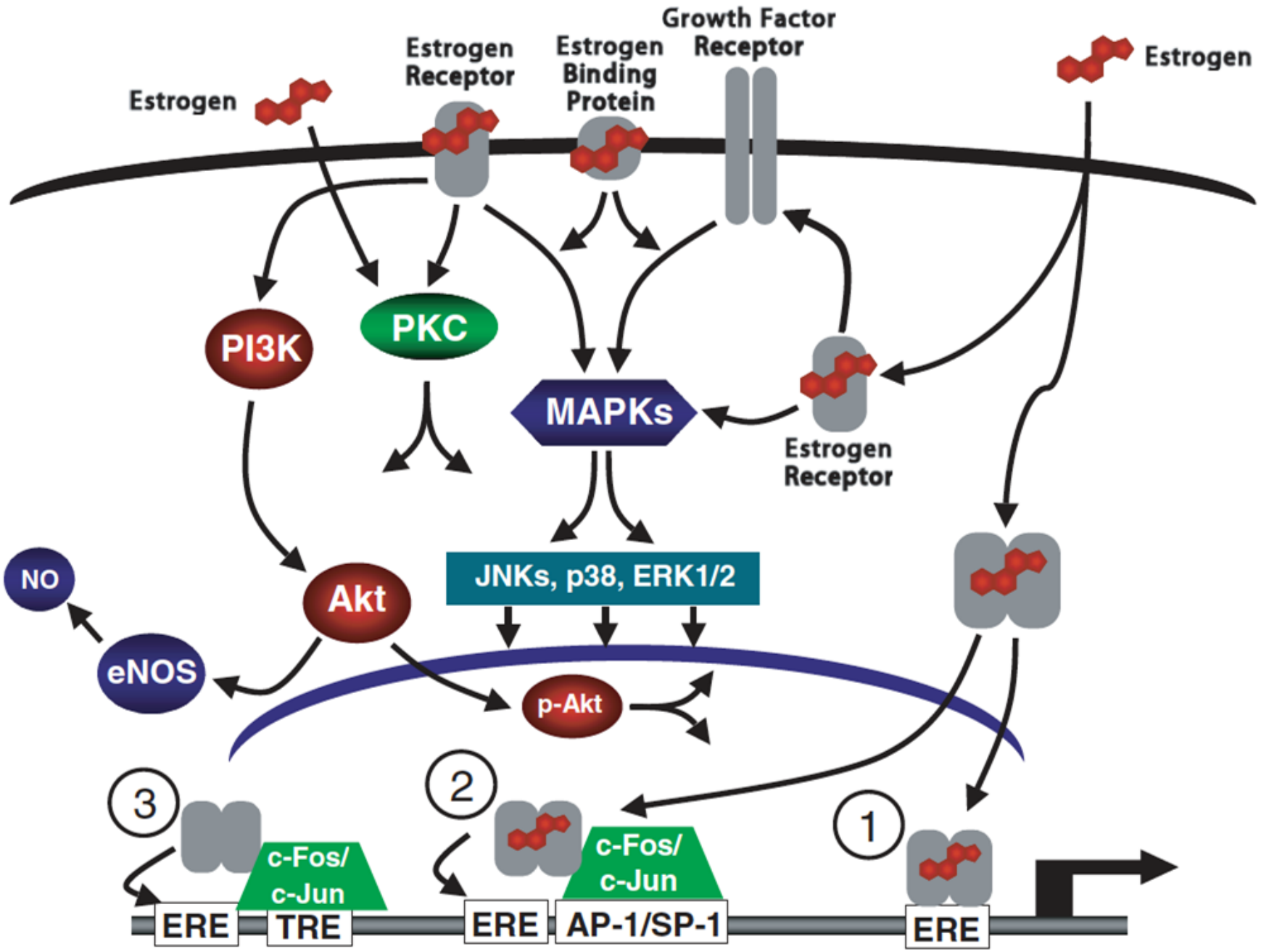
Circulation. 2018;138:198–205. DOI: 10.1161/CIRCULATIONAHA.118.034271

The influence of comorbidities on the development of HFpEF in women



Circulation. 2018;138:198–205. DOI: 10.1161/CIRCULATIONAHA.118.034271

Schematic representation of estrogen action in the cardiomyocyte



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Lancet. 1999 Jan 16;353(9148):205-6.

