IL RISCHIO CARDIOVASCOLARE NELLE DONNE

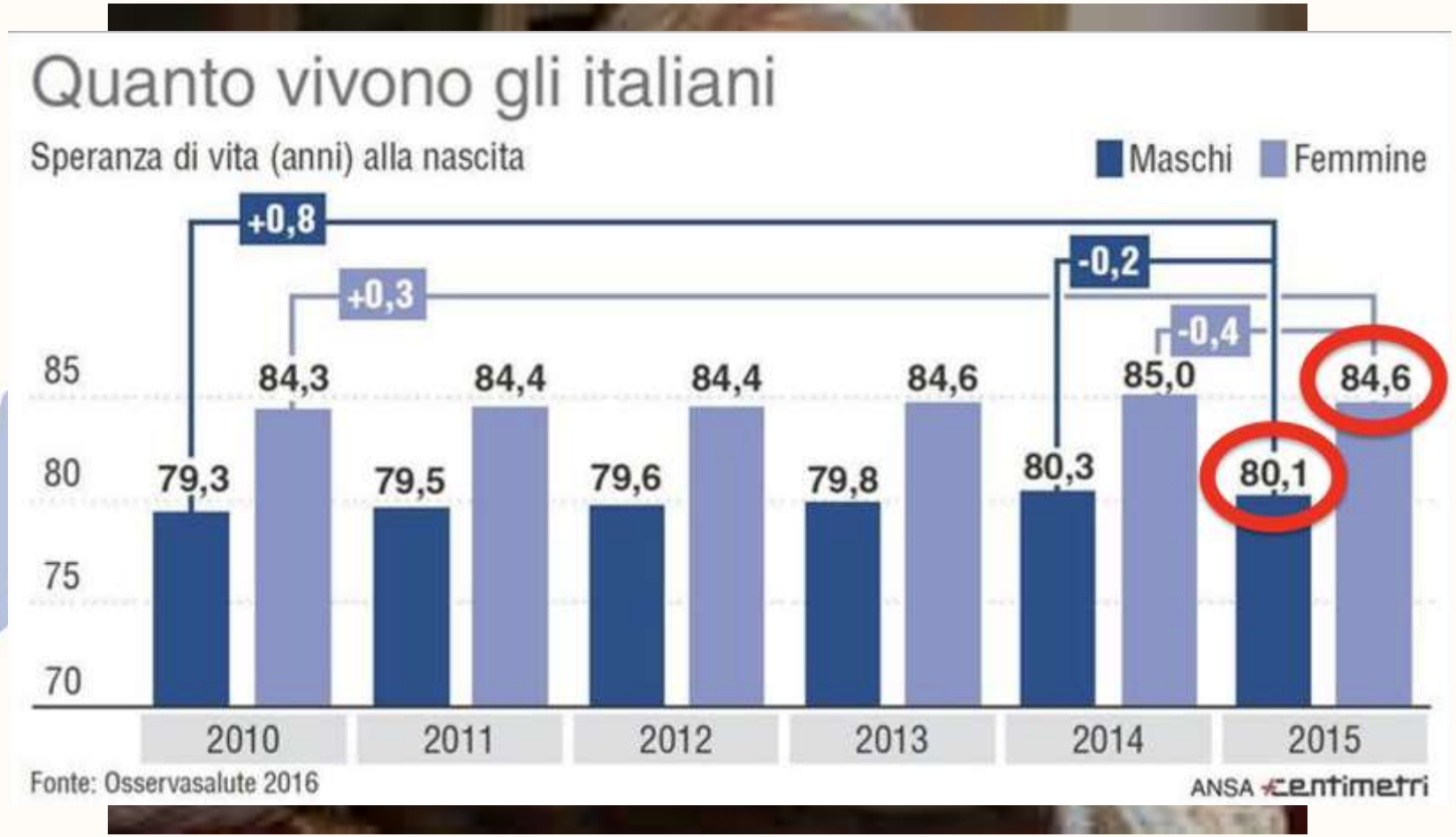
Dott.ssa Elisa Lodi

Prof.ssa Maria Grazia Modena

Medicina di Genere:
dal piano Nazionale alla clinica,
la salute delle differenze

PARADOSSO DONNA…

La donna vive più a lungo dell'uomo;



…. alla longevità non corrisponde una miglior qualità di vita. Rispetto all'uomo…

DAI DATI ISTAT:
Le donne hanno peggior stato di salute degli uomini (8.3% contro 5.3%)

Allergie + 8%	Ipertensione +30%
Diabete + 9%	Malattie Tiroide + 500%
Cataratta + 80%	Osteoporosi + 736%
Depressione + 138%	Anoressia + 900%
Sindr.Metabolica + 200%	Alzheimer + 100%

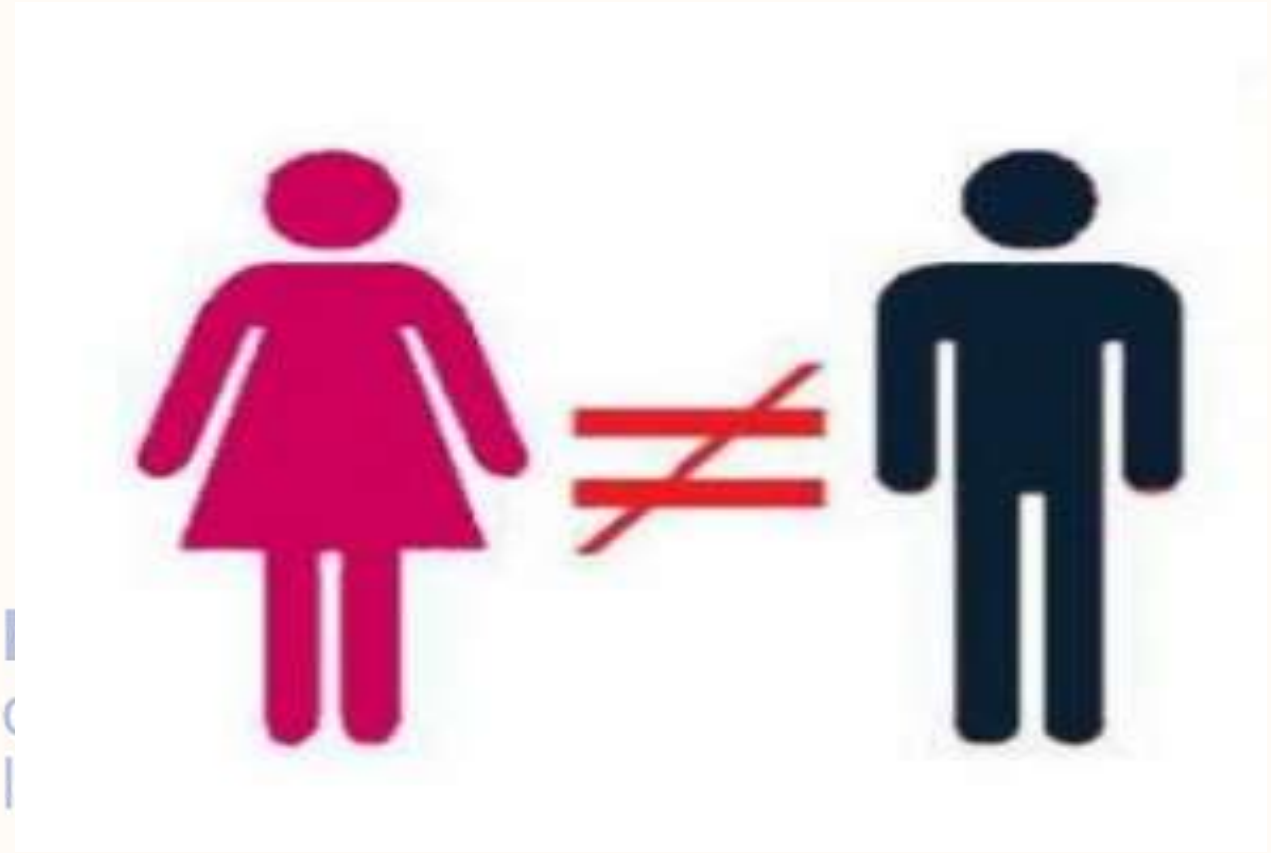
- **Si ammala più frequentemente**
- **Manifesta più spesso sintomi dolorosi**
- **Entra con maggior frequenza in contatto con gli operatori sanitari**

EPPURE...

Fin dalle sue origini, la medicina ha avuto un'impostazione androcentrica:

Medicina di Genere:
dal piano Nazionale alla clinica,
la salute delle differenze

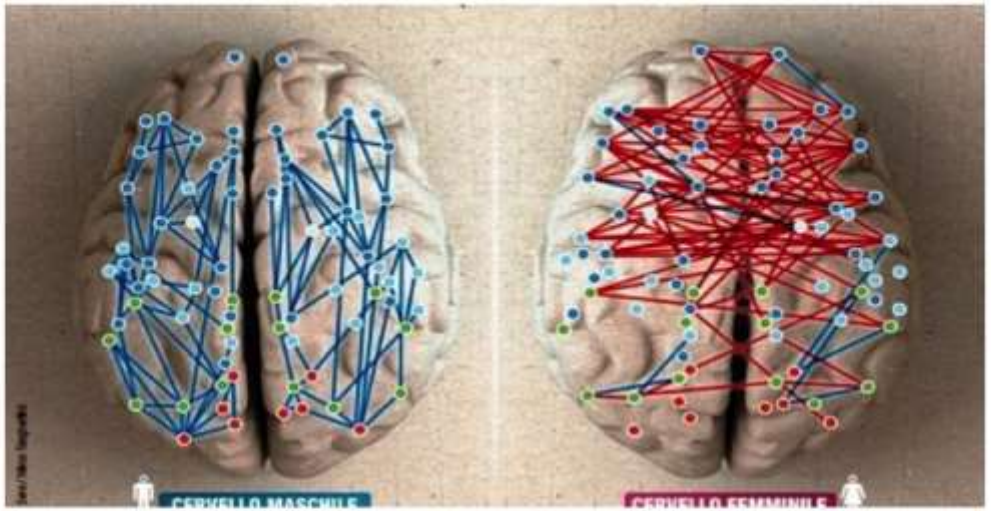
IN REALTA'...



Differenze di sesso: cervello

Sex differences in the structural connectome of the human brain

Madhura Ingalhalikar[a,1], Alex Smith[a,1], Drew Parker[a], Theodore D. Satterthwaite[b], Mark A. Elliott[c], Kosha Ruparel[b], Hakon Hakonarson[d], Raquel E. Gur[b], Ruben C. Gur[b], and Ragini Verma[a,2]



I modelli di connettività del cervello **maschile** conferiscono ai maschi un sistema di coordinamento fra esperienze percettive e azione più efficiente, mentre i modelli di connettività dei cervelli **femminili** facilitano l'integrazione delle modalità di ragionamento analitico e sequenziale dell'emisfero sinistro con quelle spaziali e intuitive dell'emisfero destro.

