



Cause ambientali delle principali patologie cronico-degenerative ed oncologiche

Sansepolcro, 22 Gennaio 2020



Agostino DI CIAULA
Presidente Comitato Scientifico ISDE



January 2019



United Nations
Environment Assembly of the
United Nations Environment
Programme

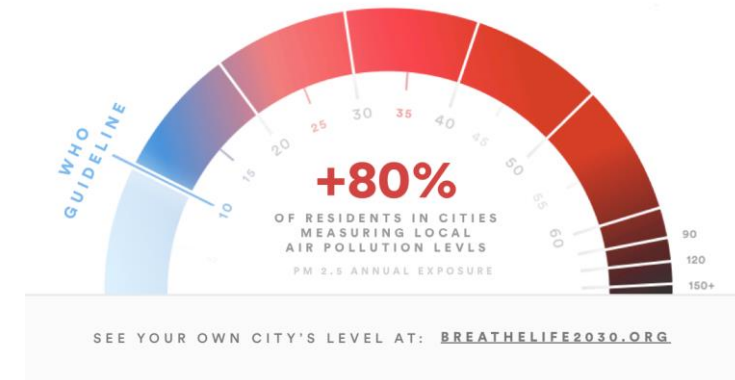
- Nel 2018 commercializzate circa 60,000 sostanze chimiche diverse, il 62% pericolose per la salute umana
- Il ritmo di crescita della produzione di sostanze chimiche supererà quello della popolazione mondiale entro il 2030
- I processi di produzione, l'utilizzo e lo smaltimento dei prodotti contaminano aria, acqua, suolo, cibo, oggetti, oltre a generare enormi quantità di rifiuti
- Meno del 9% dei rifiuti plastici viene riciclato. Il 12% è incenerito, il 79% finisce in discarica o nell'ambiente
- La produzione di 1Kg di farmaco genera, in media, almeno 25Kg di emissioni, 25-100Kg di rifiuti e quantità difficilmente calcolabili di gas clima-alteranti



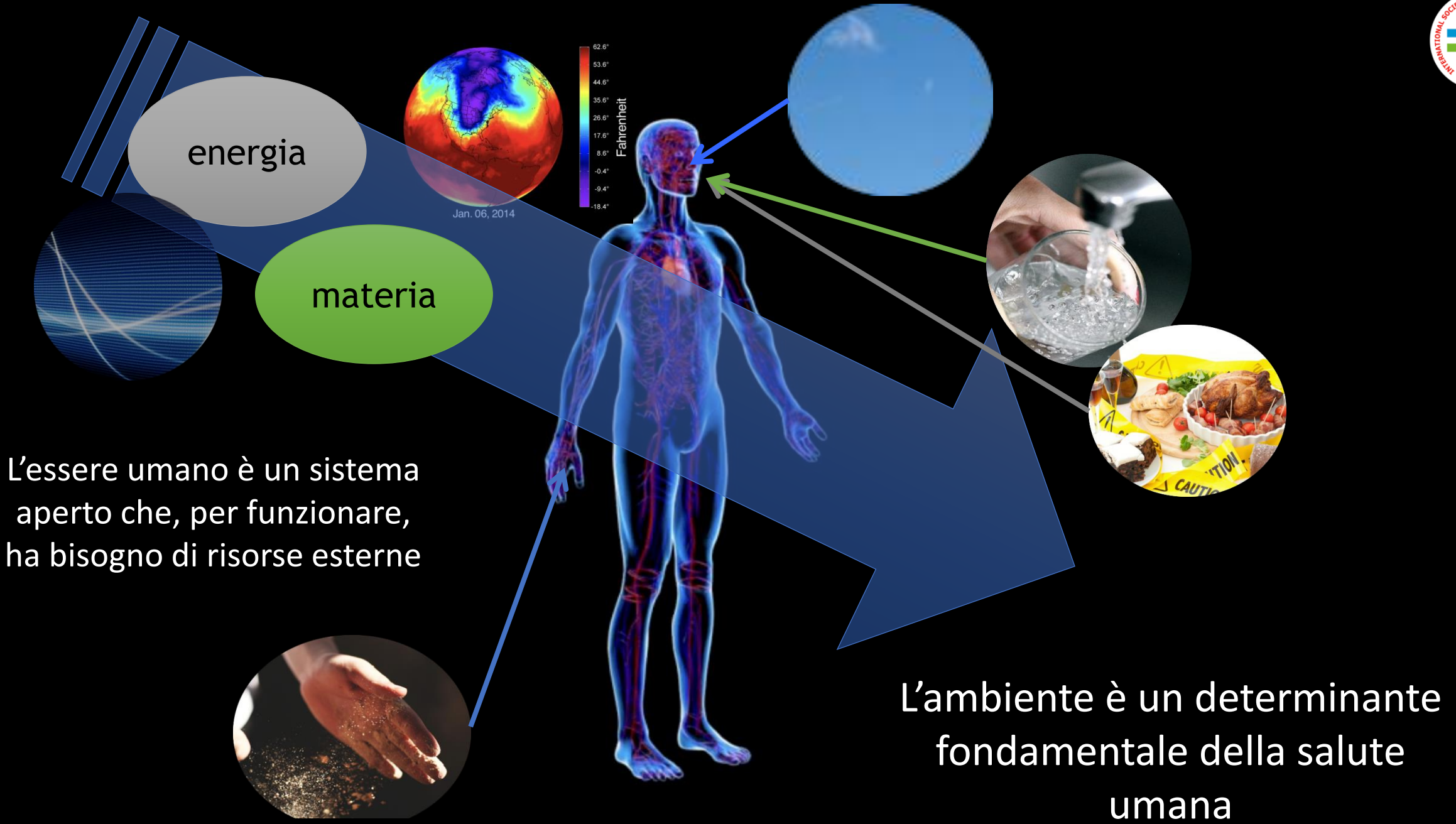
World Health
Organization

AIR POLLUTION ISSUE GLOBALLY

Over 80% of urban residents are exposed to air quality levels that exceed WHO limits

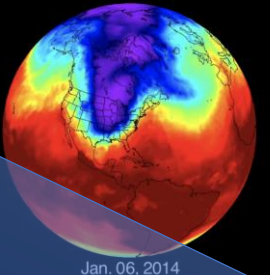


50 milioni di utenze cellulari attive in Italia



energia

materia



Fahrenheit
62.6°
53.6°
44.6°
35.6°
26.6°
17.6°
8.6°
-0.4°
-9.4°
-18.4°

L'essere umano è un sistema aperto che, per funzionare, ha bisogno di risorse esterne

L'ambiente è un determinante fondamentale della salute umana

1 Ischaemic heart disease	-33.6% (-37.8 to -29.0)
2 Low back pain	11.2% (5.0 to 17.3)
3 Alzheimer's disease and other dementias	77.9% (68.4 to 87.2)
4 Diabetes	36.6% (23.1 to 50.4)
5 Headache disorders	4.5% (1.1 to 8.2)
6 Stroke	-32.9% (-37.1 to -28.2)
7 Tracheal, bronchus, and lung cancer	-14.9% (-20.7 to -8.8)
8 Neck pain	25.3% (21.9 to 28.9)
9 Chronic obstructive pulmonary disease	12.1% (3.8 to 20.6)
10 Age-related and other hearing loss	54.8% (50.3 to 60.2)
11 Falls	11.9% (7.3 to 15.8)
12 Depressive disorders	-1.7% (-6.7 to 3.3)
13 Colon and rectum cancer	9.7% (1.1 to 18.6)
14 Anxiety disorders	2.0% (-3.4 to 7.9)
15 Breast cancer	-8.3% (-17.4 to 0.4)
16 Road injuries	-53.4% (-57.2 to -49.5)
17 Other musculoskeletal disorders	27.6% (15.7 to 40.9)
18 Cirrhosis and other chronic liver diseases	-43.1% (-48.1 to -38.1)
19 Hypertensive heart disease	45.1% (-7.6 to 62.4)
20 Blindness and vision impairment	28.0% (24.3 to 32.2)
21 Pancreatic cancer	39.7% (28.4 to 51.7)
22 Chronic kidney disease	16.1% (8.7 to 24.1)
23 Stomach cancer	-42.2% (-46.6 to -37.7)
24 Liver cancer	-0.6% (-10.2 to 10.1)
25 Neonatal disorders	-50.8% (-58.7 to -42.6)

29 Congenital birth defects	-37.9% (-45.7 to 27.1)
30 Drug use disorders	-26.3% (-33.1 to -19.8)
31 Self-harm	-25.5% (-31.6 to -18.7)
42 Cardiomyopathy and myocarditis	-62.8% (-67.2 to 49.4)

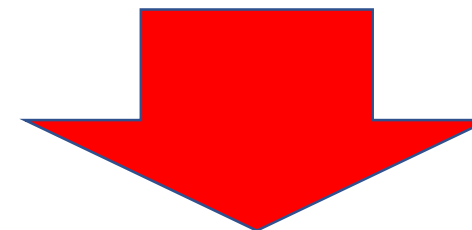
Le principali 25 cause di disabilità in Italia

- confronto con anno 2010 -
(Lancet Public Health, GBD, nov. 2019)

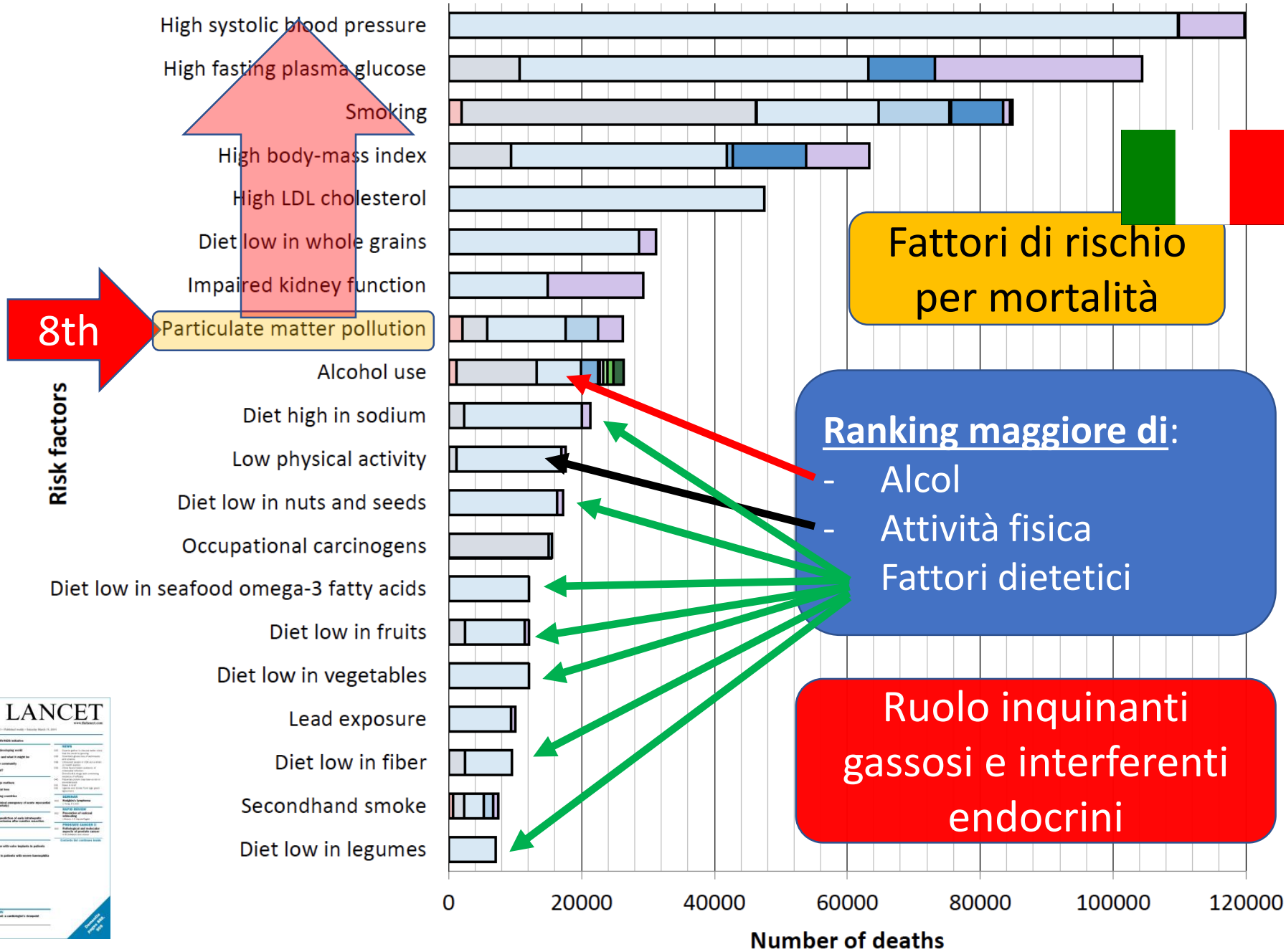


Cardiopatia e encefalopatia ischemica: conservano ruolo di rilievo, anche se in decremento