A brief clinic

Rockwood K, Sta

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Journal of Gerontology: MEDICAL SCIENCES
2001, Vol. 56A, No. 3, M146–M156

Copyright 2001 by The Gerontological Society of America

Frailty in Older Adults: Evidence for a Phenotype

J Nutr Health Aging. 2008 Jan;12(1):29-37.

The I.A.N.A Task Force on frailty assessment of older people in clinical practice.

CrossMark

Frailty in elderly people

Andrew Clegg, John Young, Steve Iliffe, Marcel Olde Rikkert, Kenneth Rockwood

Lancet 2013; 381: 752–62

Published Online
February 8, 2013
http://dx.doi.org/10.1016/S0140-6736(12)62167-9

This online publication has been corrected. The corrected version first appeared at thelancet.com on October 18, 2013

See Online for a video interview with Andrew Clegg

Frailty is the most problematic expression of population ageing. It is a state of vulnerability to poor resolution of homoeostasis after a stressor event and is a consequence of cumulative decline in many physiological systems during a lifetime. This cumulative decline depletes homoeostatic reserves until minor stressor events trigger disproportionate changes in health status. In landmark studies, investigators have developed valid models of frailty and these models have allowed epidemiological investigations that show the association between frailty and adverse health outcomes. We need to develop more efficient methods to detect frailty and measure its severity in routine clinical practice, especially methods that are useful for primary care. Such progress would greatly inform the appropriate selection of elderly people for invasive procedures or drug treatments and would be the basis for a shift in the care of frail elderly people towards more appropriate goal-directed care.

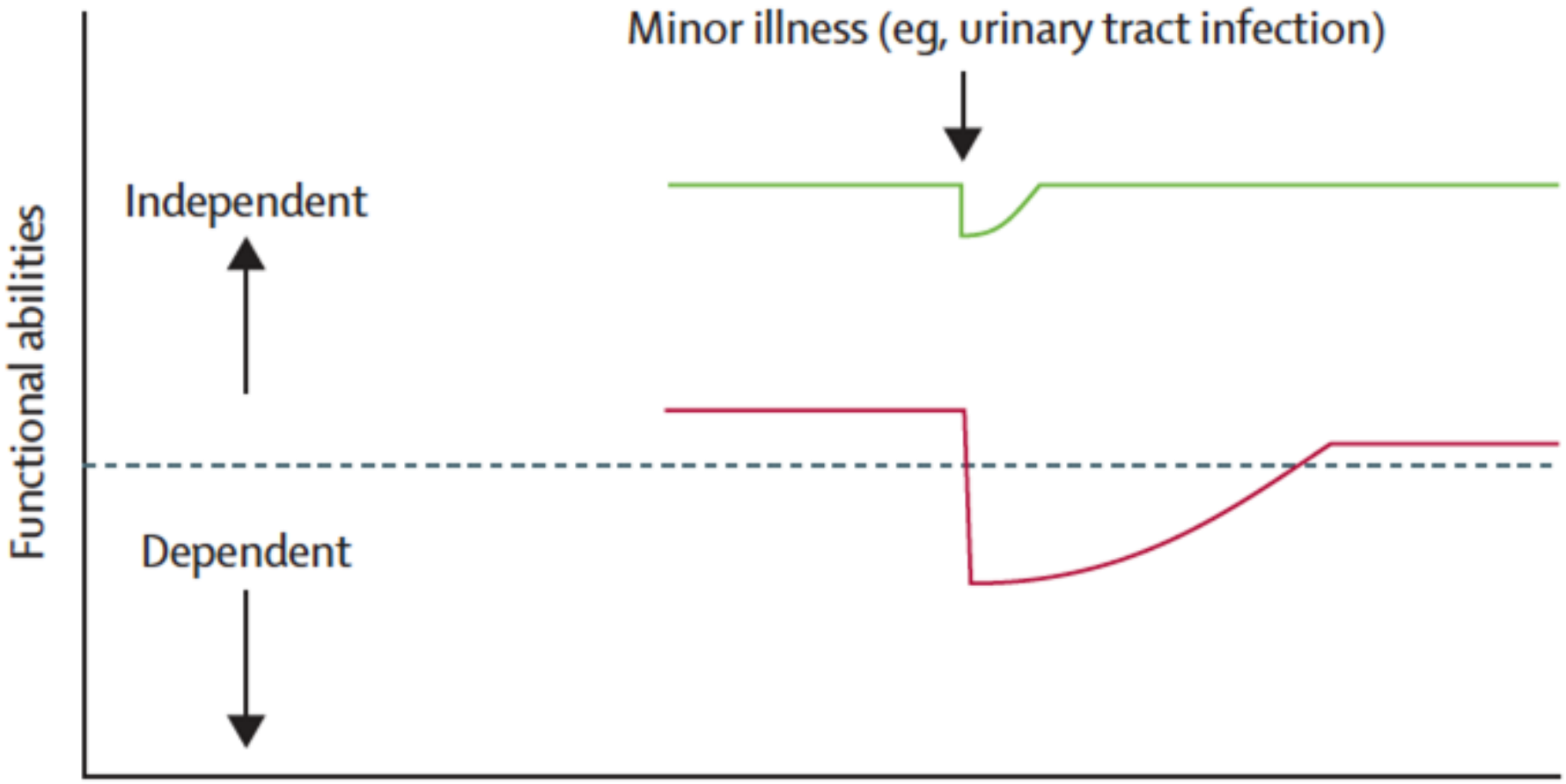
John E. Morley, MB, BCh[a,*], Bruno Vellas, MD[b,c], G. Abellan van Kan, MD[b,c], Stefan D. Anker, MD, PhD[d,e], Juergen M. Bauer, MD, PhD[f], Roberto Bernabei, MD[g], Matteo Cesari, MD, PhD[b,c], W.C. Chumlea, PhD[h], Wolfram Doehner, MD, PhD[d,i], Jonathan Evans, MD[j], Linda P. Fried, MD, MPH[k], Jack M. Guralnik, MD, PhD[l], Paul R. Katz, MD, CMD[m], Theodore K. Malmstrom, PhD[a,n], Roger J. McCarter, PhD[o], Luis M. Gutierrez Robledo, MD, PhD[p], Ken Rockwood, MD[q], Stephan von Haehling, MD, PhD[r], Maurits F. Vandewoude, MD, PhD[s], and Jeremy Walston, MD[t]