Università della Pennsylvania a Filadelfia. "Proceedings of the National Academy of Sciences", Ragini Verma et al

Differenze di sesso: geni

Gershoni and Pietrokovski *BMC Biology* (2017) 15:7
DOI 10.1186/s12915-017-0352-z

BMC Biology

RESEARCH ARTICLE Open Access

The landscape of sex-differential transcriptome and its consequent selection in human adults

Moran Gershoni* and Shmuel Pietrokovski

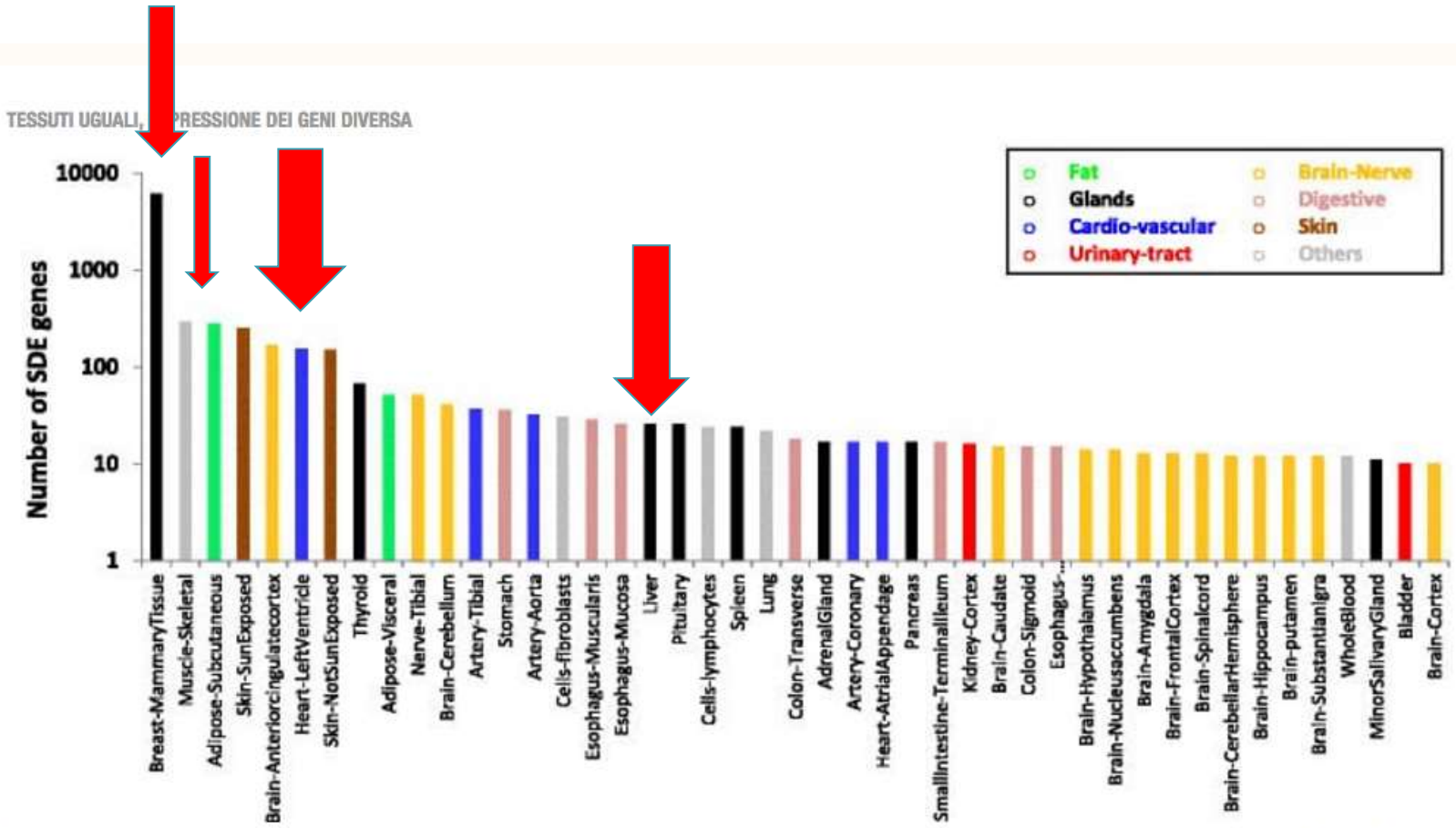
Donne e uomini sono geneticamente diversi per 6.500 motivi: i ricercatori hanno analizzato 20.000 geni di maschi e femmine e hanno scoperto che 6.500 di questi determinano alcune differenze tra i due sessi

Abstract

Background: The prevalence of several human morbid phenotypes is sometimes much higher than intuitively expected. This can directly arise from the presence of two sexes, male and female, in one species. Men and women have almost identical genomes but are distinctly dimorphic, with dissimilar disease susceptibilities. Sexually dimorphic traits mainly result from differential expression of genes present in both sexes. Such genes can be subject to different, and even opposing, selection constraints in the two sexes. This can impact human evolution by differential selection on mutations with dissimilar effects on the two sexes.

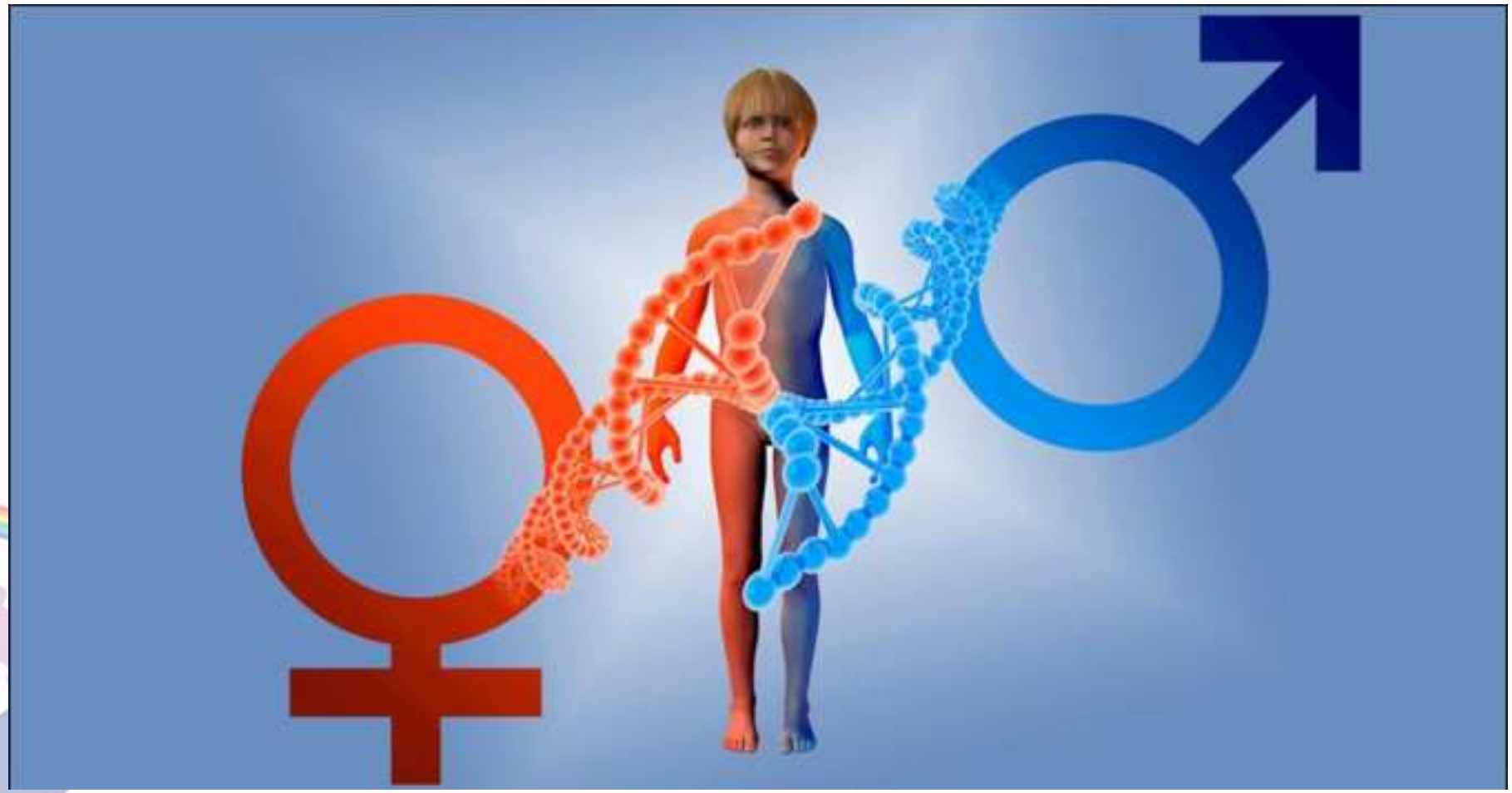
Results: We comprehensively mapped human sex-differential genetic architecture across 53 tissues. Analyzing available RNA-sequencing data from 544 adults revealed thousands of genes differentially expressed in the reproductive tracts and tissues common to both sexes. Sex-differential genes are related to various biological systems, and suggest new insights into the pathophysiology of diverse human diseases. We also identified a significant association between sex-specific gene transcription and reduced selection efficiency and accumulation

Differenze di sesso: geni



Numero di geni espressi in modo differente in maschi e femmine in 45 tessuti comuni a entrambi i sessi. (Cortesia M. Gershoni, S. Pietrokovski/BCM Biology)

Il genoma di base è più o meno lo stesso per tutti ,
ma è utilizzato in maniera diversa dal corpo a seconda degli individui.