- Alzheimer e demenze + 78% (3° posto)
- Diabete + 36.6% (4° posto)
- Cardiopatia ipertensiva +45%
- BPCO +12%
- IRC + 16%
- K colon +9.7%
- K pancreas +40%



Vistoso incremento epidemiologico nonostante diagnosi sempre più precoci e terapie sempre più efficaci



- HIV/AIDS and sexually transmitted infections
- Respiratory infections and tuberculosis
- Enteric infections
- Neglected tropical diseases and malaria
- Other infectious diseases
- Maternal and neonatal disorders
- Nutritional deficiencies
- Neoplasms
- Cardiovascular diseases
- Chronic respiratory diseases
- Digestive diseases
- Neurological disorders
- Mental disorders
- Substance use disorders
- Diabetes and kidney diseases
- Skin and subcutaneous diseases
- Sense organ diseases
- Musculoskeletal disorders
- Other non-communicable diseases
- Transport injuries
- Unintentional injuries
- Self-harm and interpersonal violence





**American
Heart
Association®**

Particulate Matter Air Pollution and Cardiovascular Disease An Update to the Scientific Statement From the American Heart Association

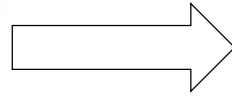
Robert D. Brook, MD, Chair; Sanjay Rajagopalan, MD; C. Arden Pope III, PhD;
Jeffrey R. Brook, PhD; Aruni Bhatnagar, PhD, FAHA; Ana V. Diez-Roux, MD, PhD, MPH;
Fernando Holguin, MD; Yuling Hong, MD, PhD, FAHA; Russell V. Luepker, MD, MS, FAHA;
Murray A. Mittleman, MD, DrPH, FAHA; Annette Peters, PhD; David Siscovick, MD, MPH, FAHA;
Sidney C. Smith, Jr, MD, FAHA; Laurie Whitsel, PhD; Joel D. Kaufman, MD, MPH; on behalf of the
American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in
Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism

“Short-term increases in PM_{2.5} levels lead to the early mortality of tens of thousands of individuals per year in the United States alone”

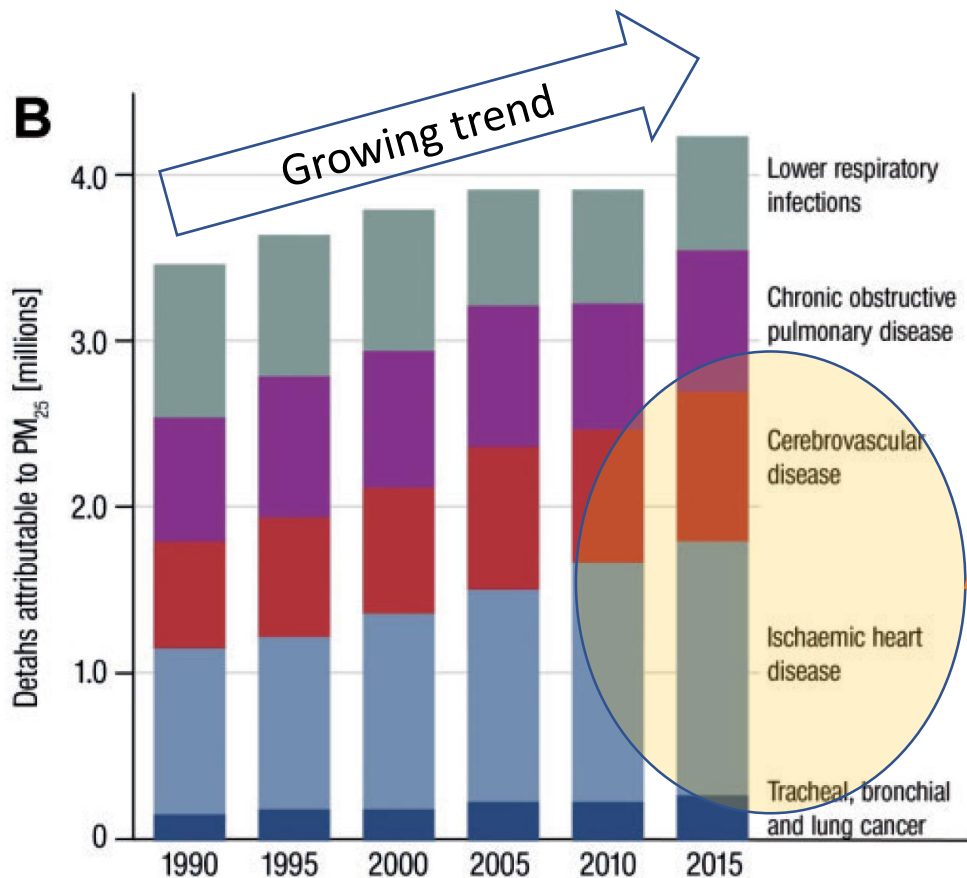
- Short term: RR of **daily cardiovascular mortality** increases **0.4% to 1.0% per 10µg/m³** increase in mean 24-hour PM_{2.5} (more evident in susceptible people)
- Long term: RR increase between **6% and 76%** per 10 µg/m³ PM_{2.5}
→ ***Rischio molto più elevato per esposizioni croniche !!***

The Lancet: Global Burden of Diseases Study

Ambient particulate matter
(*group 1 IARC*)



9 million premature deaths/yr



- “three times more deaths than from AIDS, TBC and malaria combined”

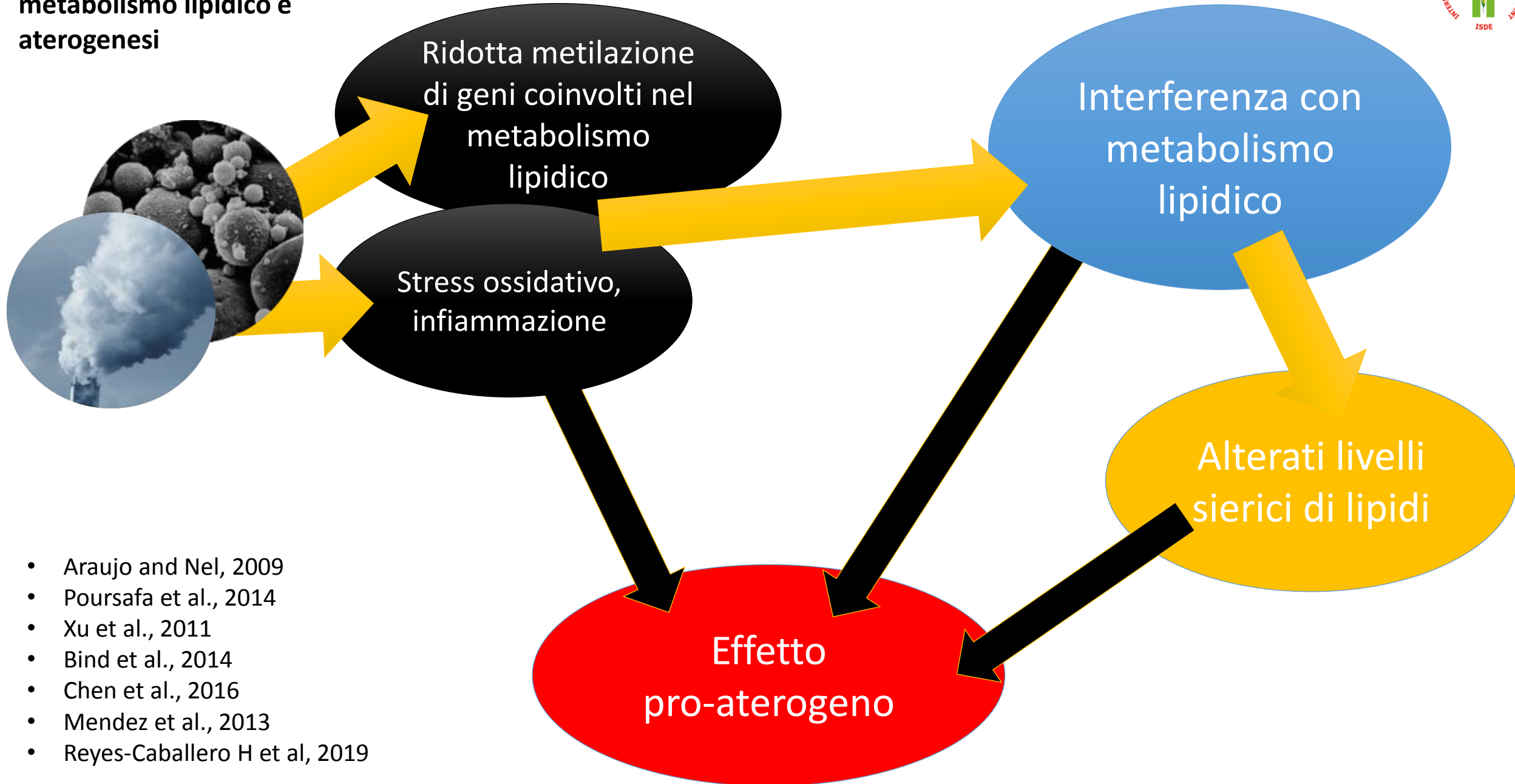
- “15 times more than from all wars and other forms of violence”



Atherogenesis-linked

→ Indirect and direct **METABOLIC** effects of pollution

Effetto diretto su metabolismo lipidico e aterogenesi

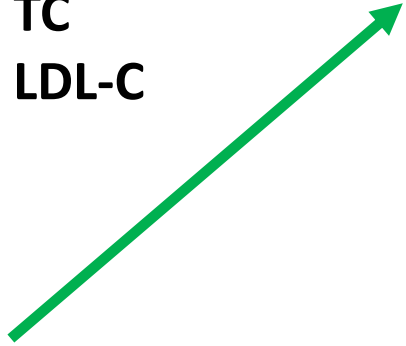


- Araujo and Nel, 2009
- Poursafa et al., 2014
- Xu et al., 2011
- Bind et al., 2014
- Chen et al., 2016
- Mendez et al., 2013
- Reyes-Caballero H et al, 2019