Physical Frailty Is an Important Medical Syndrome

The group defined frailty as

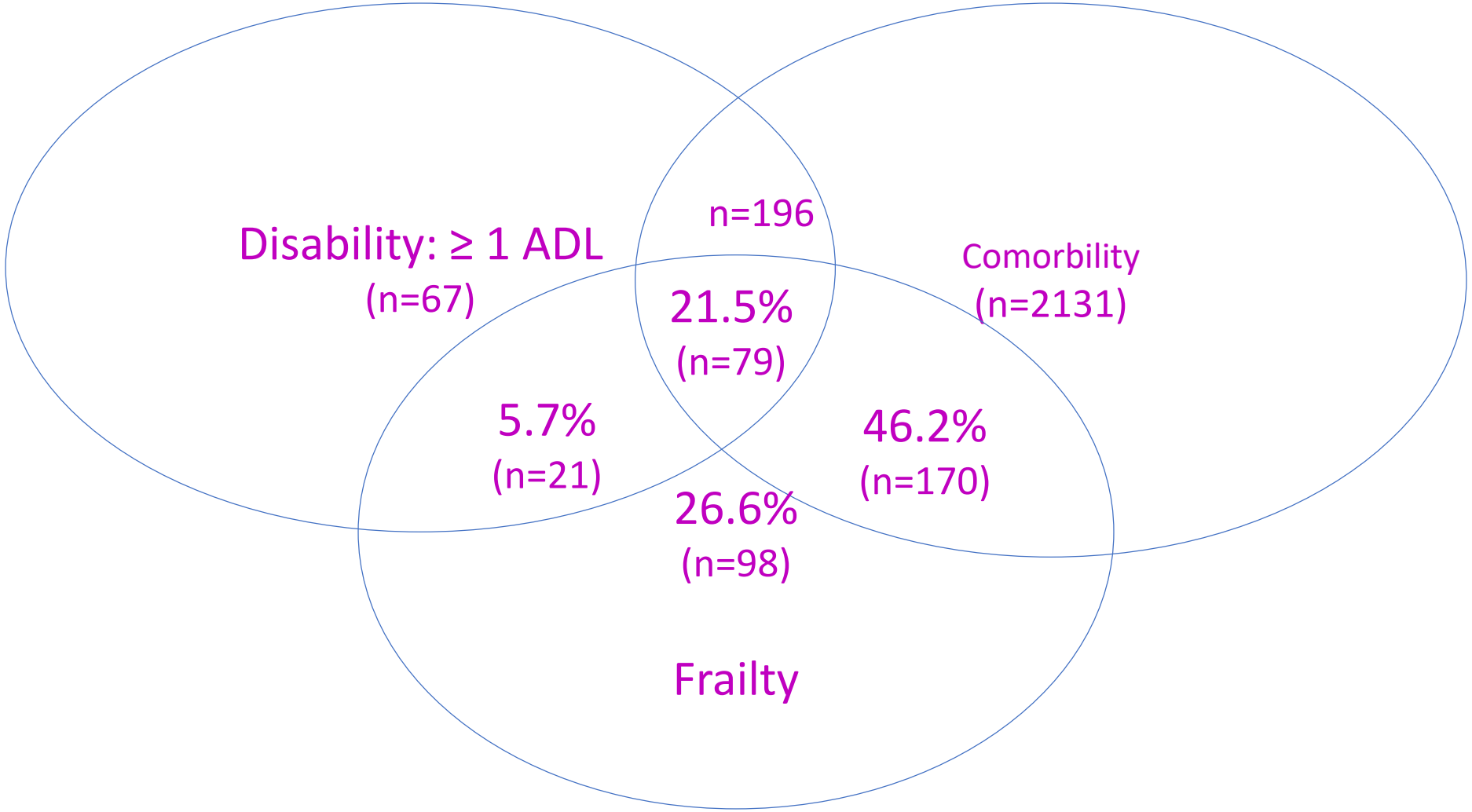
> "A medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death."

Vulnerability of frail elderly people to a sudden change in health status after a minor illness



Clegg et al. Lancet 2013; 381: 752–62

Venn diagram displaying extent of overlap of frailty with ADL disability and comorbidity (≥2 diseases).



the Journals of gerontology Series a

The Gerontological Society of America

Fried et al J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.