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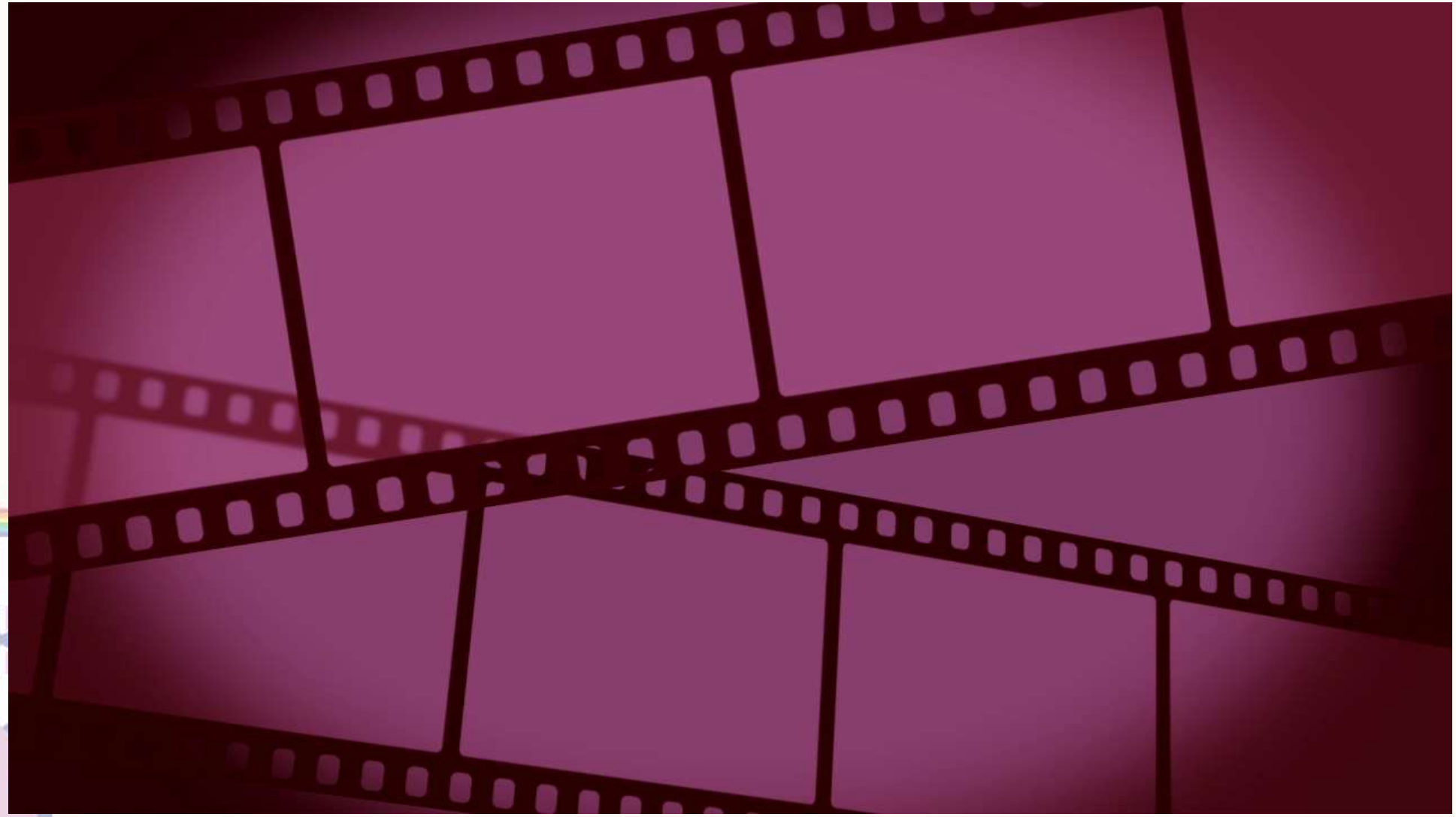
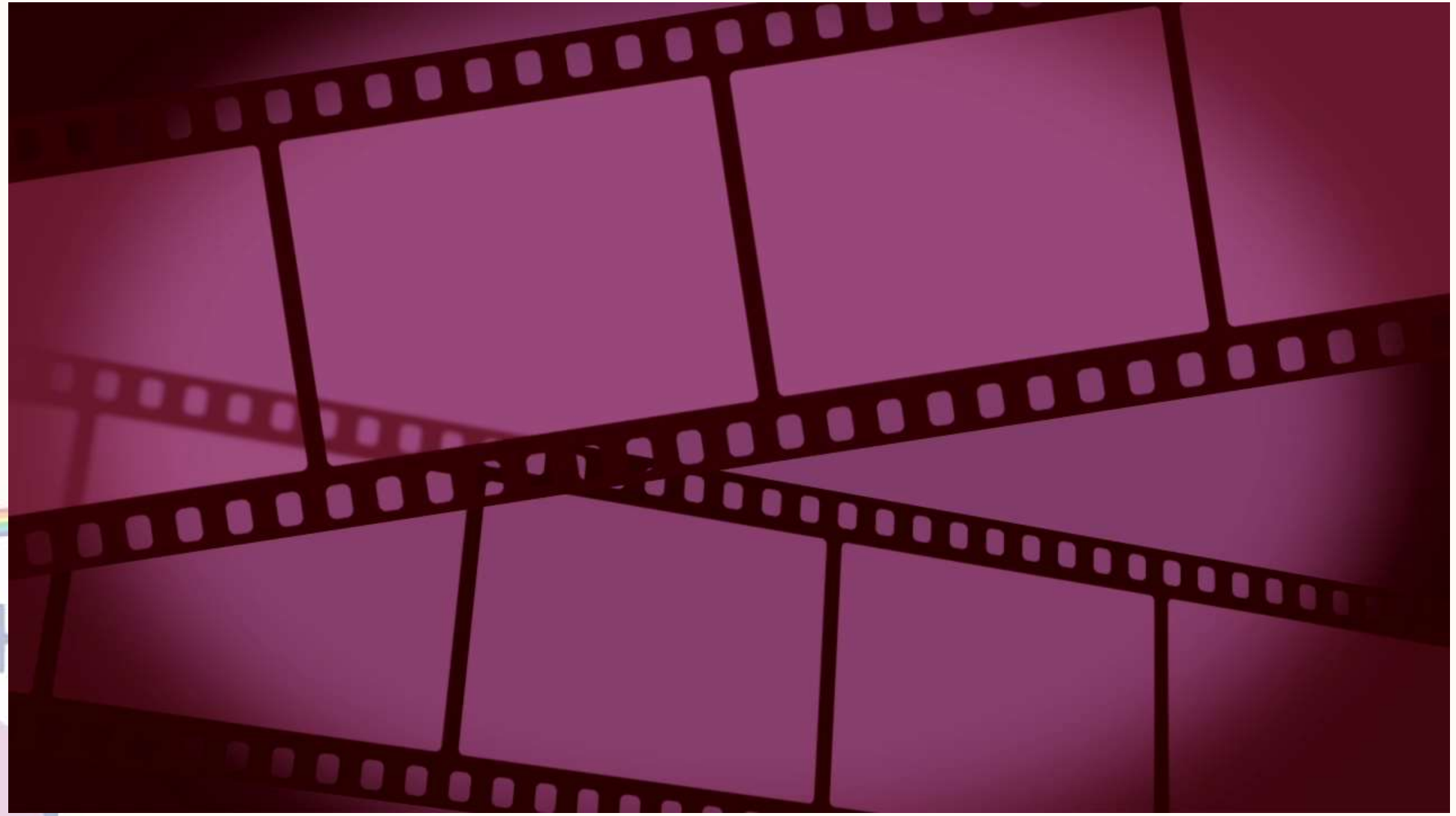
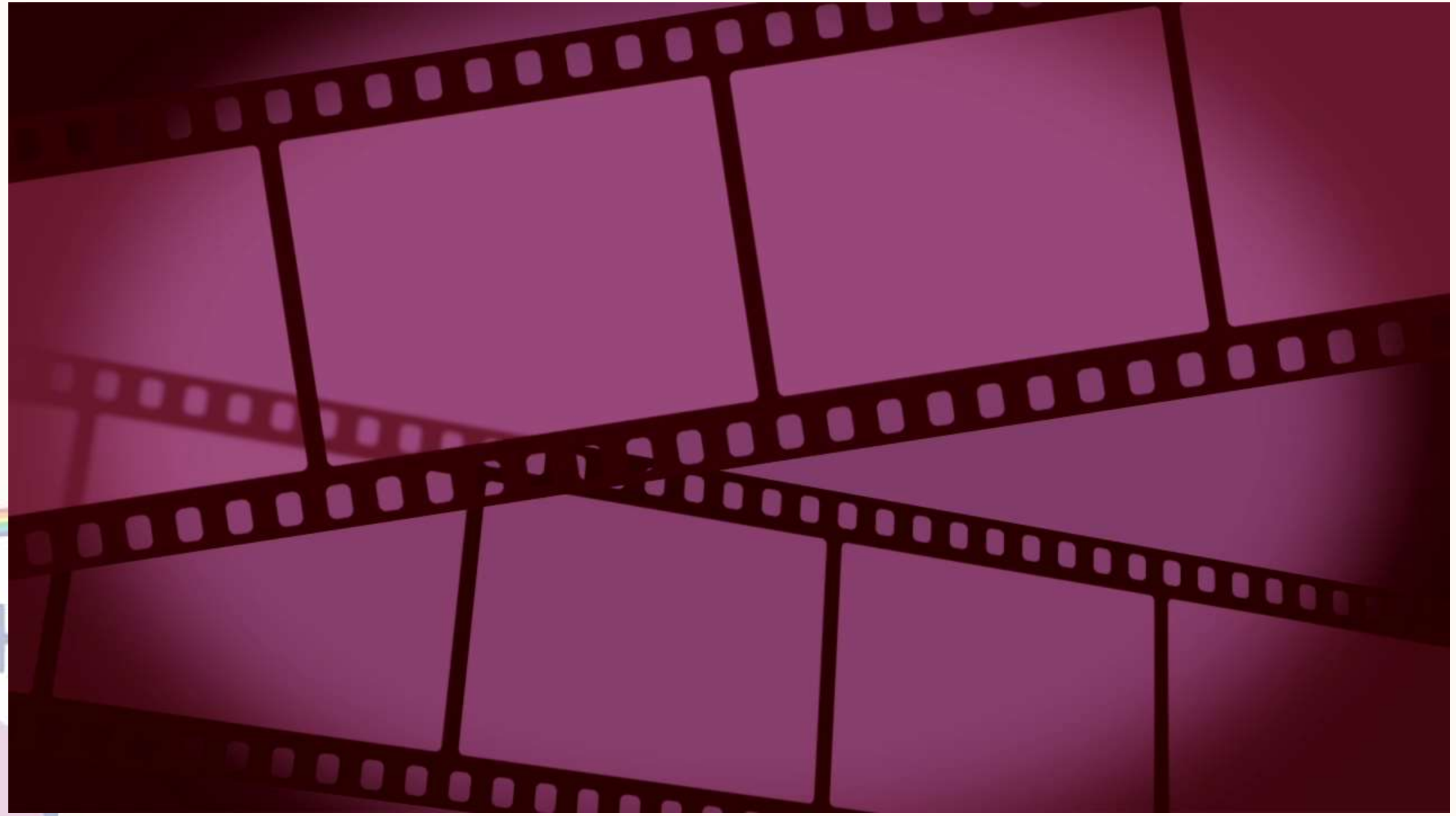
THE YENTL SYNDROME

YENTL, the 19th-century heroine of Isaac Bashevis Singer's short story,[1] had to disguise herself as a man to attend school and study the Talmud. Being "just like a man" has historically been a price women have had to pay for equality. Being different from men has meant being second-class and less than equal for most of recorded time and throughout most of the world. It may therefore be sad, but not surprising, that women have all too often been treated less than equally in social relations, political endeavors, business, education, research, and health care.







INOLTRE...

La comunità ha sempre guardato alla salute della donna con un approccio a 'bikini', considerando essenzialmente solo il **seno e il sistema riproduttivo**, vale a dire ignorando quasi totalmente il resto dell'organismo femminile nell'ambito dei problemi di salute

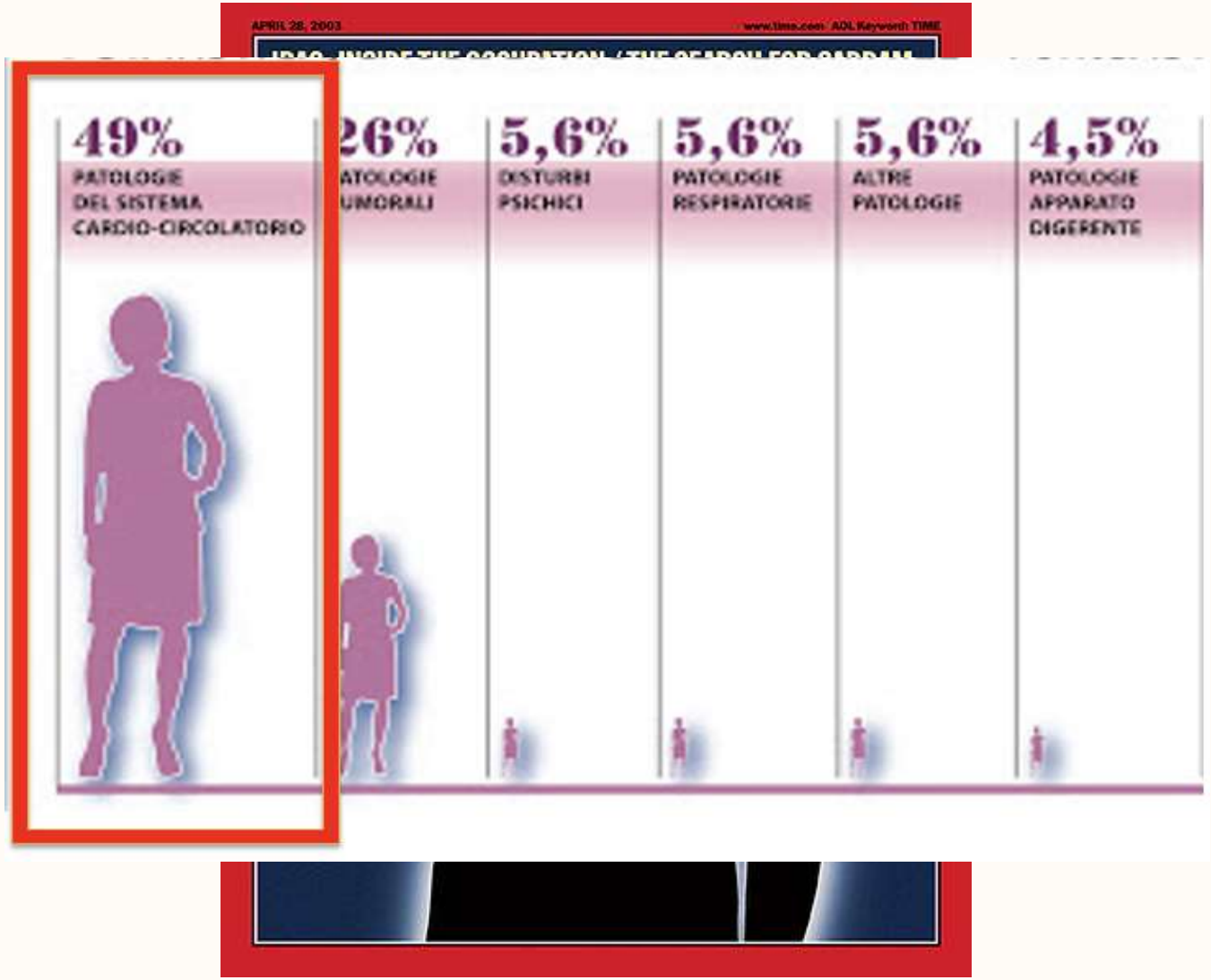
Nanette Wenger, MD

2001: PBS documentary "A Woman's Heart"