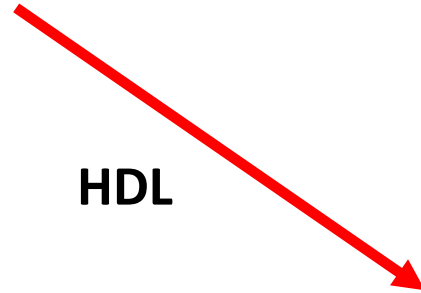
Inquinamento atmosferico (PM10, PM2.5, NO2) e dislipidemie

Relazione lineare e senza soglia

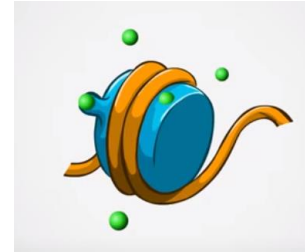
TC
LDL-C



HDL



Alterazioni epigenetiche, mitocondriali e citoplasmatiche



Effetti più evidenti:
M, >65 anni, obesi, diabetici

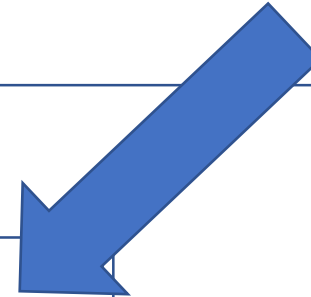
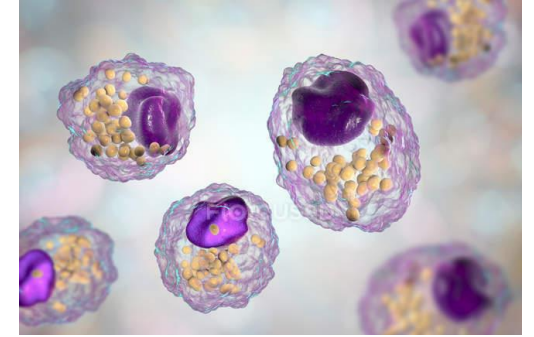


- Sørensen M et al, Environ International 2015
- Mao S et al, Environ Pollution 2019
- Adar SD et al, PLOS med 2013
- Kalsch H et al, Eur Heart Journal 2014
- Kaufman JL et al, Lancet 2016
- Yitshak et al, J Clin Endocrinol Metab 2016

Non solo dislipidemia !



- Accumulo lipidi intracellulari
- Incremento ox-LDL
- Incremento ROS
- Danno mitocondriale
- Apoptosi

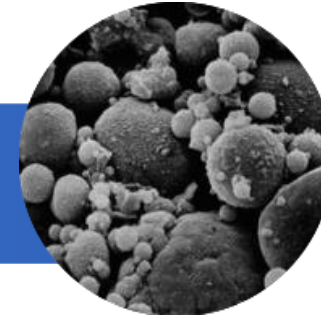


Formazione e progressione
lesione vascolare

- Adar SD et al, PLOS Med 2013
- Liu J et al, Environ Poll 2019
- Reyes-Caballero H et al, Nature Sci Rep 2019
- Rao X et al, Circul Res 2014
- Araujo J et al, Particle and Fibre Toxicol 2009
- Nelsey RH et al, Environ Epigen 2017
- Kaufman JD et al, Lancet 2016
- Yang S et al, European Heart Journal 2019

Metabolic effects of particulate matter: *INSULIN* resistance

- Di Ciaula et al, Curr Med Chem 2019
- Di Ciaula A, Porticasa P, Springer Ed. 2020
- Di Ciaula A. EJIM 2014



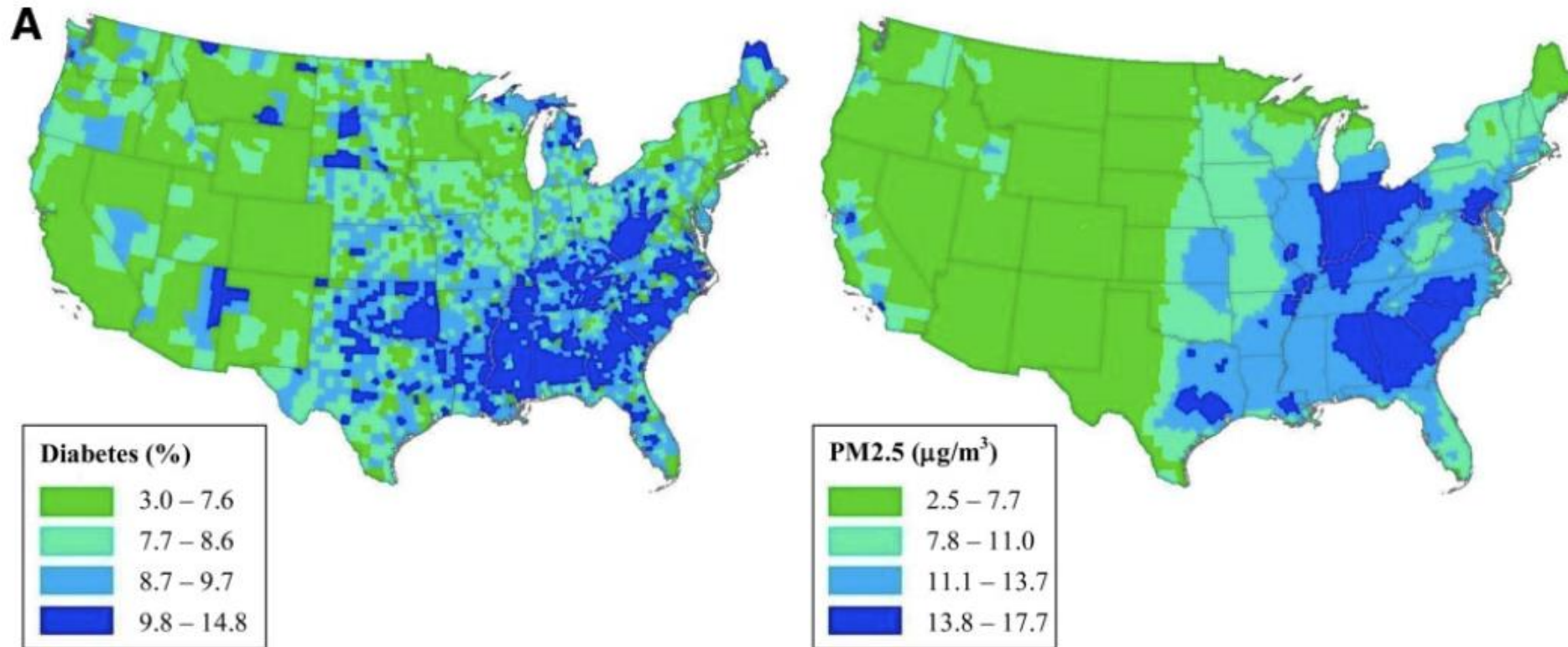
- **Chronic systemic low-grade inflammation**
- Oxidative stress altering insulin signaling cascades
- Mitochondrial alterations
- **Direct actions on insulin signaling**
- **Altered expression or synthesis of molecules causally related to IR**
(adipokines, inflammatory mediators)

Insulin Resistance

- Obesity
- Diabetes
- MetS
- Cancer

Diabetes prevalence increment with increasing PM_{2.5} concentrations (+ 1% increase each 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} exposure)

Association of particulate matter and diabetes





Contents available at ScienceDirect

Diabetes Research
and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres



International
Diabetes
Federation



Type I diabetes in paediatric age in Apulia (Italy): Incidence and associations with outdoor air pollutants

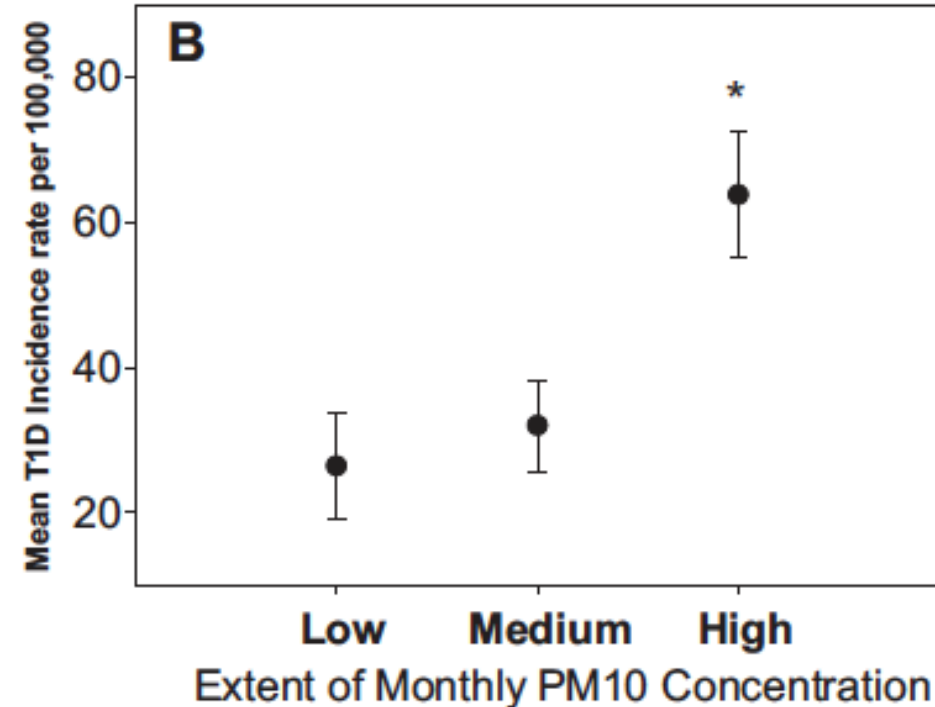


Agostino Di Ciaula ^{a,b,*}

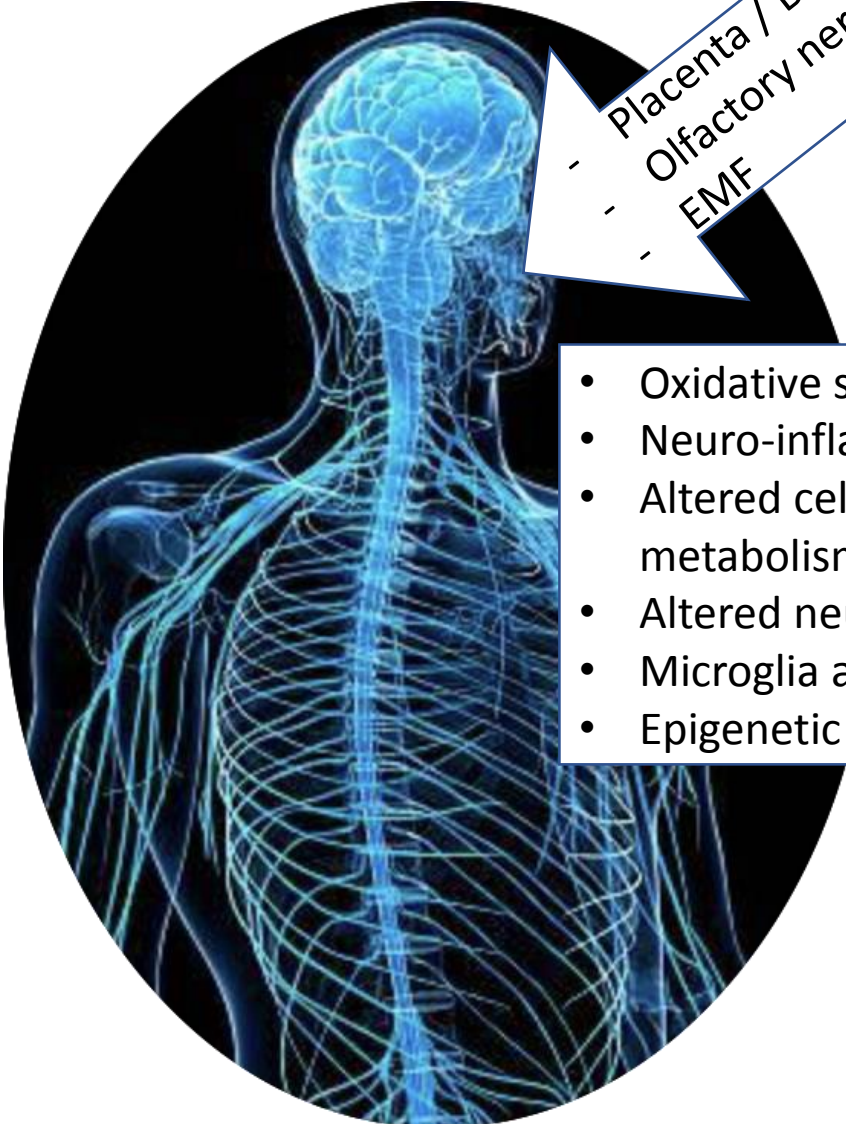
^aDivision of Internal Medicine, Hospital of Bisceglie (ASL BAT), Bisceglie, Italy