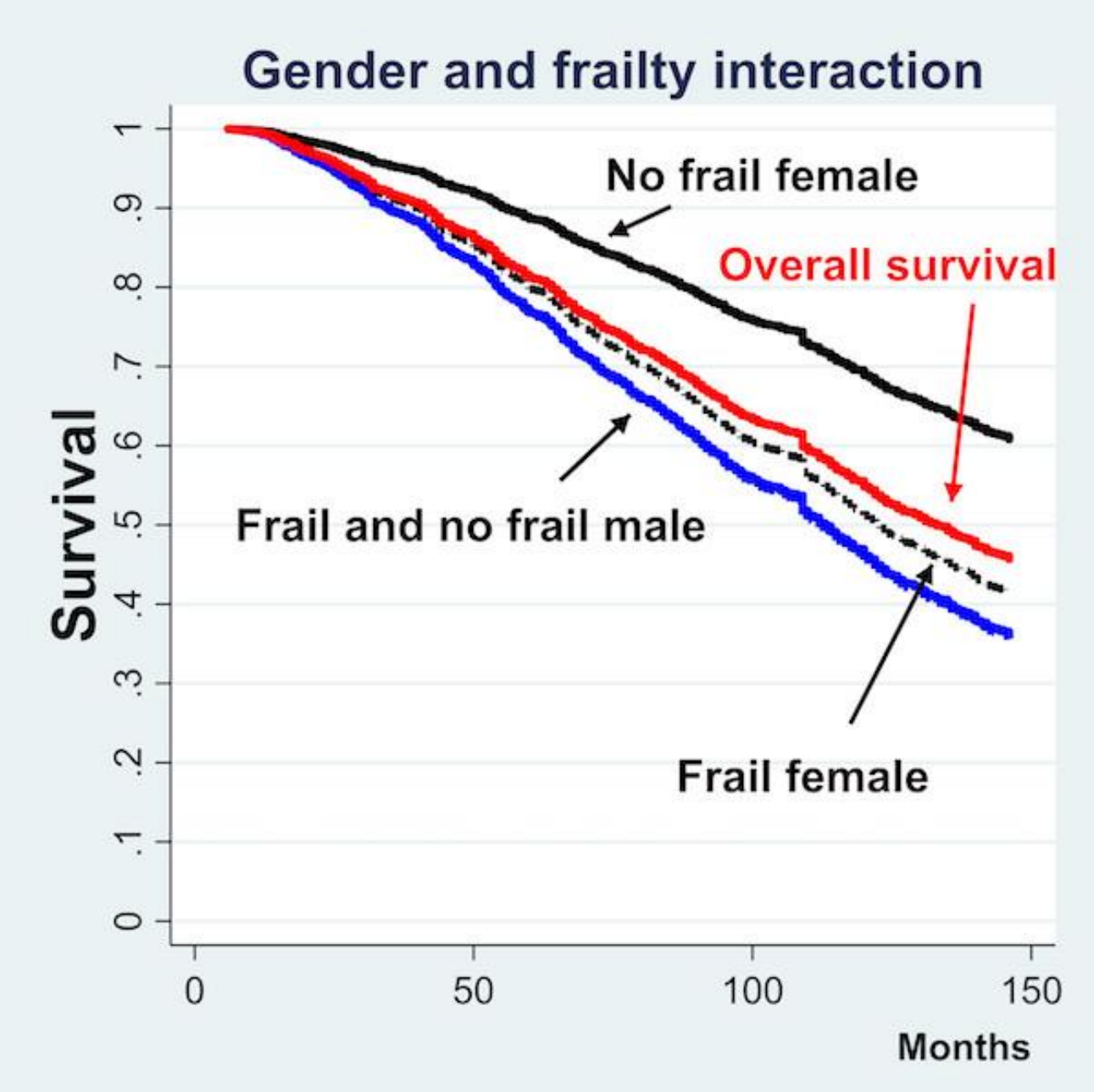
SCIENTIFIC REPORTS | nature research

Inter-relationships between Gender, Frailty and 10-Year Survival in Older Italian Adults: an observational longitudinal study

Graziamaria Corbi[1]*,MD, PhD, Francesco Cacciatore[2], MD, Klara Komici[1], MD, Giuseppe Rengo[2,3], MD, PhD, Dino Franco Vitale[4], MD, Giuseppe Furgi[3], MD, Gennaro Pagano[5], MD, PhD, Leonardo Bencivenga[2], MD, Sergio Davinelli[1], PhD, Nicola Ferrara[2,3], MD.

in press

Gender and frailty interaction directly adjusted survival curves



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Corbi et al in press

Gender Differences in the Incidence and Determinants of Components of the Frailty Phenotype Among Older Adults: Findings From the SABE Study