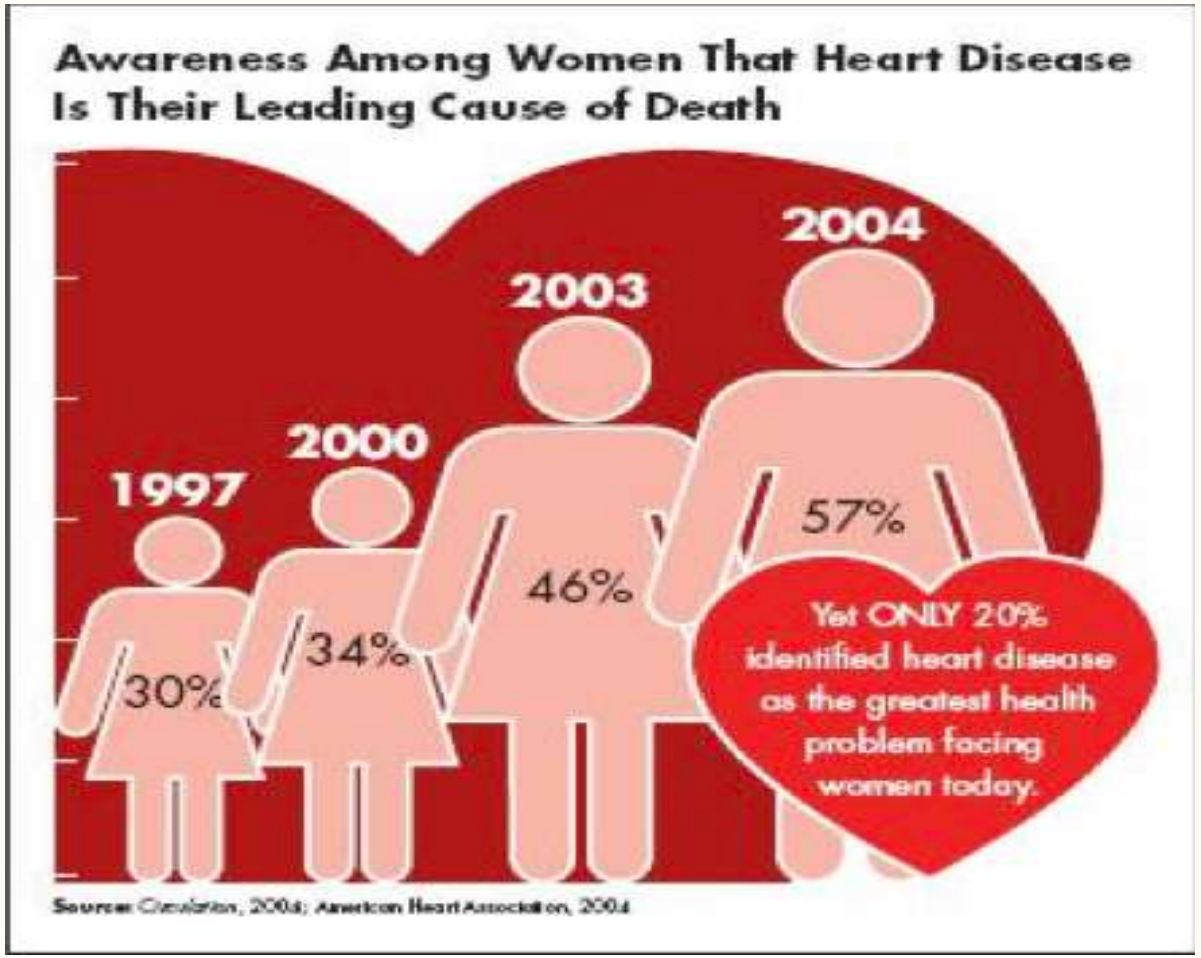
IL MITO

La coronaropatia è una patologia prettamente maschile

LA REALTA'


APRIL 28, 2003
49%
PATOLOGIE DEL SISTEMA CARDIO-CIRCOLATORIO
26%
ATOLOGIE UMORALI
5,6%
DISTURBI PSICHICI
5,6%
PATOLOGIE RESPIRATORIE
5,6%
ALTRE PATOLOGIE
4,5%
PATOLOGIE APPARATO DIGERENTE

WHO KNEW?



80% AMERICAN WOMEN DID NOT

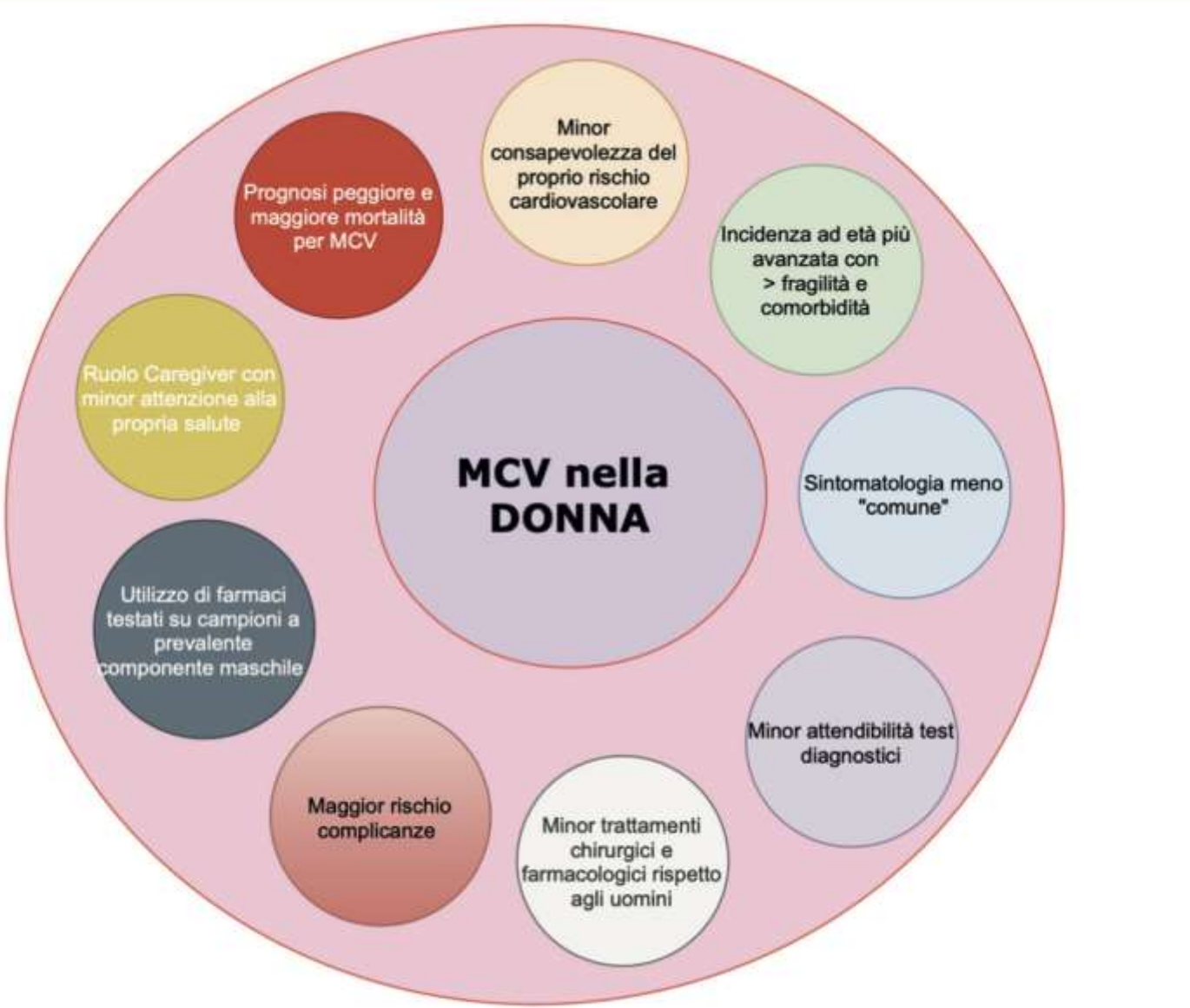


Figura 29. Le malattie cardiovascolari (MCV) nella donna.

FATTORE DI RISCHIO:

Definizione:

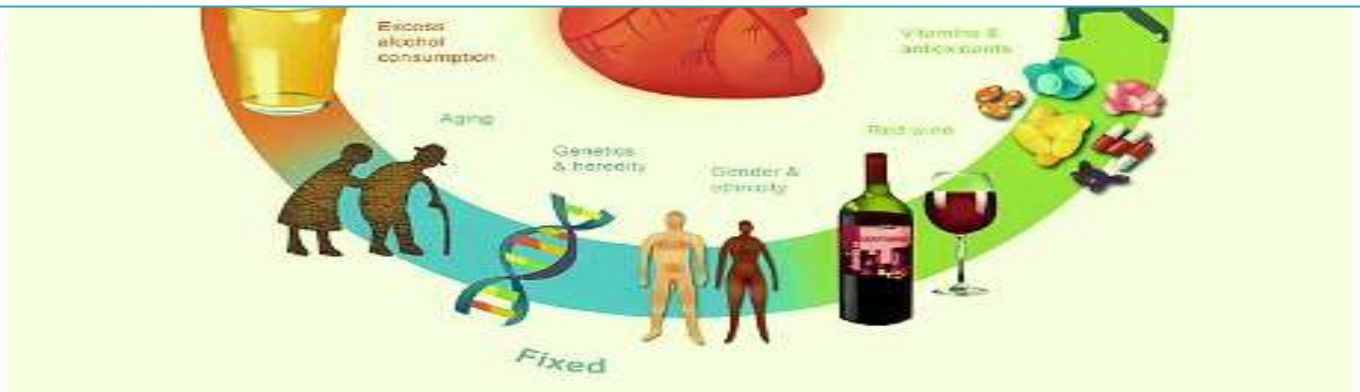
tutto ciò che aumenta in maniera statisticamente significativa
la probabilità di sviluppare una certa patologia.