^bInternational Society of Doctors for Environment (ISDE), Arezzo, Italy

631,275 subjects 0-14 yrs
1,501 T1D children
Period: 2001-2013



Neurologic effects of pollutants



Placenta / BBB
Olfactory nerves
EMF

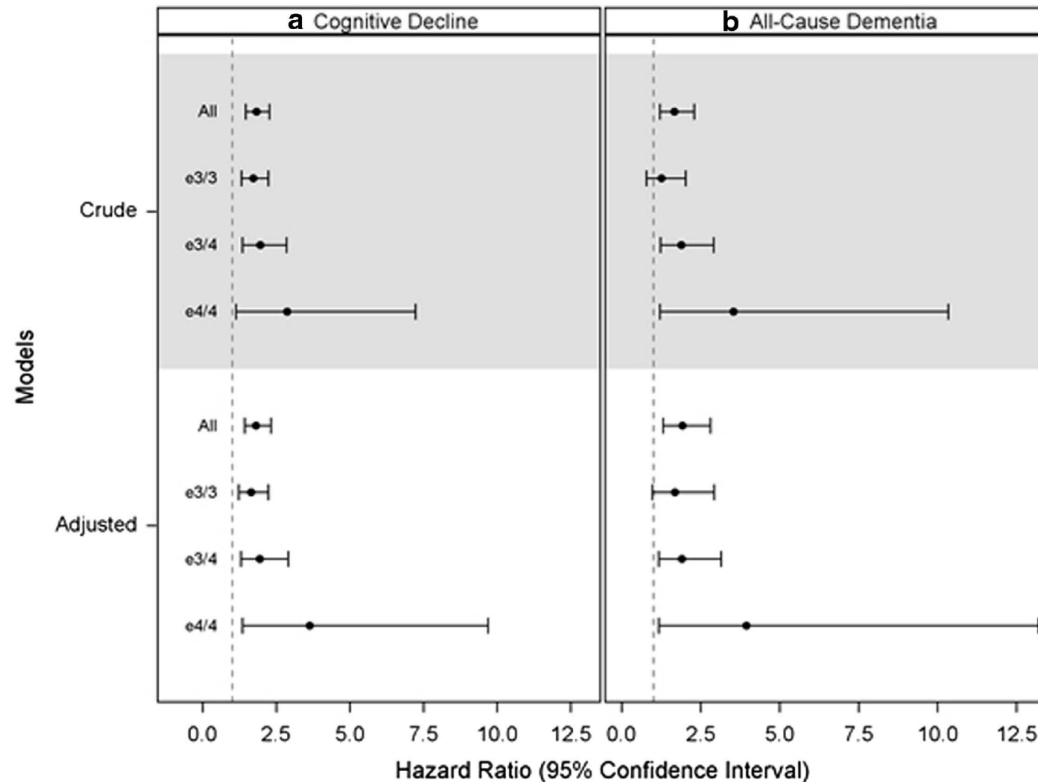
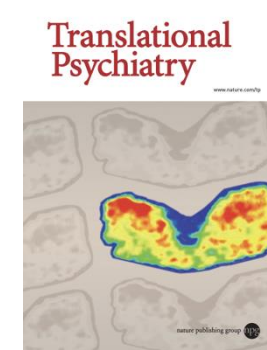
Sintesi delle evidenze disponibili



- Oxidative stress
- Neuro-inflammation and neuro-degeneration
- Altered cell proliferation, differentiation and metabolism
- Altered neuro-transmissions
- Microglia activation
- Epigenetic mechanisms

- Neuro-developmental alterations
- Disabilities
- Late neuro-cognitive effects
- Extrapiramidal disorders (PD)
- Neuro-psychiatric disorders
- Cancer

Particulate air pollutants, APOE alleles and their contributions to **cognitive impairment** in older women and to amyloidogenesis in experimental models.
(Cacciottolo M et al, Transl Psychiatry 2017)



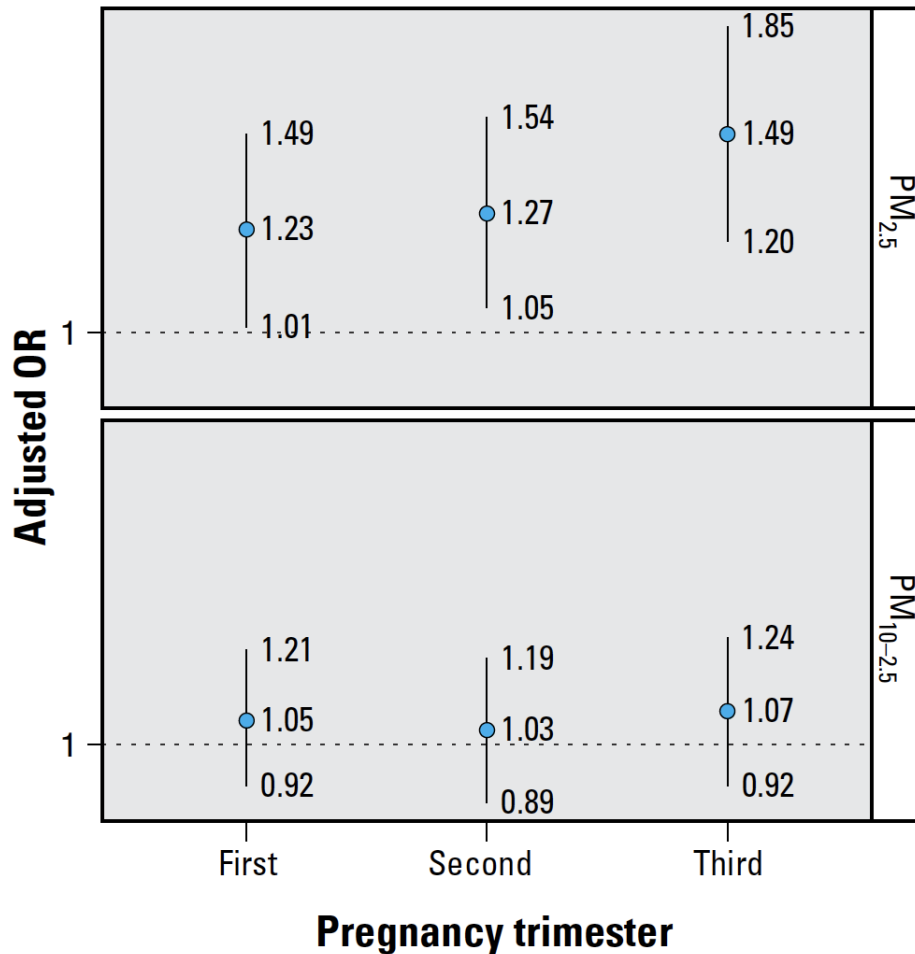
Residing in places with fine PM > EPA standards (PM2.5 concentrations above 12 µg/m³):

Increased risks for

- global cognitive decline (+81%)
- all-cause dementia (+92%)

Stronger adverse effects in APOE ε4/4 carriers

Esposizione prenatale

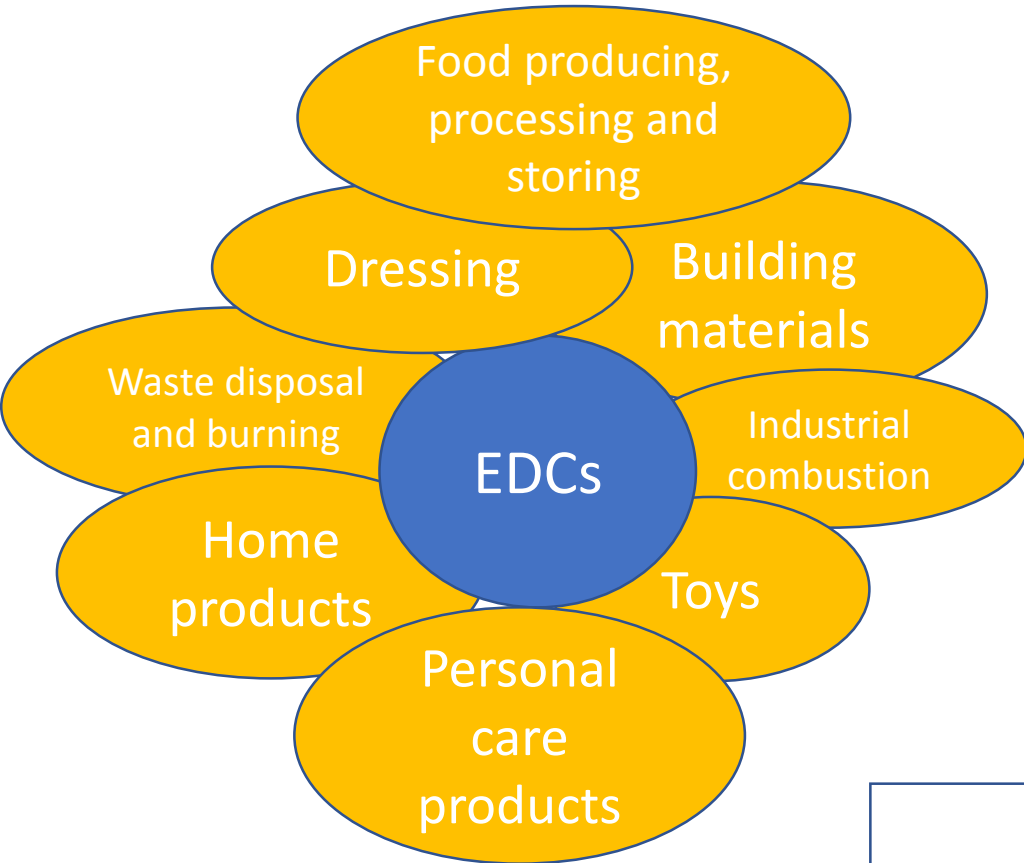


- nested case-control study of participants in the Nurses' Health Study II (NHS II)
- Monthly average of **PM2.5 and PM10**, georeferentiation, adjustment for confounders
- **Higher maternal exposure to PM2.5** (not PM10) during pregnancy was associated with **greater odds of a child having ASD**

Altri due studi caso-controllo (2013) avevano mostrato risultati simili (esposizione in gravidanza a PM2.5):

- JAMA Psych 2013;70(1):71-7
- EHP 2013;121(3):380-6

Endocrine Disrupting Chemicals (pesticides, POPs, PCB, PFAS, BPA, phatalates...)