Journal of Aging and Health
1–23
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DOI: 10.1177/0898264316671228
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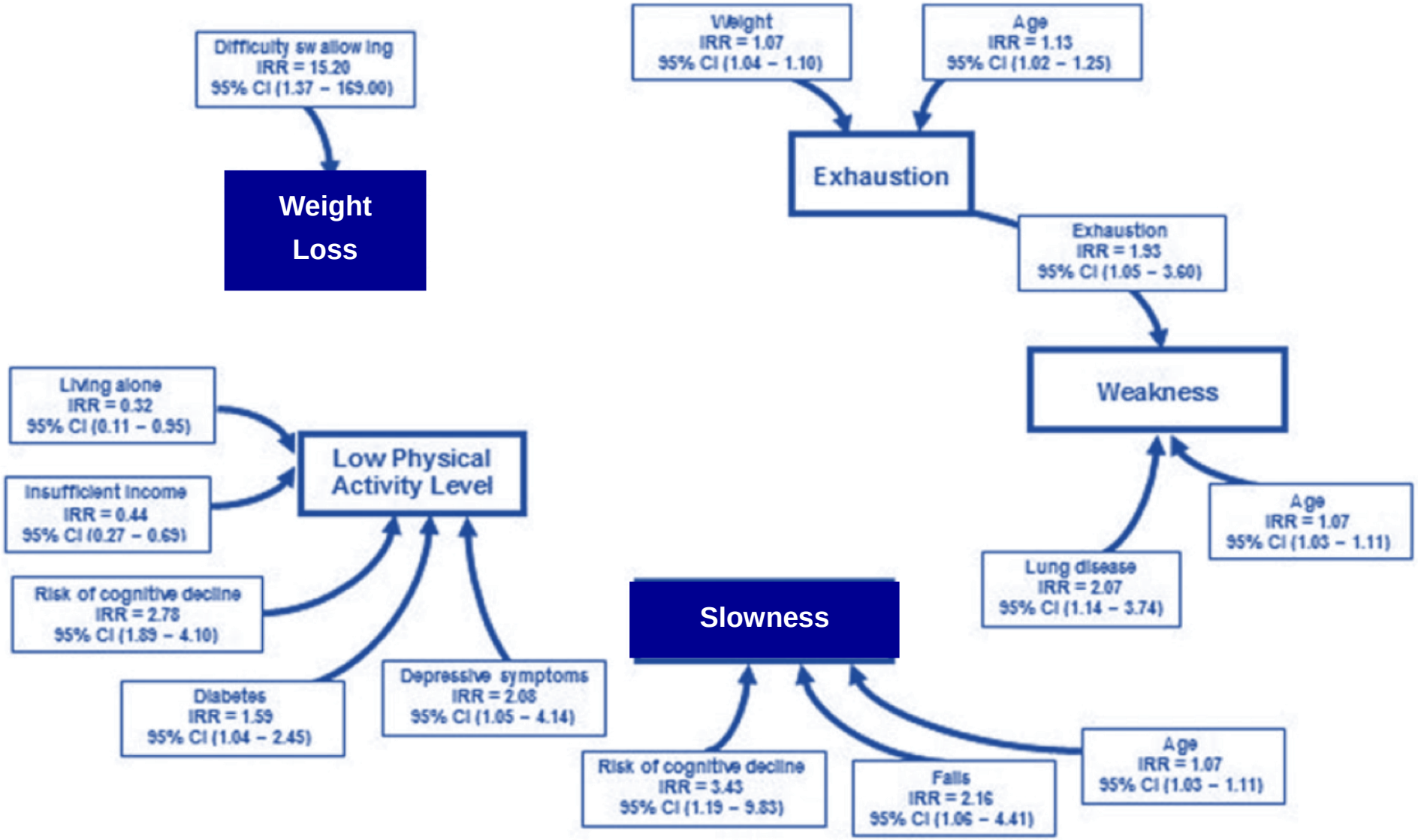
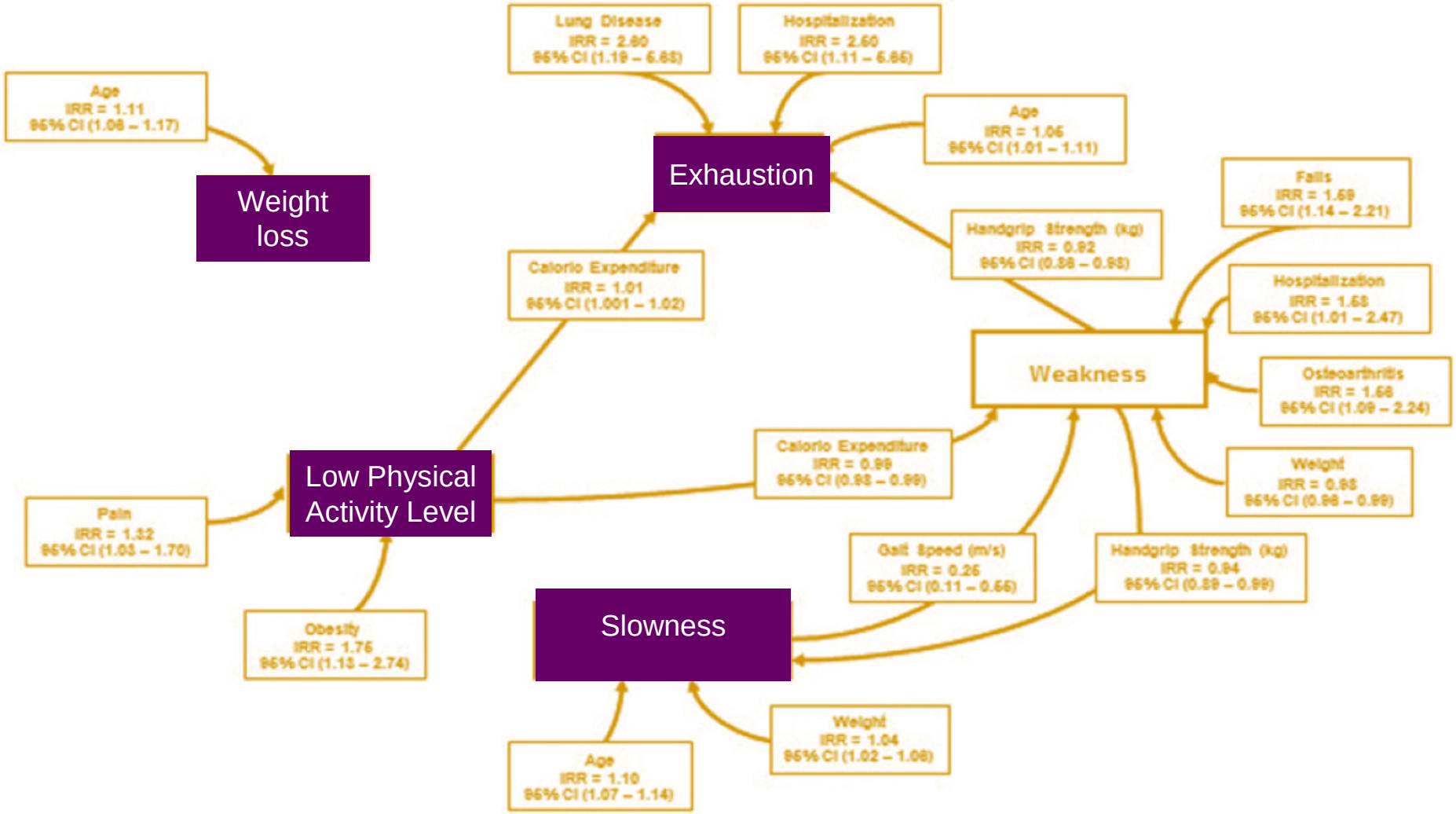
Factors associated with incidence of 5 components of frailty in older men - 2006 to 2010 - SABE Study.