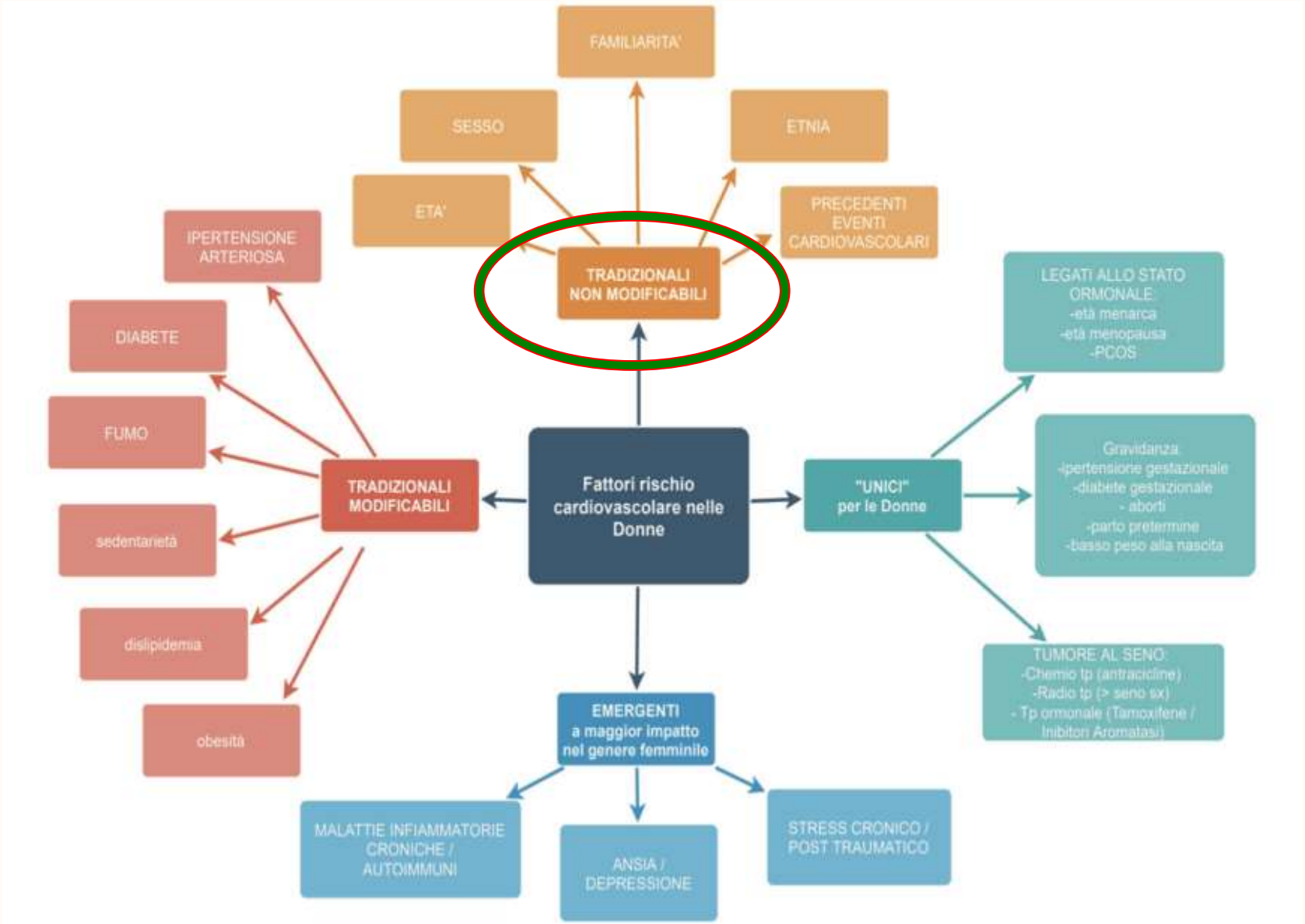
Medicina di Genere:
dal piano Nazionale alla clinica,
la salute delle differenze

- Condizioni statisticamente correlate all'insorgenza di una malattia cardiovascolare, che, se presenti in un soggetto

Effetto SINERGICO

ASSENZA ≠ ESCLUSIONE MALATTIA

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sedentarietà
dislipidemia
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-età menopausa
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-diabete gestazionale
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-parto pretermine
-basso peso alla nascita
TUMORE AL SENO
-Chemio tp (antracicline)
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EMERGENTI a maggior impatto nel genere femminile
MALATTIE INFIAMMATORIE CRONICHE / AUTOIMMUNI
ANSIA / DEPRESSIONE
STRESS CRONICO / POST TRAUMATICO

FATTORI DI RISCHIO

TRADIZIONALI
(fattori di rischio FRAMINGHAM)

Fasi del processo aterosclerotico nelle diverse decadi.
(Pepine CJ.Am j Cardiol 1998;82)

NON MODIFICABILI
non suscettibili di una possibile correzione tramite misure preventive o interventi farmacologici

- **ETA'**
- **SESSO**
- **FAMILIARITA'**

FATTORI DI RISCHIO

TRADIZIONALI

(fattori di rischio FRAMINGHAM)

MODIFICABILI

Legati allo stile di vita e suscettibili di una possibile correzione tramite misure preventive o interventi farmacologici

- **Fumo di sigaretta**
- **Obesità e inattività fisica**
- **Diabete**
- **Ipertensione arteriosa**
- **Dislipidemie**
- **IRC**

COMUNI ... MA DIVERSI

PESO DI RISCHIO

Research

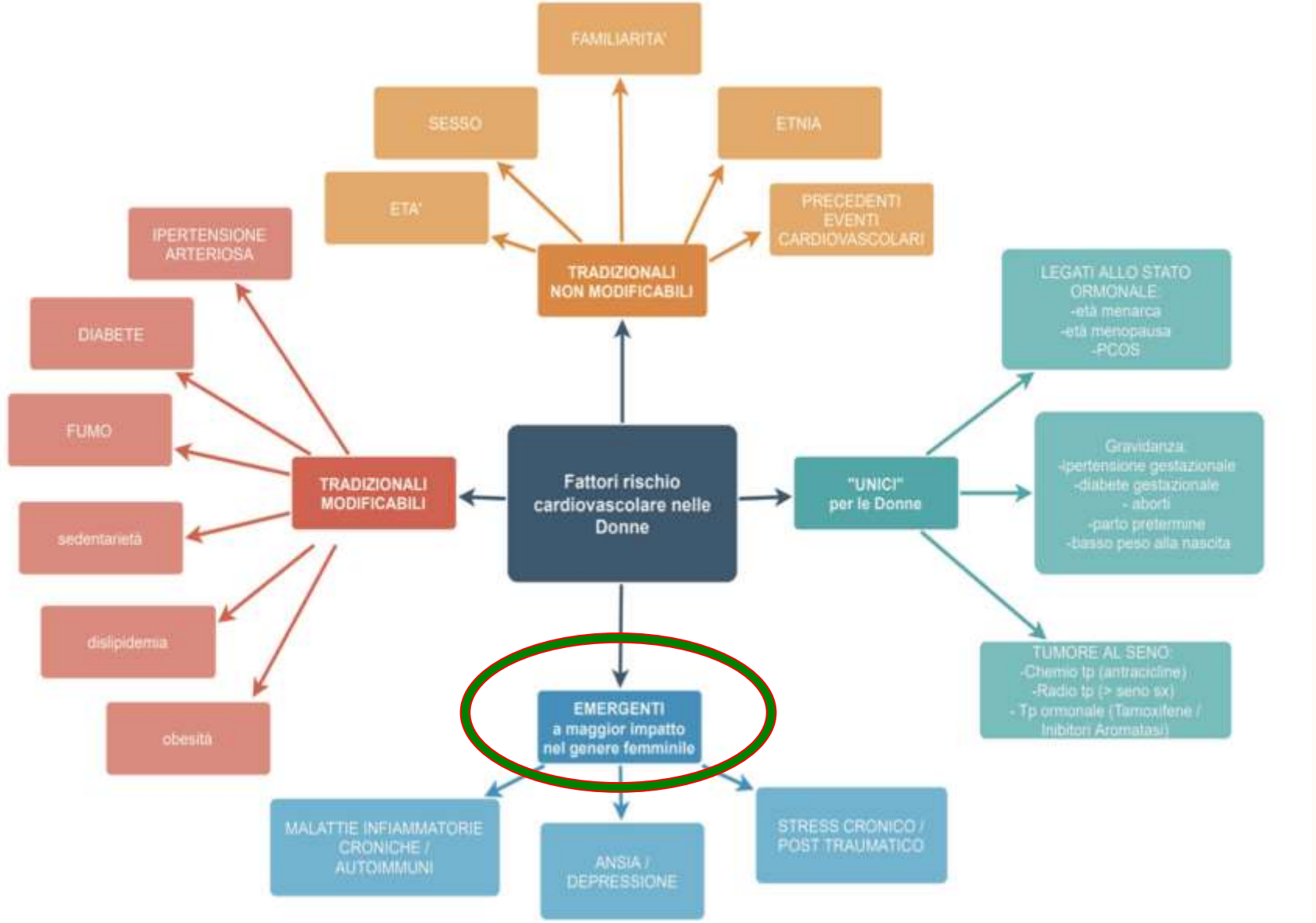
Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants

BMJ 2018 ; 363 doi: https://doi.org/10.1136/bmj.k4247 (Published 07 November 2018)

Cite thi

Results 5081 participants (1463 (28.8%) of whom were women) had MI over seven years' mean follow-up, resulting in an incidence per 10 000 person years of 7.76 (95% confidence interval 7.37 to 8.16) for women and 24.35 (23.57 to 25.16) for men. Higher blood pressure indices, smoking intensity, body mass index, and the presence of diabetes were associated with an increased risk of MI in men and women, but associations were attenuated with age. In women, systolic blood pressure and hypertension, smoking status and intensity, and diabetes were associated with higher hazard ratios for MI compared with men: ratio of hazard ratios 1.09 (95% confidence interval 1.02 to 1.16) for systolic blood pressure, 1.55 (1.32 to 1.83) for current smoking, 2.91 (1.56 to 5.45) for type 1 diabetes, and 1.47 (1.16 to 1.87) for type 2 diabetes. There was no evidence that any of these ratios of hazard ratios decreased with age (P>0.2). With the exception of type 1 diabetes, the incidence of MI was higher in men than in women for all risk factors.

Conclusions Although the incidence of MI was higher in men than in women, several risk factors were more strongly associated with MI in women compared with men. Sex specific associations between risk factors and MI declined with age, but, where it occurred, the higher relative risk in women remained. As the population ages and the prevalence of lifestyle associated risk factors increase, the incidence of MI in women will likely become more similar to that in men.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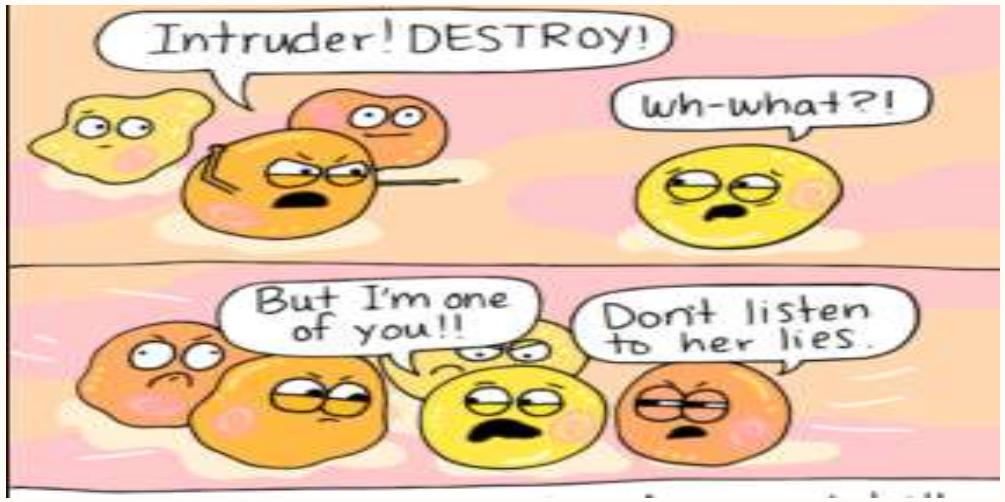
FRCV EMERGENTI PREDOMINANTI NELLE DONNE

Le malattie autoimmuni

- sono condizioni caratterizzate da una risposta **impropria** ed **esagerata** del sistema immunitario.
- tendono a colpire prevalentemente il **sesso femminile** (la prevalenza è da 2 a 50 volte superiore nella donna rispetto all'uomo) visto il ruolo immunostimolante esercitato dagli estrogeni



Malattie Autoimmuni

Crescenti evidenze suggeriscono che i pazienti affetti da alcune malattie au… CV, pr… ne po… ce e …

CURIOSITA':
Il LES pare ad oggi la malattia autoimmune con maggiore rischio CV,
il rischio di CVD è **4-8 volte superiore** rispetto alla popolazione generale

(P.C. Teixeira, et al.)

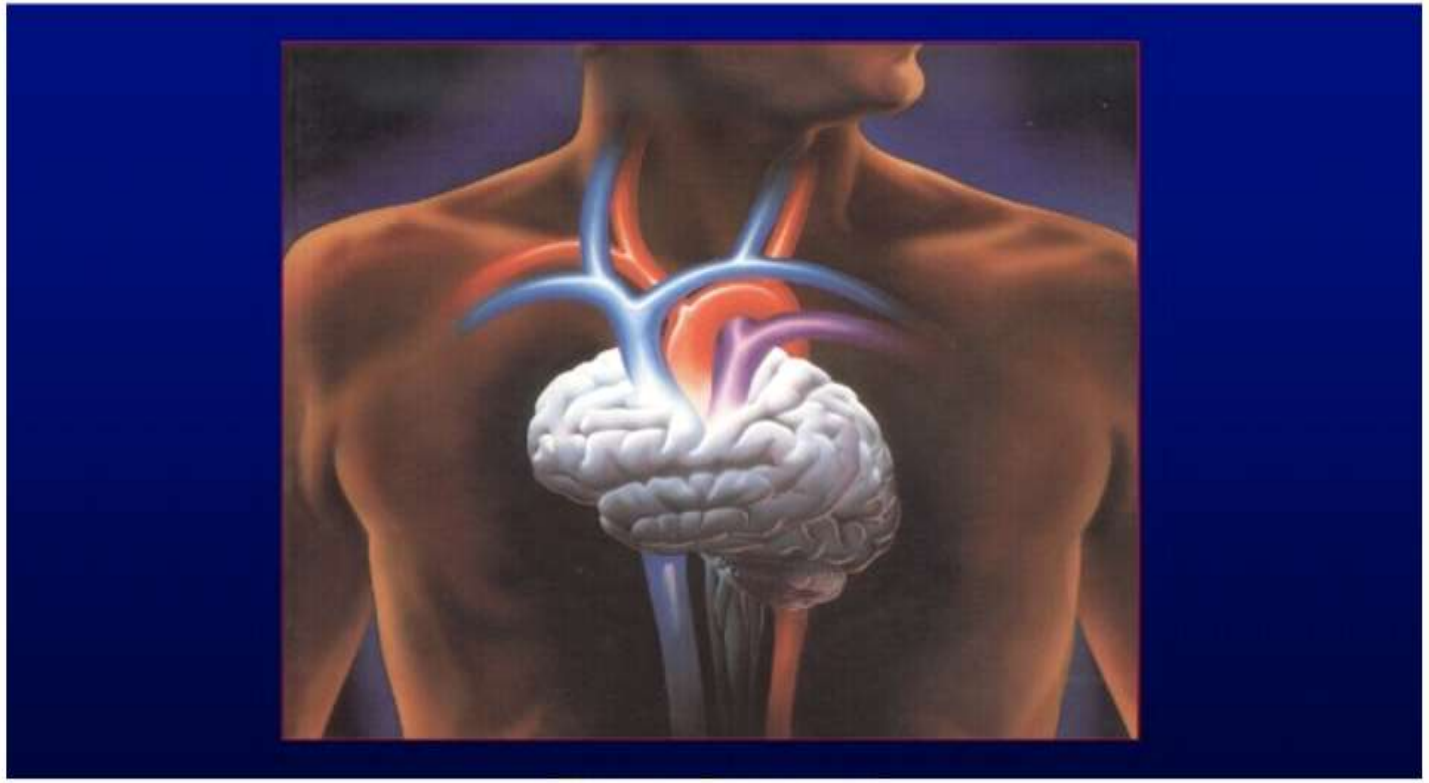
- …in pazienti con LES.
- …R,

CURIOSITA'
L'AR si associa a **una diminuzione di 10-15 anni della spettanza di vita** nei confronti della popolazione general. Circa la **metà di tutte le morti nei pazienti con AR sono riconducibili a cause cardiovascolari.**

FRCV EMERGENTI PREDOMINANTI NELLE DONNE

Depressione e stress psicologico:

i nuovi killer silenziosi



"For every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart."

Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study

THE LANCET

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Quynh A Truong, Udo Hoffmann,

FAST TRACK — ARTICLES | VOLUME 364, ISSUE 9438, P953-962, SEPTEMBER 11, 2004

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Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 INTERHEART study)

Prof Annika Rosengren, MD · St

Mohammad Zubaid, MD · Wael

Published: September 11, 2004

e. We imaged the amygdala,

second corrected version appeared on February 23, 2017.

See Comment page 770

*These authors contributed equally

†These authors contributed

between and card amygdala (path) an

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Circulation

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Psychological distress and mortality in stable coronary heart disease: persistence of high distress means increased risk

PDF

Gjin Ndrepepa

Correspondence to

Dr Gjin Ndrepepa, Department of Adult Cardiology, Deutsches Herzzentrum München, Technical University, Munich 80636, Germany;

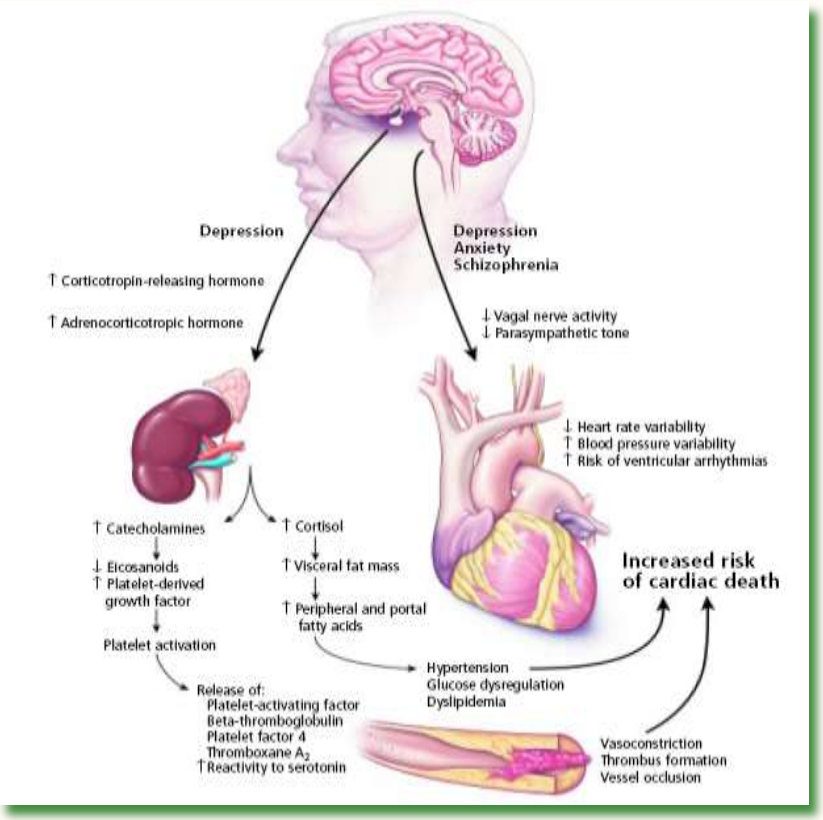
ndrepepa@dhm.mhn.de

Mechanisms by which depression may lead to cardiac events and mortality

BEHAVIOURAL MECHANISMS

- Dietary factors
- Lack of exercise
- Medication non-adherence
- Poor social support
- Unhealthy lifestyle

BIOLOGICAL MECHANISMS

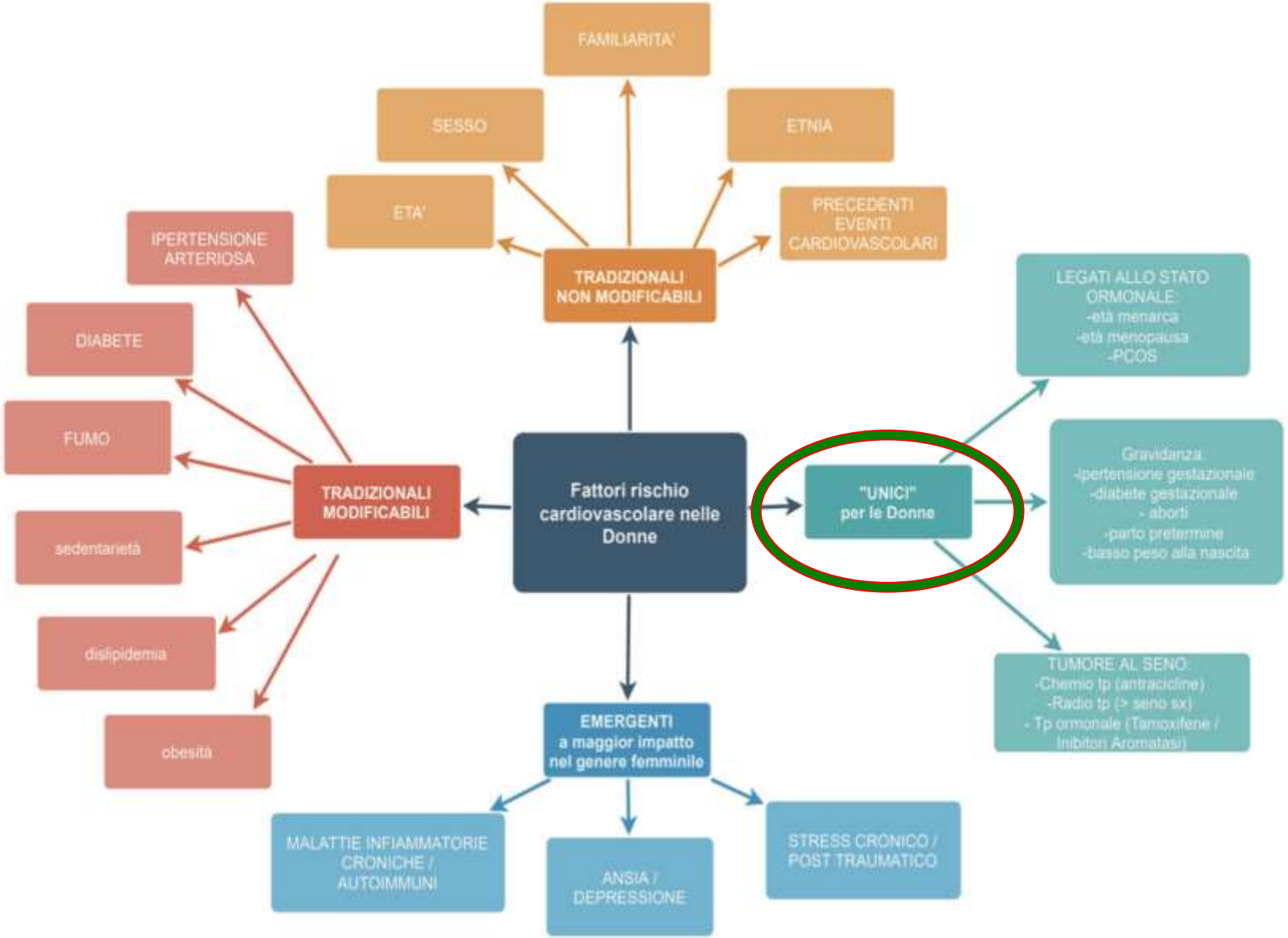


European Heart Journal (2003) 24, 2027–2037

Clinical research

Depression and cardiovascular morbidity and mortality: cause or consequence?

Ralph A. H. Stewart[a,f*], Fiona M. North[b], Teena M. West[a], Katrina J. Sharples[b], R. John Simes[c], David M. Colquhoun[d,e], Harvey D. White[a,e], Andrew M. Tonkin[g,h,i], for the Long-Term Intervention With Pravastatin in Ischaemic Disease (LIPID) Study Investigators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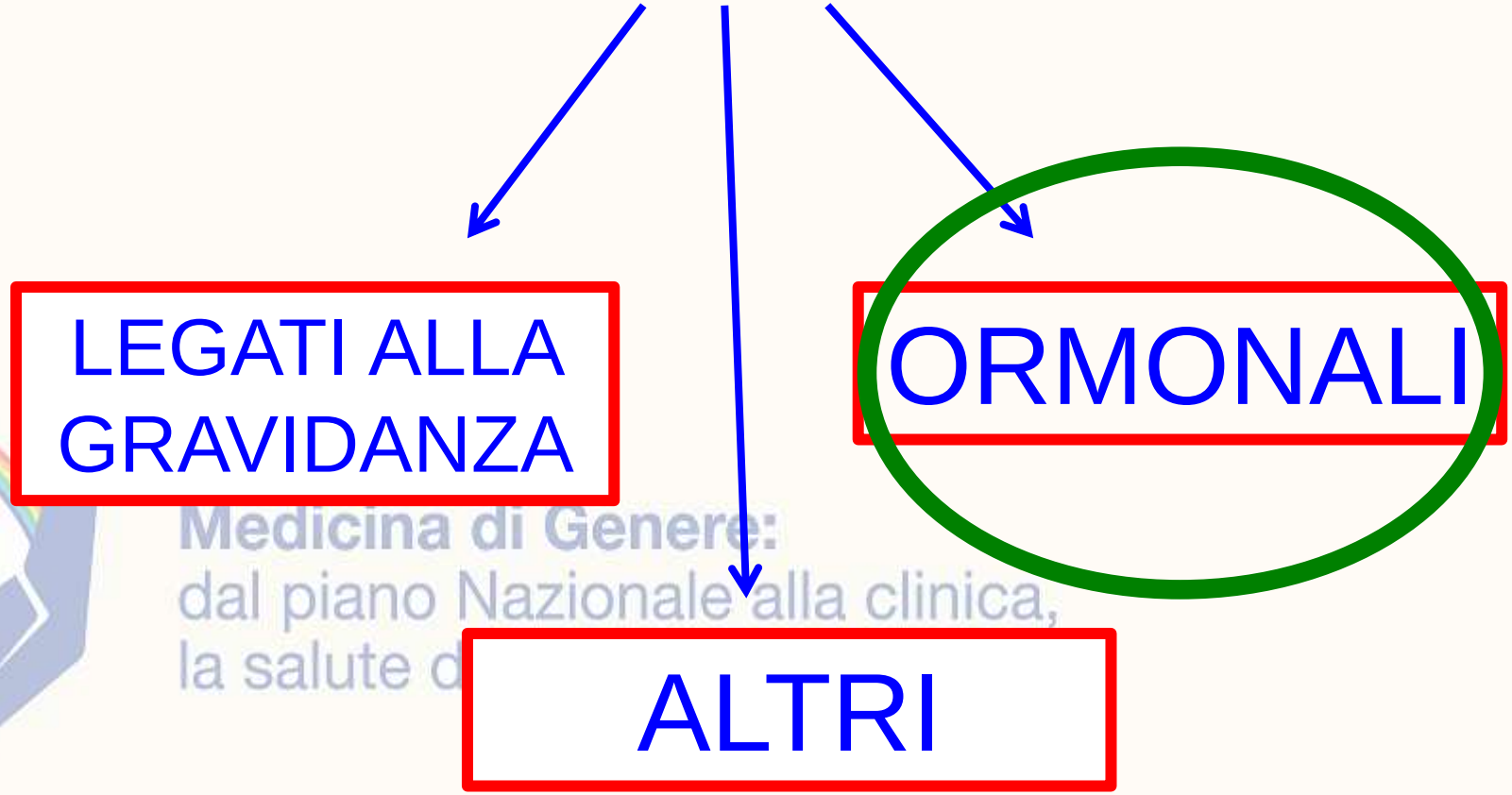
STRESS CRONICO / POST TRAUMATICO

FATTORI DI RISCHIO SPECIFICI PER LE DONNE:



Menarca precoce e tardivo

Circulation

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Home > Circulation > Vol. 131, No. 3 > Age at Menarche and Risks of Coronary Heart and Other Vascular Diseases in a La

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ARTICLE

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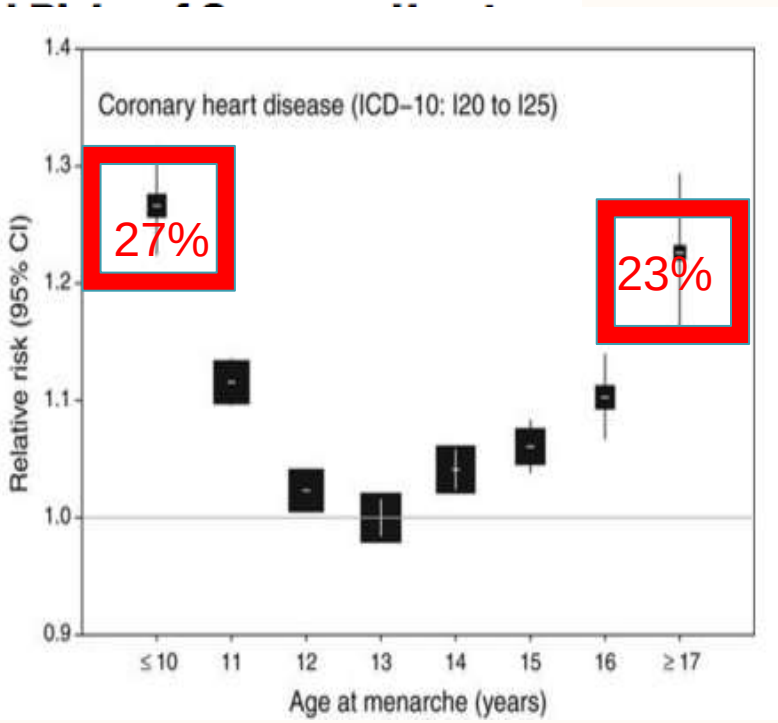
Age at Menarche and Other Vascul Cohort

Dexter Canoy, Valerie B Mary E. Kroll, Gillian K. Re and for the Million Women

Conclusions—

In this cohort, the relation of age at menarche to vascular disease risk was U shaped, with both early and late menarche being associated with increased risk. Associations were weaker for cerebrovascular and hypertensive disease than for CHD.



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Original Investigation FREE

October 2016

Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality

A Systematic Review and Meta-analysis

Taulant Muka, MD, PhD[1]; Clare Oliver-Williams, PhD[2]; Setor Kunutsor, MD, PhD[2]; et al

Findings In this meta-analysis of 32 observational studies, premature or early-onset menopause in women younger than 45 years were associated with an increased risk of coronary heart disease and all-cause mortality. Time since onset of menopause in relation to vascular outcomes was reported in 4 studies and showed inconsistent results.

Meaning Our findings underscore a potential increased risk of adverse cardiovascular outcomes in women who experience premature or early-onset menopause.

Menopausa precoce (POF)

scomparsa dei cicli mestruali ad un'età < 45 anni

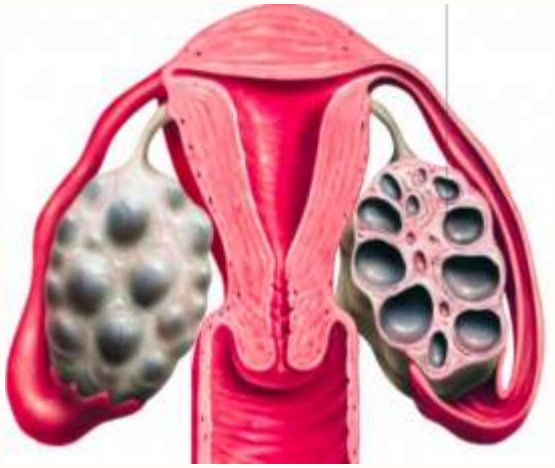
La menopausa:	
	FAVOREVOLE
Lipidi	↓ Colesterolo LDL ↑ Colesterolo HDL
Coagulazione	↓ Fibrinogeno
Infiammazione	↓ Molecole di adesione
Funzione endoteliale e pressione arteriosa	↓ Attività dell' enzima ACE ↑ Sintesi Ossido Nitrico ↓ Endotelina-1 ↓ Proliferazione delle cellule muscolari lisce

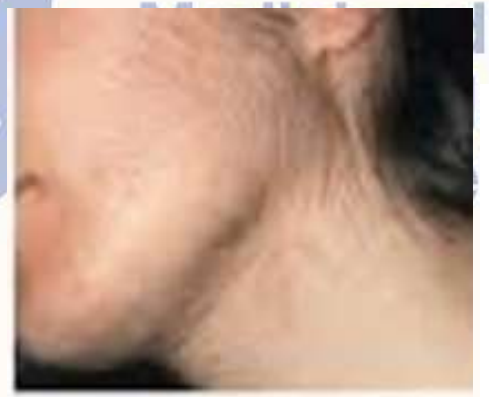
PCOS
(Sindrome dell'ovaio policistico)

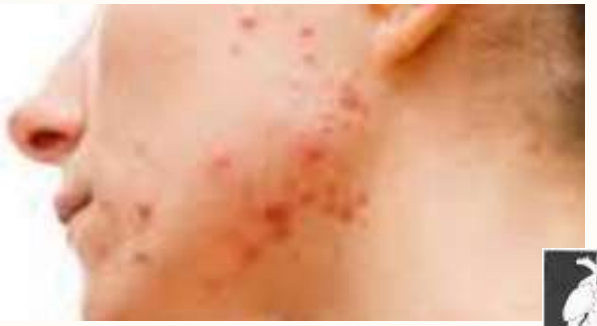
La PCOS è diagnosticata in presenza di due tra i tre criteri seguenti:

1. ovaie policistiche all'ecografia pelvica
2. oligo-anovulazione
3. evidenza clinica o biochimica di iperandrogenismo

(Rottherdam ESHRE-ASRM 2003)







PCOS
(Sindrome dell'ovaio policistico)

- Disordini mestruali
- Irsutismo
- Contraccezione
- Salute sessuale
- Infertilità

→

- Complicanze gravidiche
- Qualità della vita
- Diabete di Tipo 2
- Malattie Cardiovascolari
- Rischio Cancro (?)

Human Repreduction 2012, 27(1): 14-24

FATTORI DI RISCHIO SPECIFICI PER LE DONNE:

LEGATI ALLA GRAVIDANZA

ORMONALI

ALTRI

FR specifici per donne legati alla gravidanza

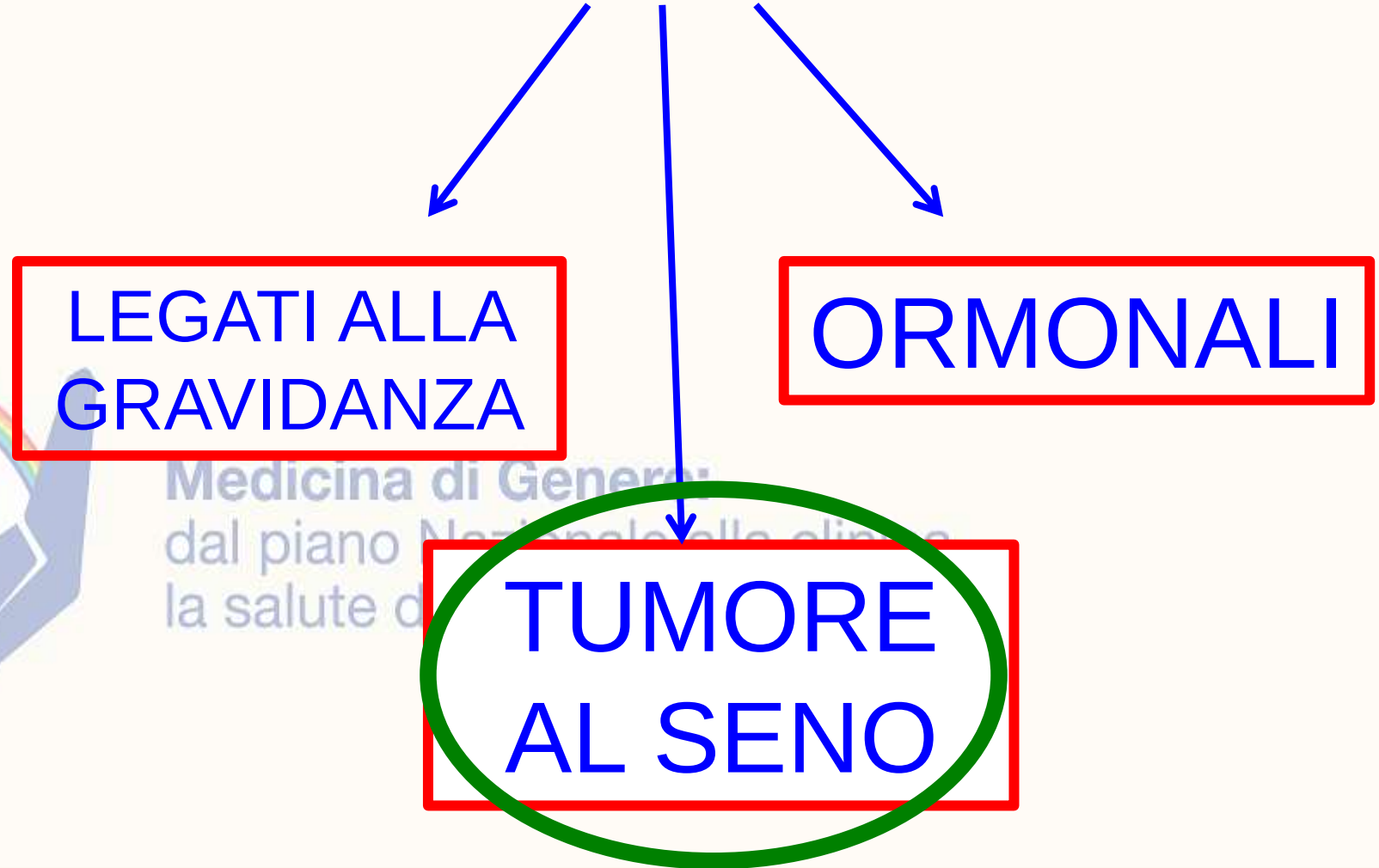
ABORTO SPONTANEO – maggiore rischio di infarto miocardico nel corso della loro vita, gli aborti ricorrenti possono essere associati a stati procoagulanti e proinfiammatori.

PARTO PRETERMINE - Le donne che hanno avuto un parto naturale prima delle 37 settimane di gestazione, sembrano avere un maggiore rischio di malattia CV

IPERTENSIONE GESTAZIONALE, PRE-ECLAMPISIA (ipertensione, proteinuria e/o edemi) **ED ECLAMPSIA** (convulsioni generalizzate dovute ad encefalopatia associata a pre-eclampsia) aumenta il rischio di sviluppare ipertensione post-partum, infarto miocardico ed ictus ed aumenta di 4 volte il rischio di svillupare diabete tipo 2; inoltre, i figli di madre con pre-eclampsia hanno un rischio > di sviluppare ipertensione arteriosa

DIABETE IN GRAVIDANZA - le donne che sviluppano DG hanno un rischio 7 volte più elevato di sviluppare DM di tipo 2, inoltre, aumenta anche il rischio di malattia CV indipendentemente dallo sviluppo di diabete manifesto. I figli nati da madri con DG hanno a loro volta un rischio maggiore di andare incontro ad intolleranza glucidica.

FATTORI DI RISCHIO SPECIFICI PER LE DONNE:



Tumore al seno

Circulation

AHA SCIENTIFIC STATEMENT

Cardiovascular Disease and Breast Cancer: Where These Entities Intersect

A Scientific Statement From the American Heart Association

ABSTRACT: Cardiovascular disease (CVD) remains the leading cause of mortality in women, yet many people perceive breast cancer to be the number one threat to women's health. CVD and breast cancer have several overlapping risk factors, such as obesity and smoking. Additionally, current breast cancer treatments can have a negative impact on cardiovascular health (eg, left ventricular dysfunction, accelerated CVD), and for women with pre-existing CVD, this might influence cancer treatment decisions by both the patient and the provider. Improvements in early detection and treatment of breast cancer have led to an increasing number of breast cancer survivors who are at risk of long-term cardiac complications from cancer treatments. For older women, CVD poses a greater mortality threat than breast cancer itself. This is the first scientific statement from the American Heart Association on CVD and breast cancer. This document will provide a comprehensive overview of the prevalence of these diseases, shared risk factors, the cardiotoxic effects of therapy, and the prevention and treatment of CVD in breast cancer patients.

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CHEMIOTERAPIA

European Heart Journal (2016) 37, 2768–2801
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

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the European Society of Cardi

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Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m² 550 mg/m² 700 mg/m²	 3–5 7–26 18–48
Idarubicin (>90 mg/m²)	5–18
Epirubicin (>900 mg/m²)	0.9–11.4
Mitoxanthone >120 mg/m²	2.6
Liposomal anthracyclines (>900 mg/m²)	2
Alkylating agents	
Cyclophosphamide	7–28
Ifosfamide <10 g/m² 12.5–16 g/m²	 0.5 17
Antimetabolites	
Clofarabine	27

RADIOTERAPIA

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2013 VOL. 368 NO. 11

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

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ennet, Ph.D.,
utter, F.R.C.R.,
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ll, Ph.D.

BACKGROUND
Radiotherapy for breast cancer o
to ionizing radiation. The effect
heart disease is uncertain.

METHODS
We conducted a population-base
myocardial infarction, coronary
disease) in 2168 women who u
1958 and 2001 in Sweden and D
coronary events and 1205 cont
from hospital records. For each w
and to the left anterior descendi
therapy chart.

RESULTS
The overall average of the mean
27.72). Rates of major coronary
heart by 7.4% per gray (95% con
parent threshold. The increase
and continued into the third de
in the rate of major coronary
women without cardiac risk fact

CONCLUSIONS
Exposure of the heart to ionizi
increases the subsequent rate o
tional to the mean dose to the h
continues for at least 20 years.
greater absolute increases in risk
Cancer Research UK and others.

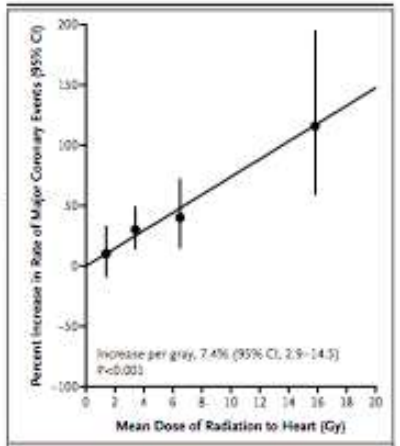

Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

Major coronary events included myocardial infarction, coronary revascularization, and death from ischemic heart disease. The values for the solid line were calculated with the use of dose estimates for individual women. The circles show values for groups of women, classified according to dose categories; the associated vertical lines represent 95% confidence intervals. All estimates were calculated after stratification for country and for age at breast-cancer diagnosis, year of breast-cancer diagnosis, interval between breast-cancer diagnosis and first major coronary event for case patients or index date for controls (all in 5-year categories), and presence or absence of a cardiac risk factor. The radiation categories were less than 2, 2 to 4, 5 to 9, and 10 Gy or more, and the overall averages of the mean doses to the heart of women in these categories were 1.4, 3.4, 6.5, and 15.8 Gy, respectively.

Clinical Trial Service Unit
M., D.C., R.P., C.T.) and the
ntre for Healthcare Innovation
rsity of Oxford, Oxford, and
ment of Medical Physics, Royal
ity Hospital and Surrey Univer-
ord (A.N.) — both in the Unit-
n; the Department of Oncolo-
University Hospital, Institute
Research, University of South-
rk, Odense (M.E.), the Oncol-
tment, Aalborg Hospital, Aal-
), and the Danish Breast
operative Group, Rigshospi-
hagen (M.-B.J.) — all in Den-
Department of Medical Epide-
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ision of Cardiovascular Epide-
stitute of Environmental Med-
Division of Cardiovascular
Department of Clinical Sci-
deryd Hospital (B.G.), Karolin-
et, and the Departments of
(U.B.-G.) and Medical Physics
olinska University Hospital —
holm; and the H. Lee Moffitt
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2013;368:987-98.
6/NEJMoa1209825

Il tasso di eventi coronarici aumenta del **7,4% per ogni aumento di 1 Gy** della dose di radiazione

Prevenire è meglio che curare…
ma per prevenire bisogna conoscere

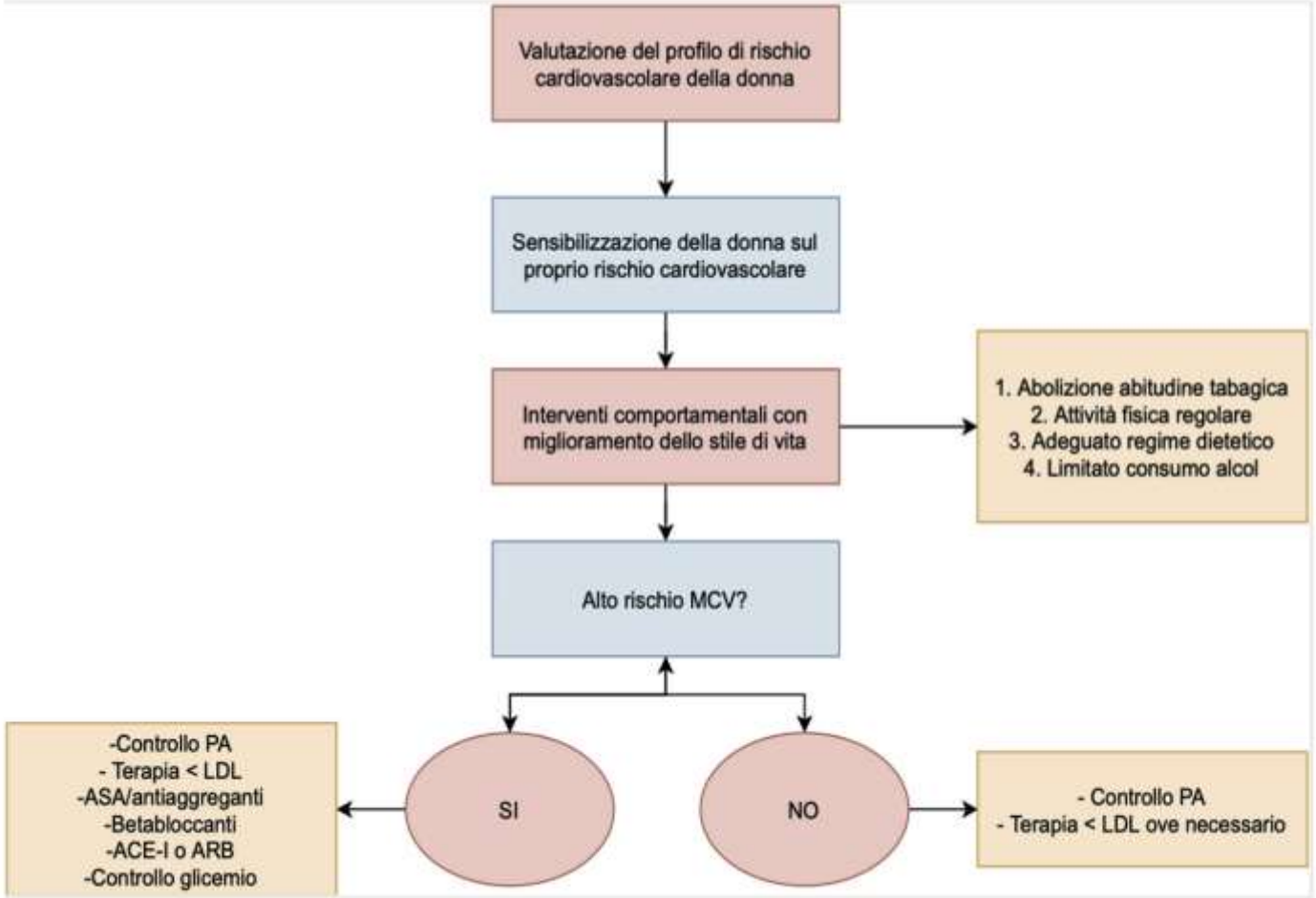

Figura 32. Algoritmo per la prevenzione cardiovascolare nelle donne.

La Donna vive di più,
ma con maggiori comorbilità, che condizionano la sua qualità di vita.

Occorrono maggiori conoscenze, più sensibilità

e mirati programmi di prevenzione

per rendere la vita delle Donne

Età di Serenità

piuttosto che era di malattie

e di invalidità

Medicina di Genere:
dal piano Nazionale alla clinica,
la salute delle differenze

Buona prevenzione
e grazie per l'attenzione!

Medicina di Genere:
dal piano Nazionale alla clinica,
la salute delle differenze

TERAPIA ORMONALE

Effettuata per i tumori ER e/o PR positivi include

- Tamoxifene nelle donne in pre-menopausa
- inibitori dell'aromatasi in quelle i post-menopausa

Diversi studi hanno evidenziato un trend verso una maggiore incidenza di tossicità CV degli **inibitori dell'aromatasi** rispetto al Tamoxifene che, avendo un impatto favorevole sul profilo lipidico, ha un effetto cardioprotettivo.