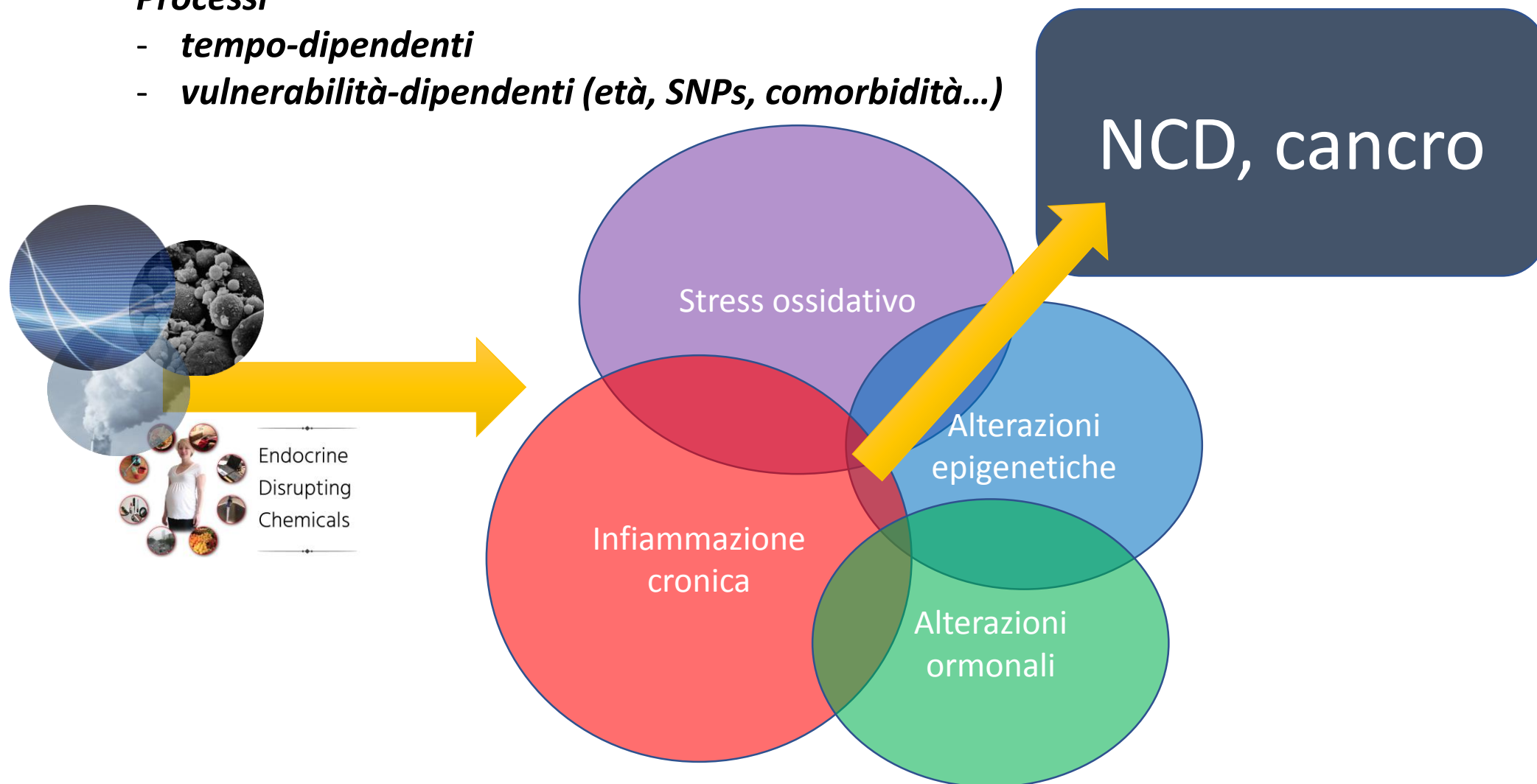
- Chronic inflammation
- Altered immunologic response
- Altered adipogenesis / fat storage
- Altered cell differentiation / maturation
- Altered liver and pancreatic function
- Neurologic effects (mainly CNS)
- Receptor agonism / antagonism
- Altered adipokines levels
- Epigenetic mechanisms
- ***Linear, but also non-monotonic dose-response curves***

- Metabolic effects
- Neuro-developmental effects
- Endocrine disorders
- Cancer onset/progression

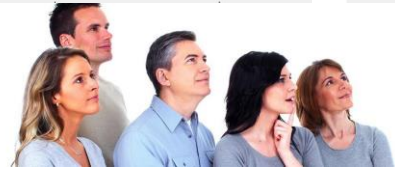
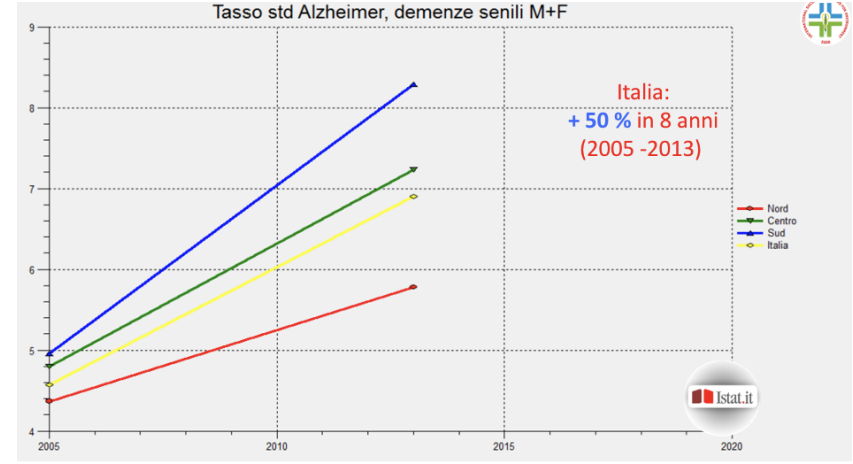
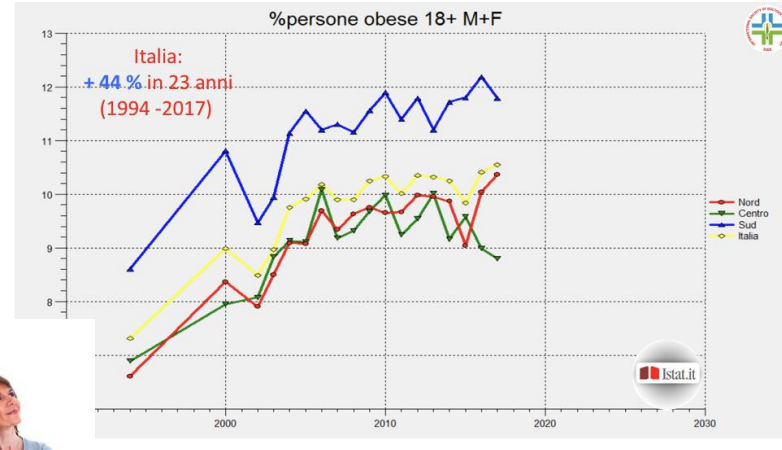
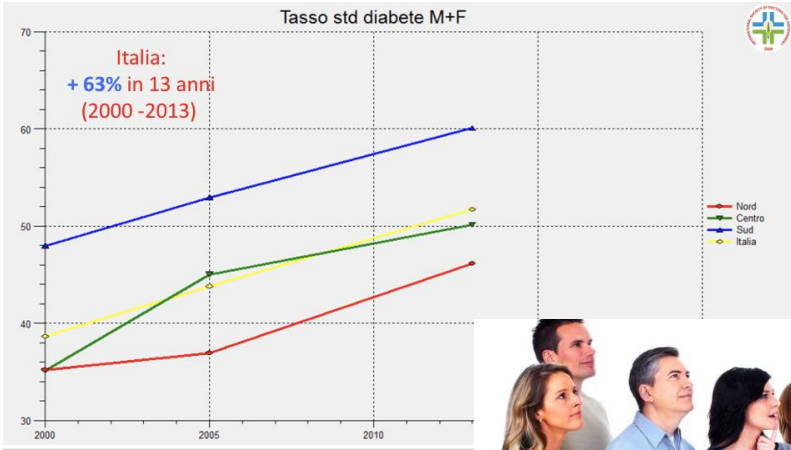
Dall'esposizione alla patologia → meccanismi di azione comuni

Processi

- *tempo-dipendenti*
- *vulnerabilità-dipendenti (età, SNPs, comorbidità...)*

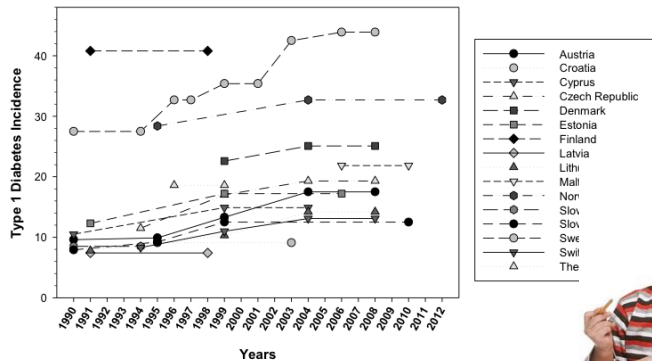


L'epidemia delle malattie non-comunicabili

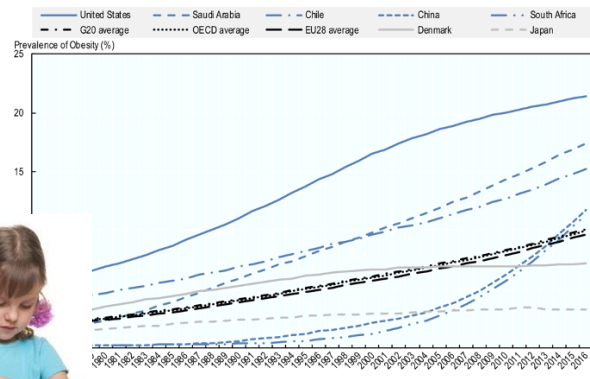


Type 1 Diabetes Epidemic in Europe

(A. Di Ciaula, Adv. in Res 2014)

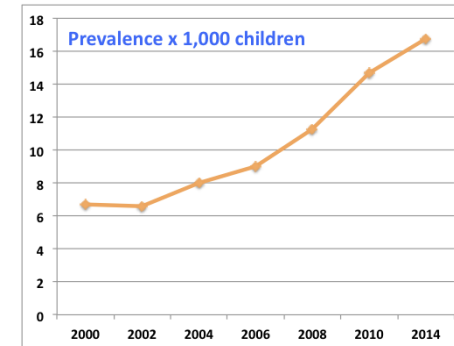


Obesity trends in children aged 5 to 19 from 1975 to 2016



Organizzazione per la cooperazione e lo sviluppo economico (OECD) - 2019

The Autism epidemic



year	1 in X children
2000	1 in 150
2002	1 in 150
2004	1 in 125
2006	1 in 110
2008	1 in 88
2010	1 in 68
2014	1 in 59

Source: USA CDC - data from ADDM Network 2000 - 2014

Cancer in children

Eva Steliarova-Foucher et al, Lancet oncol 2017

“Since the 1980s, the global age-standardised **incidence** rates of registered cancers in children aged 0–14 years **has increased** from **124.0** (95% CI 123.3–124.7) to **140.6** (140.1–141.1) per million person-years”.

Incidenza più alta in Europa meridionale (Croazia, Cipro, **Italia**, Malta, Portogallo, Spagna)

6 registri (Umbria, Modena, Parma e Romagna, Taranto, BAT) superano i 200 casi (0-14 anni) per milione/anno, rispetto a una media globale di 140 nel 2010

- Tra 1 e 14 anni di età il **26,1% dei decessi** è dovuto ai tumori, che rappresentano la **prima causa di morte** (ISTAT)
- Ruolo limitato per dieta e stili di vita

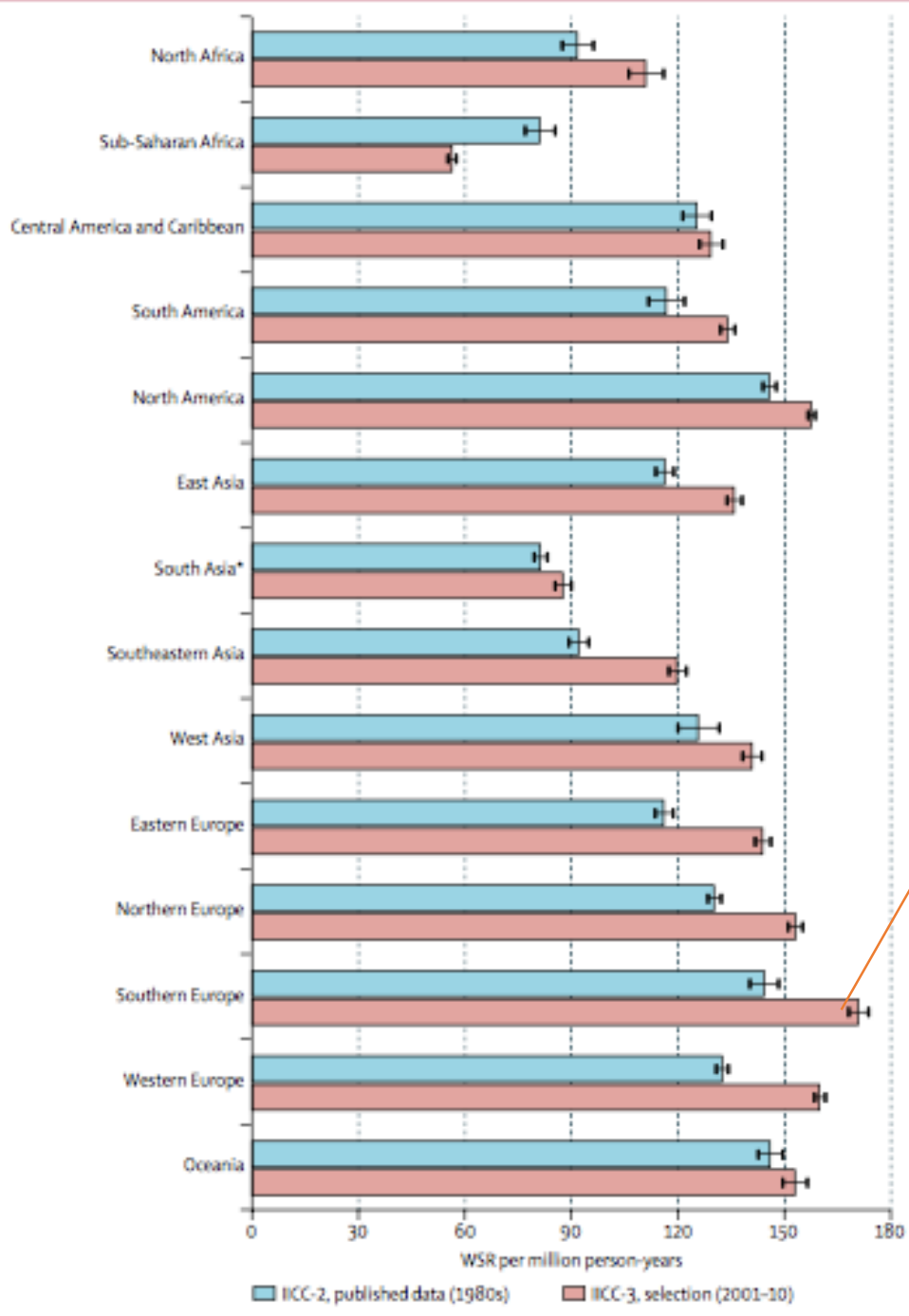


Figure 5: Comparison of incidence of neoplasms in children aged 0–14 years in 1980–89 and 2001–10, by region

Il cancro nell'adulto

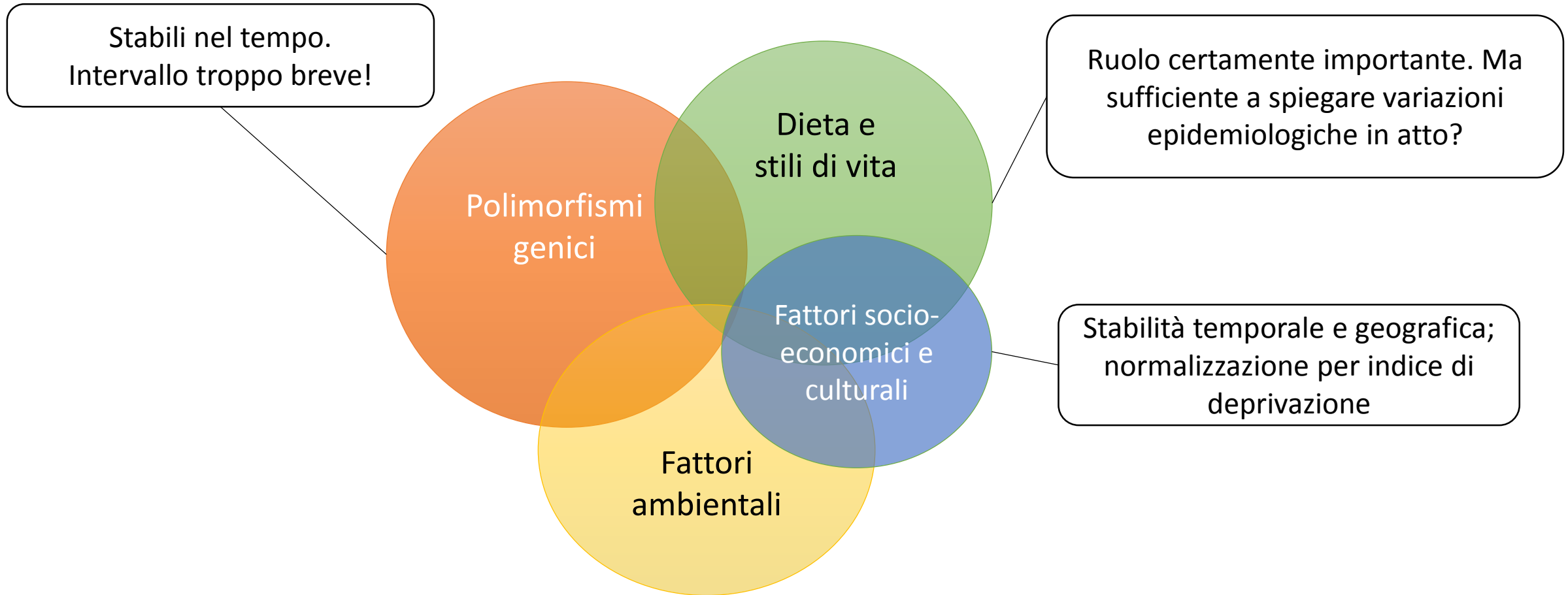
Incidenza in **riduzione**

- Stomaco
- Colon-retto
- Polmone (uomini)
- Prostata
- Utero

Incidenza in **aumento**

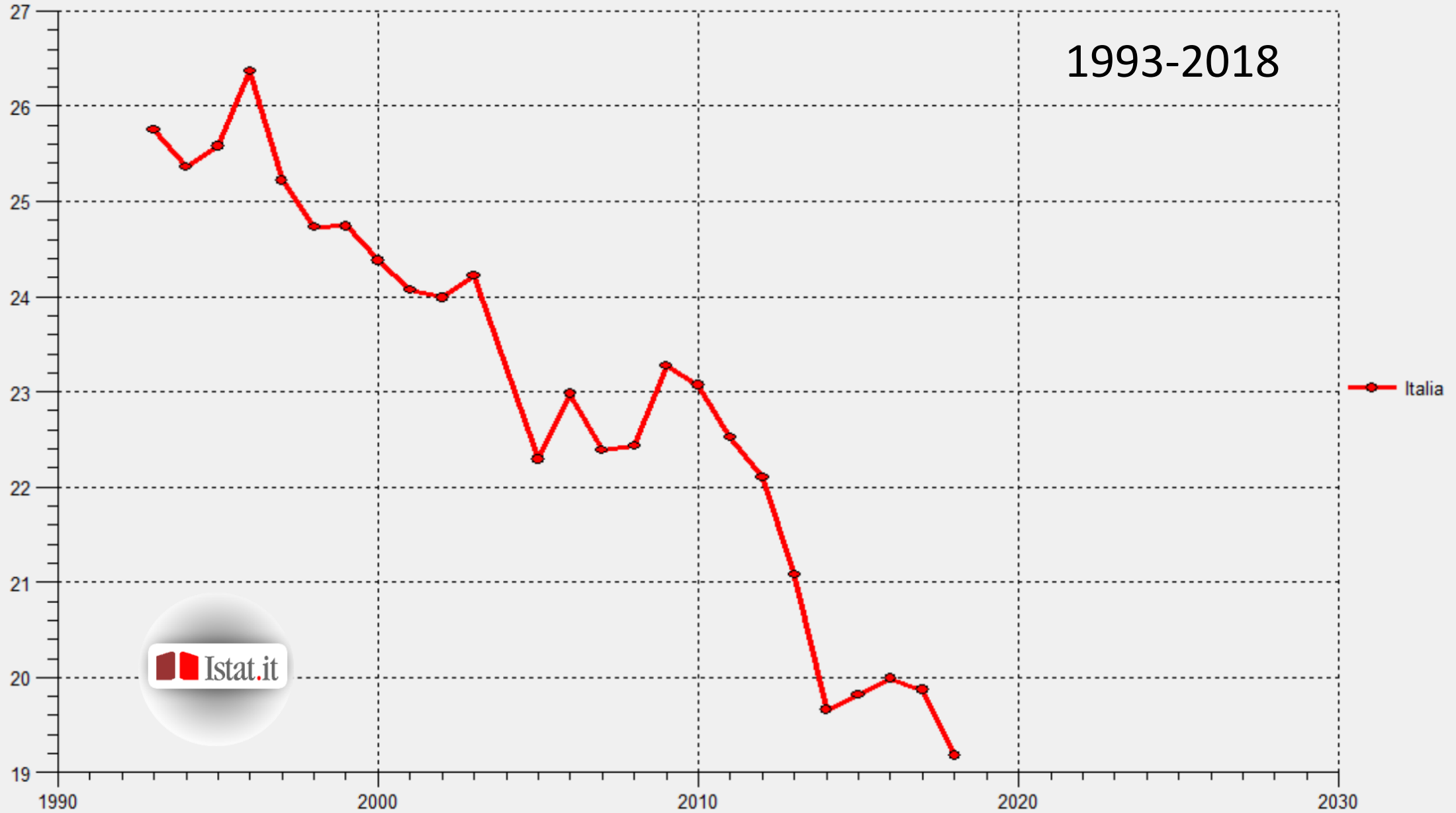
- Melanoma
- Pancreas
- Testicolo
- Polmone (donne)
- Tiroide
- Mammella

Determinanti di salute e incrementi epidemiologici in atto



%fumatori 15+ M+F

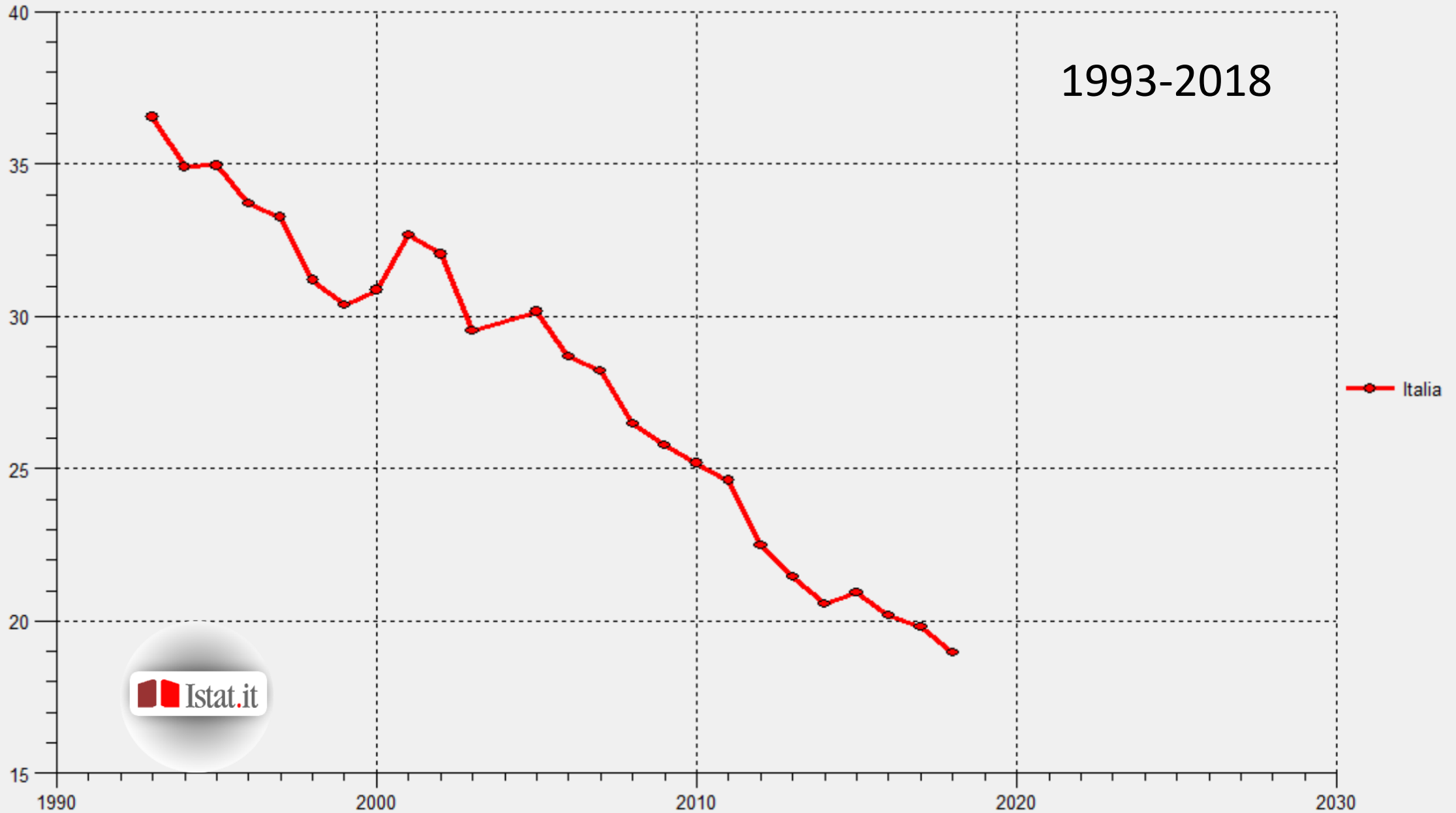
1993-2018



Istat.it

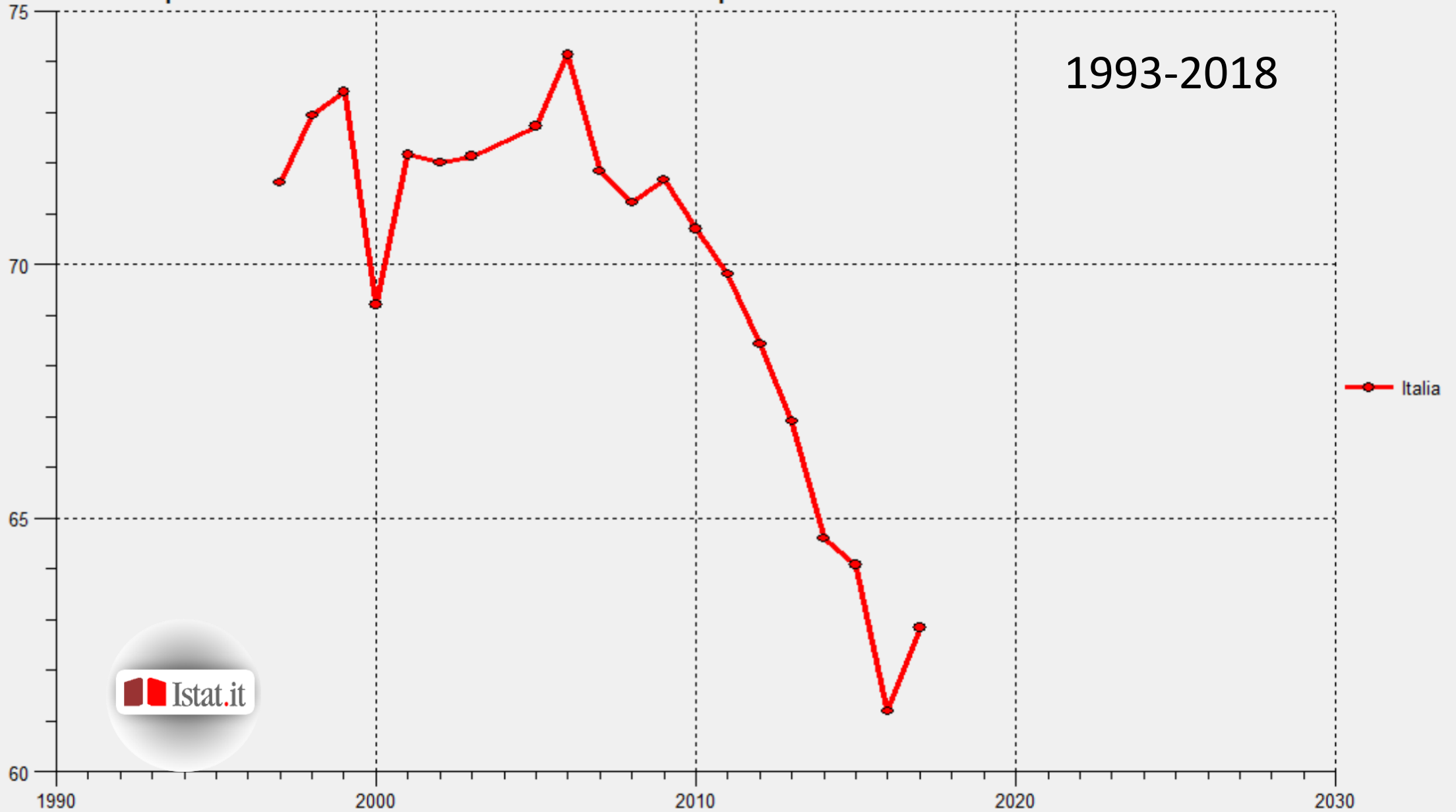
%consumatori abituali vino 15+ M+F

1993-2018

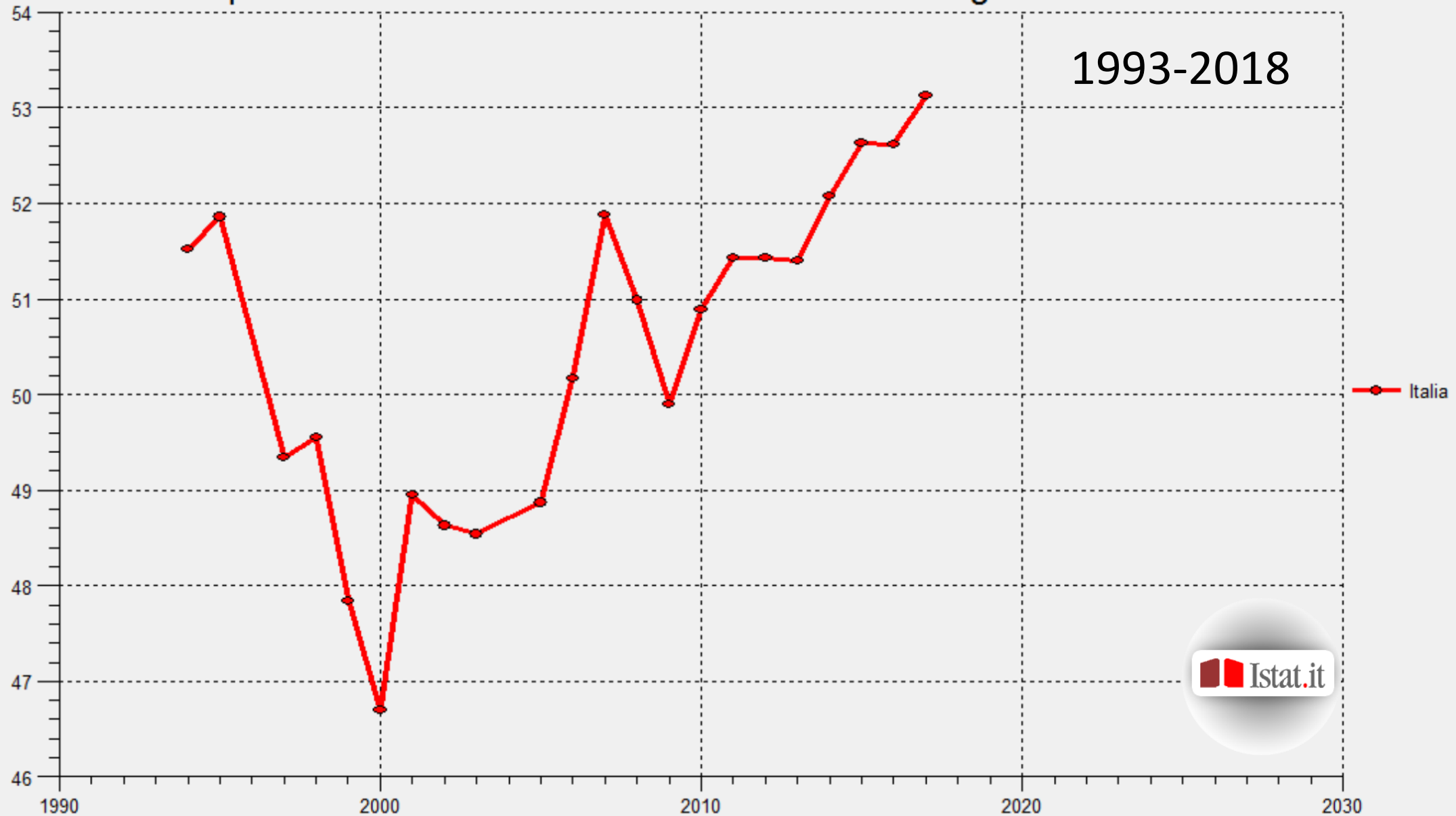


Istat.it

%persone consumano carni bovine qualche volta la settimana 3+ M+F



%persone consumano verdura almeno 1volta al giorno 3+ M+F



%persone che praticano sport in modo continuativo 3+ M+F



Incremento incidenza K POLMONE nelle donne

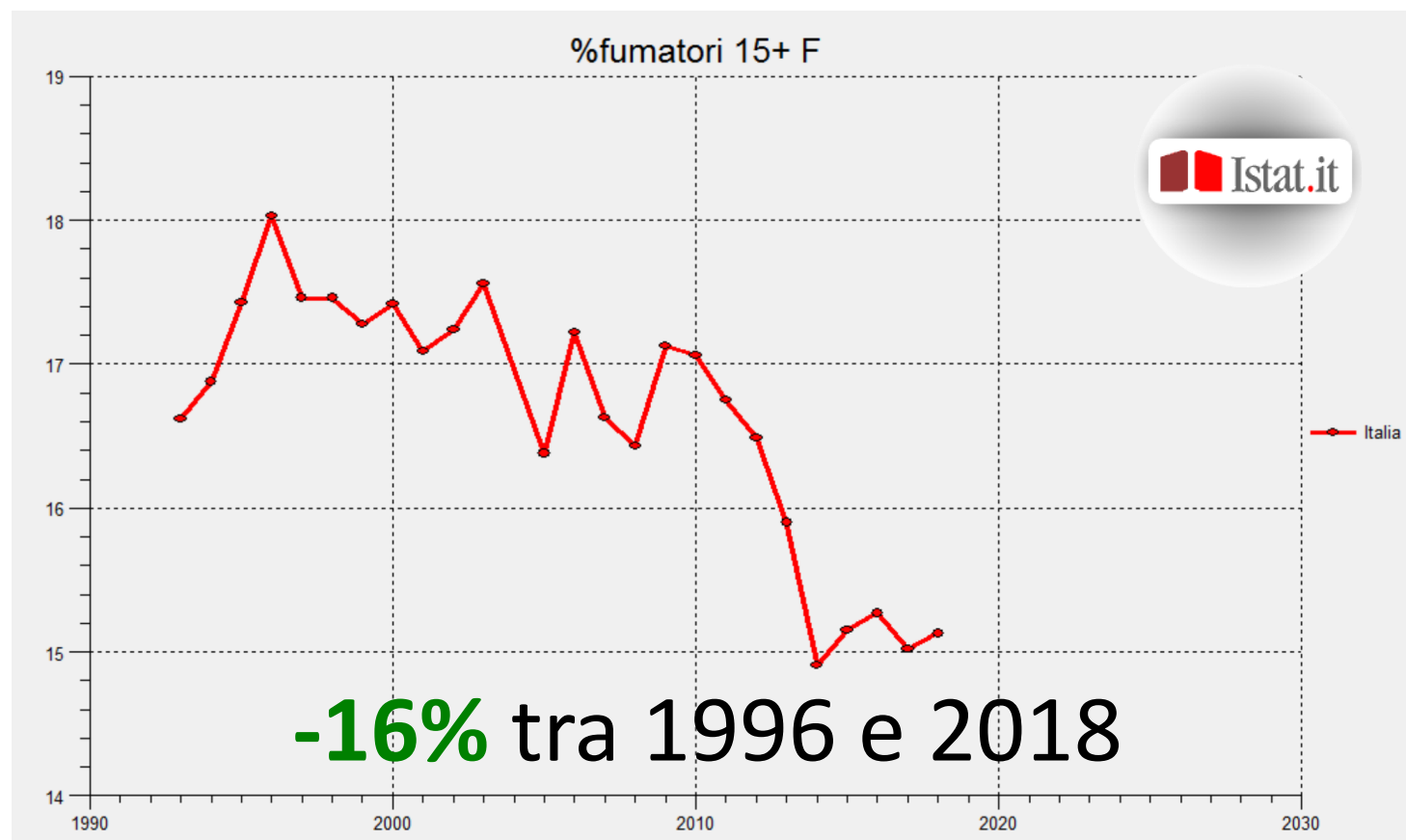
Aumento di nuovi casi +3,1% per anno da riportare all'abitudine al fumo di tabacco

Incremento incidenza K VESCICA nelle donne

- Incremento di incidenza (+0,3% per anno) da correlare al tabagismo

I NUMERI DEL CANCRO IN ITALIA 2017

Versione per pazienti e cittadini
a cura di Fondazione AIOM



Tumore vescica, in Ue un caso su 20 associato all' acqua del rubinetto

6.561 casi all'anno collegati ai contaminanti



Redazione ANSA ROMA 21 gennaio 2020 17:01

Scrivi alla redazione Stampa



ANSA 21 gennaio 2020

DALLA HOME SALUTE&BENESSERE



Tumore vescica, in Ue un caso su 20 associato all' acqua del rubinetto
Sanità

"potrebbero potenzialmente essere evitati 2.868 casi annui di tumore alla vescica" (Environmental Health Perspectives)

Incidenza in **riduzione**

- Stomaco
- Colon-retto
- Polmone (uomini)
- Prostata
- Utero

**Effetto positivo miglioramento
stili di vita**

(fumo, alcol, consumo carni rosse, attività fisica)

Incidenza in **aumento**

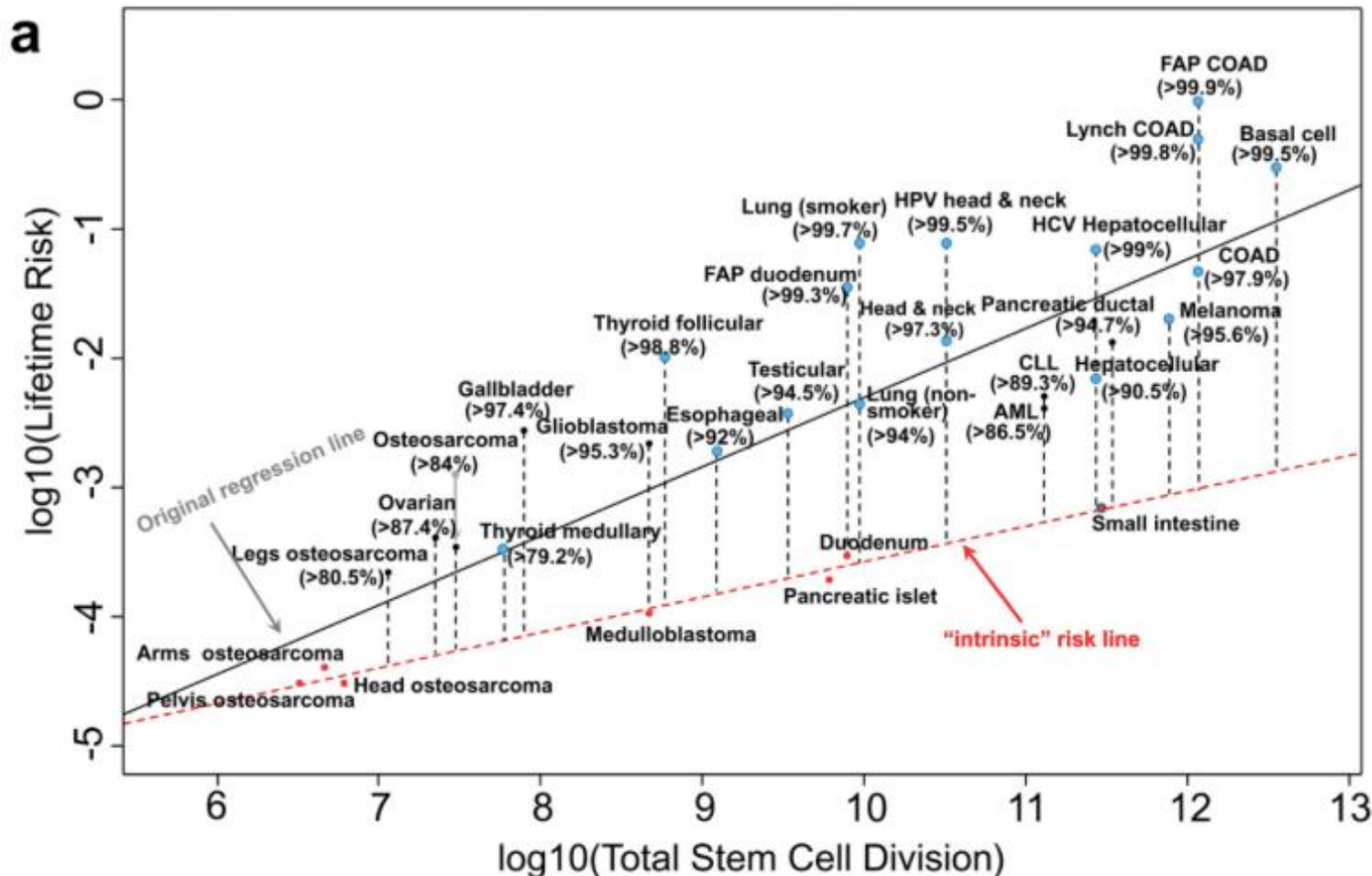
- Melanoma
- Pancreas
- Testicolo
- Polmone (donne)
- Tiroide
- Mammella

- ✓ No invecchiamento
- ✓ No stili di vita

Effetto negativo di ALTRO

Substantial contribution of extrinsic risk factors to cancer development

Song Wu, Scott Powers, Wei Zhu & Yusuf A. Hannun



- “intrinsic risk factors contribute only modestly (less than ~10-30% of lifetime risk) to cancer development”
- “the rates of endogenous mutation accumulation by intrinsic processes are not sufficient to account for the observed cancer risks.”
- “Collectively, we conclude that cancer risk is heavily influenced by extrinsic factors”.

Cancer risk paradox: grand plans fall short?

The "insatiable desire to enhance our fundamental understanding of tumour biology overshadow the health gains that could be secured by improved environmental protection? "

"...cancer as a direct result of human mismanagement of the planet"

Climate Change — A Health Emergency

Caren G. Solomon, M.D., M.P.H., and Regina C. LaRocque, M.D., M.P.H.

N Engl J Med, January 2019



The NEW ENGLAND
JOURNAL of MEDICINE

*“... Some physicians may be willing to take more direct action in protest of policies that harm health. On this question, we agree with Charles van der Horst, a North Carolina physician who was arrested for protesting... **In the face of great danger to our patients . . . remaining silent is not an option.**”*

“remaining silent is not an option...”

I medici sono in grado di trasferire efficacemente ai decisori politici conoscenze adeguate, indipendenti, intellettualmente oneste e orientare le decisioni verso misure di **prevenzione primaria**

La prevenzione primaria è l'unica strada possibile per:

- Invertire il trend epidemiologico crescente di NCD e cancro in qualunque età
- Promuovere SALUTE pubblica e non solo SANITA' pubblica
- Permettere un "healthy aging"
- Riequilibrare la spesa sanitaria
- Fornire indicazioni chiare nella strada verso la sostenibilità



Grazie per l'attenzione



Contatti:

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