J Aging Health. 2016 :898264316671228.

Factors associated with incidence of 5 components of frailty in older female - 2006 to 2010 - SABE Study.



J Aging Health. 2016 :898264316671228.

"Here's my sequence...”

In the future, the development of genetic tests - simple, fast and at low costs - will permit to make new drugs and therapy with a better risk/benefit ratio.

pharr

Cardioprotective Effects of Dietary Phytochemicals on Oxidative Stress in Heart Failure by a Sex-Gender-oriented point of view.

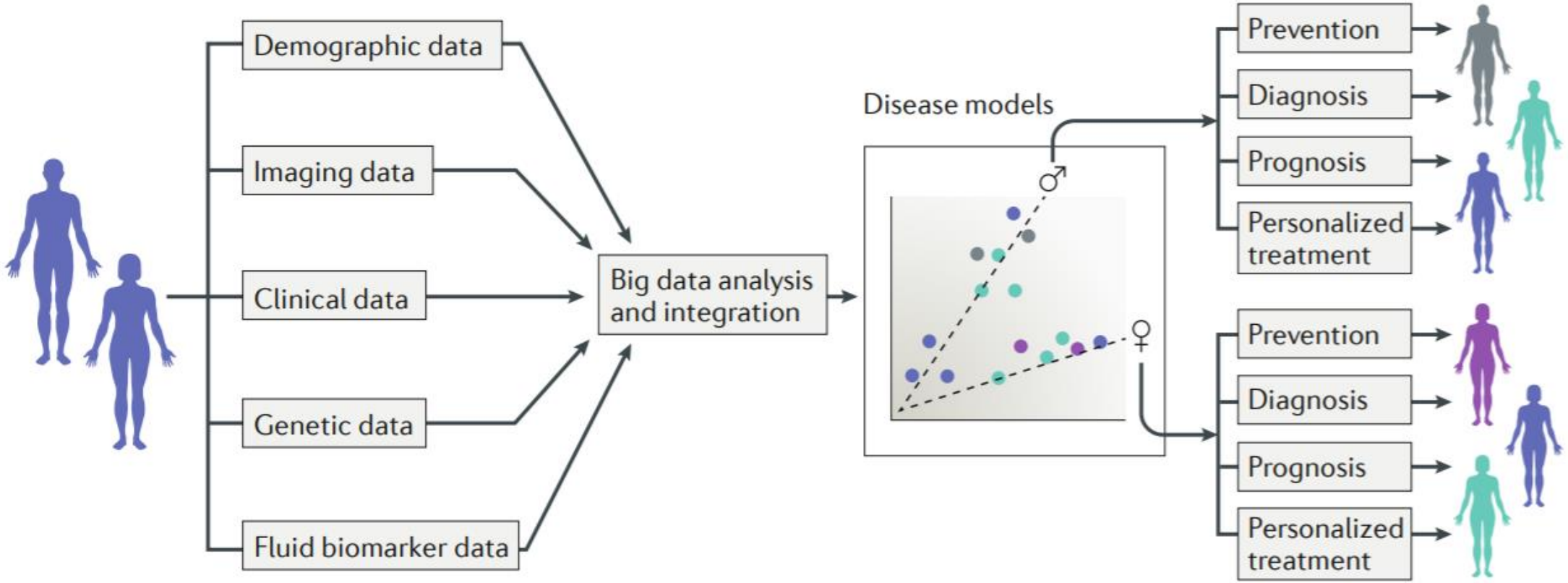
Klara Komici,[1*] Valeria Conti,[2*] Sergio Davinelli,[1] Leonardo Bencivenga,[3] Giuseppe Rengo,[3,4] Amelia Filippelli,[2] Nicola Ferrara[3,4] and Graziamaria Corbi[1].

Table 2. Phytochemical Effects on human Heart Failure Models

Overall Population	Study	Setting	Phytochemical Class	Dose	Treatment	Molecular effects	Cardiovascular Effects	References
26 M 15 F	RDBPC	Prehypertension and stage 1 Hypertension in over-weighted or obese subjects	Quercetin	325 mg twice day	4 weeks	no effect on oxidative stress	↓ SBP ↓DBP	Edwards RL. et al 2007
34 M 34 F	RDBPC	Prehypertension and stage 1 Hypertension	Quercetin	162 mg/day	6 weeks	no effect on oxidative stress and endothelial function	↓ SBP	Brull V. et al 2015
36 M 49 F	RCT	Stable CAD	Quercetin	121 mg twice per day	9 weeks	↓ TNF α, ↓ IL-1β,↓IL-10	↑ LVEF, ↑ E/A	Chekalina N.et al 2018
69 M 61 F	RDBPC	CABG patietns	Quercetin	4 g/day	8 days	↓ CRP, MDA, NT-proBNP	↑ LVEF, ↓ post MI CABG	Wongcharoen W.et al 2012
64 M 9 F	RTBPC	Stable CAD	Resveratrol	350 mg/day; 700 mg/day	12 months	↓PAI-1, ↑Adiponectin	not mentioned	Tome-Carniero J. et al 2013
71 M 45 F	RDBPC	Stable Angina Pectoris	Resveratrol/calcium fructobrate	20mg/112 mg/day	6 months	↓ hsCRP	↓ NT-proBNP	Militaru C. et al 2013
26 M 4 F	RDBPC	Stable CAD	Resveratrol	10 mg/day	3 months	no effect on inflammation	↑ FMD, ↑E/A	Magyar K. et al 2012
17 M 3 F	RCT	chronic HFrEF	Flavonol-riched chocolated	40 gr/day	4 weeks	no effect on oxidative stress	↑ FMD	Flammer EJ. et al 2012

Oxidative Medicine and Cellular Longevity *in press*

Verso una medicina personalizzata



http://www.womensbrainproject.com/

Ferretti MT et al, Nat Rev Neurol 2018

64° Congresso Nazionale SIGG

Continuità di affetti, continuità di cure

AUDITORIUM DELLA TECNICA - ROMA, 27/30 NOVEMBRE 2019

GRAZIE PER L'ATTENZIONE

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SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA