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EUROPEAN MEDICINES AGENCY

Session 3: How can real-world data (RWD) support innovation and decision-making in CV

Experience gained and lessons learned from recent and ongoing initiatives

Supporting innovation in cardiovascular medicines and medical devices in the EU

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Scene setting
One person dying from CVD every 3 minutes (UK)

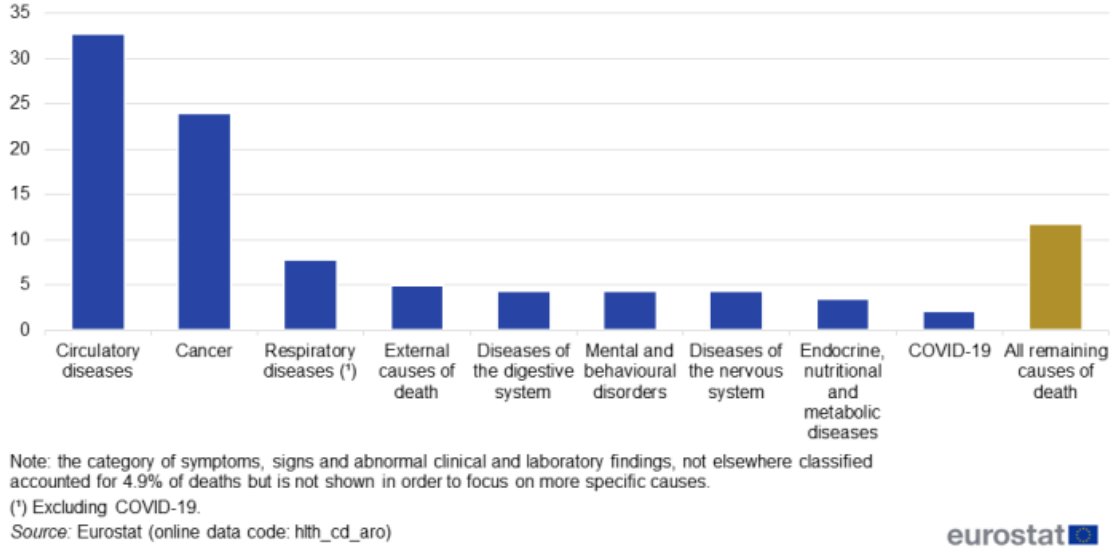

Figure 1: Share of main causes of death, EU, 2023

Source: Eurostat (hlth_cd_aro)

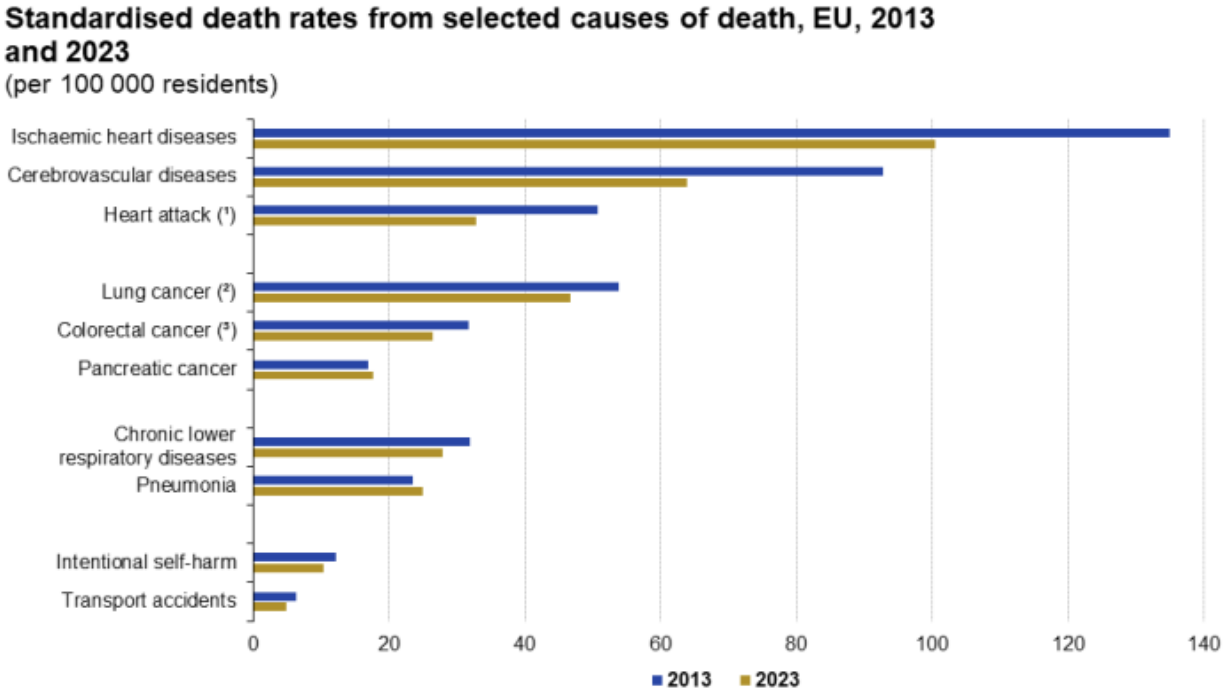

Figure 3: Standardised death rates from selected causes of death, EU, 2013 and 2023

Source: Eurostat (hlth_cd_asdr2)

Let’s roll back 80 years, to 1948: Framingham heart study (FHS)

- One of the most influential longitudinal epidemiological cohort studies in medical history
- Fundamentally shaped how we understand cardiovascular disease (CVD) risk
- Started: 1948
- Post-war setting, epidemic of CVD (44% of deaths)
- Initial cohort: ~5,200 men and women aged 30–62, free of overt CVD at baseline
- Design: Prospective cohort study with regular follow-up examinations (about every 2 years)
- Key idea: Track people over time → identify predictors of incident cardiovascular disease.

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Source: google maps
https://www.framinghamheartstudy.org/

Then came Whitehall, ARIC, MESA, and …

- 1960s, 1980s: Whitehall Studies (I & II)
- Focus: civil servants
- Impact: Social gradient of cardiovascular disease
- Psychosocial risk factors (stress, job control)

→ Shifted thinking beyond purely biological risk factors.

- 1980s: ARIC (Atherosclerosis Risk in Communities), ~15,000
- Expanded diversity (geography, race)
- Added subclinical disease markers (e.g., carotid IMT)
- Bridged epidemiology → mechanistic understanding

2000: MESA (Multi-Ethnic Study of Atherosclerosis)

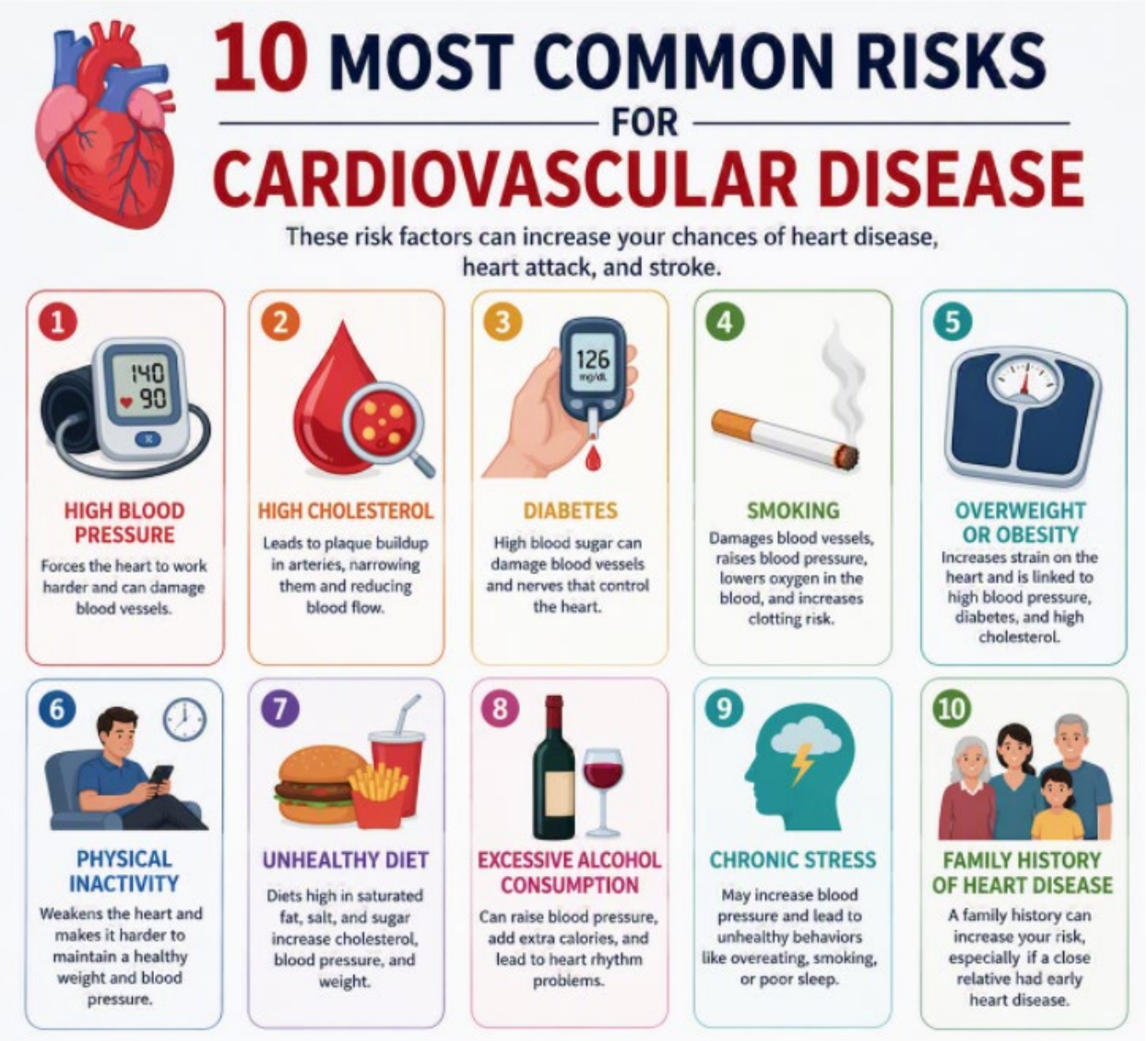
Focus on multi-ethnic populations + imaging endpoints (CAC)

Reframed risk: from clinical events → subclinical atherosclerosis trajectories

Introduced risk reclassification concepts (beyond Framingham) = stratification

And that brings us to: individual (downstream) risk factors

→ most are modifiable → diet and lifestyle advice!



Source: BHF

Risk factors → risk scores

→ screening

→ prediction, and prevention

- Guidelines
- Treatment based on individual risk score and other contributory factors

From reactive → proactive healthcare

	FRS (Framingham)	SCORE2	QRISK3
Primary Population	Originally USA (multi-ethnic). Widely used globally but often recalibrated locally.	European populations; divided by low/moderate/very-high risk geographical regions.	Specifically validated for the UK (QResearch database).
Age Range	30 to 79 years old.	40 to 69 years old (SCORE2), and 70+ (SCORE-OP).	25 to 84 years old.
What it Predicts	Coronary Heart Disease (CHD).	Both fatal and non-fatal cardiovascular events.	First cardiovascular event (stroke, heart attack, or TIA).
Unique Variables	Focuses on traditional factors: cholesterol, age, BP, smoking, and diabetes.	Focuses on age, systolic BP, total and HDL cholesterol, smoking status.	Includes traditional factors plus severe mental illness, CKD, rheumatoid arthritis, SLE, erectile dysfunction, and steroid use.

Upstream determinants of health

- Structural drivers shaping population health distribution
- Upstream determinants → Living conditions → Behaviors & exposures → Health outcomes
- Can be a source of health inequalities!

Governance and Policy Effects

Policies like increasing minimum wage improve income and access to healthy **food**, **housing**, and **healthcare**, reducing chronic diseases.

Trade and Commercial Determinants

Global trade agreements, liberalization raises **(ultra-) processed food availability**, increasing obesity rates; marketing of tobacco raises health risks.

Healthcare System Influence

Universal **healthcare** increases **preventive care** and early diagnosis, lowering mortality and enhancing population health.

Climate and Social Inequities

Climate change and **social inequality** cause unequal exposure to hazards, increasing mortality and food insecurity.

Palm oil ubiquitous (saturated fat →LDL C→CVD)

UPFs >50% of average US diet calories

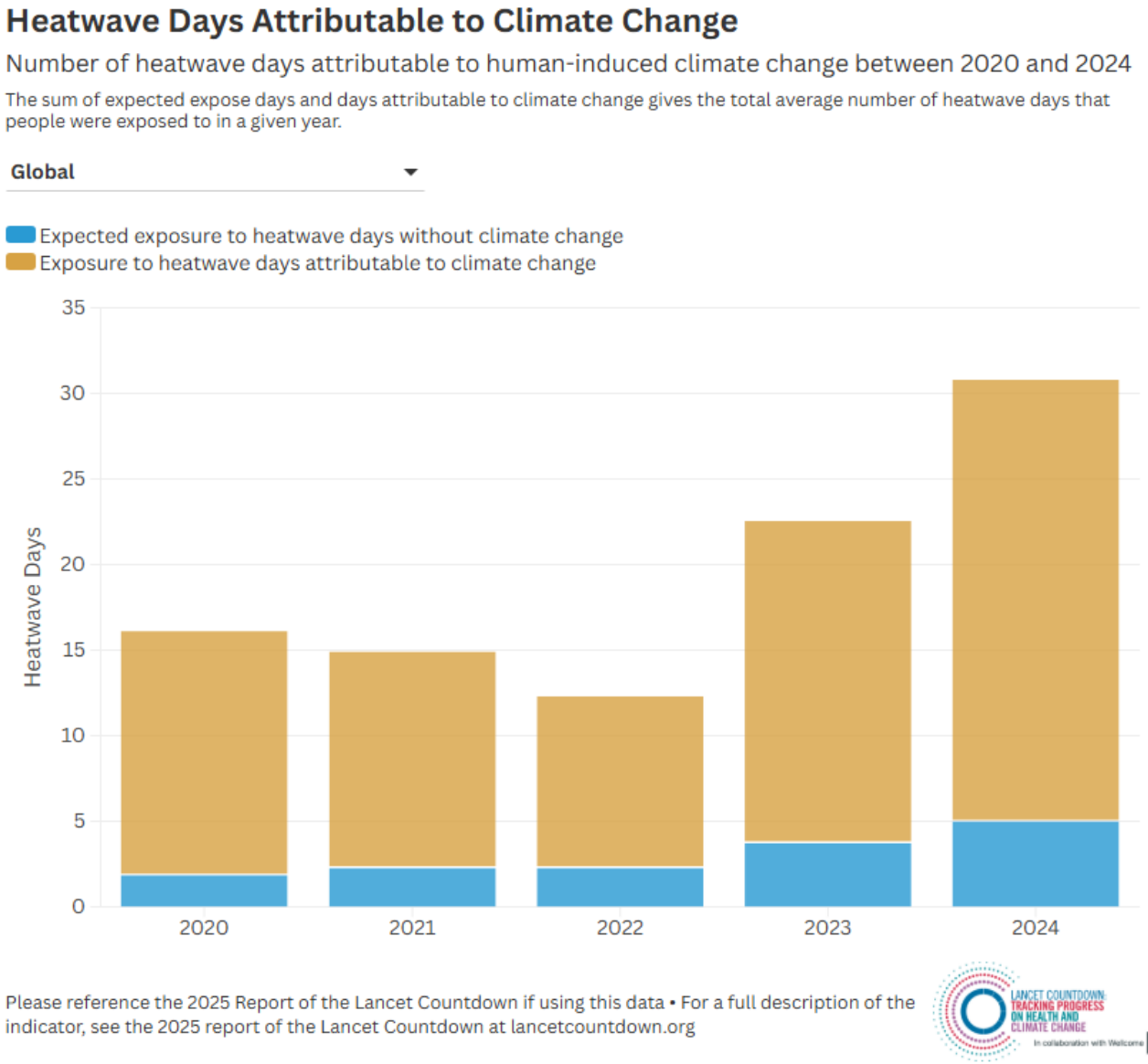
High versus low UPF intake was linked to a 25% to 58% higher risk of cardiometabolic outcomes and a 21% to 66% higher risk of mortality*.

Climate: Why does this matter?

Climate and Social Inequities
Climate change and **social inequality** cause unequal exposure to hazards, increasing mortality and food insecurity.

- Heat is an environmental health risk factor!
- The impact is increasing with global warming
- Can be studied with environmental epidemiological methods
- ~500,000 deaths globally each year '~1 every minute'
- In Europe alone in the summer of 2022, an estimated ~60,000 heat-related excess deaths occurred *(*)*.
- Heat-related mortality for people over 65 years of age increased by approximately 85% between 2000–2004 and 2017–2021 (**)
- Disproportionately affects >65s + those with prior conditions
- **Cardiovascular outcomes** are the most frequent causes of death

Climate change at play



https://lancetcountdown.org/explore-our-data/

IMPERIAL
Grantham Institute

Institute reports and analytical notes

Climate change tripled heat-related deaths in early summer European heatwave

2025

2,300 deaths in 12 cities over ~10 days in 2025!

https://doi.org/10.25560/128628

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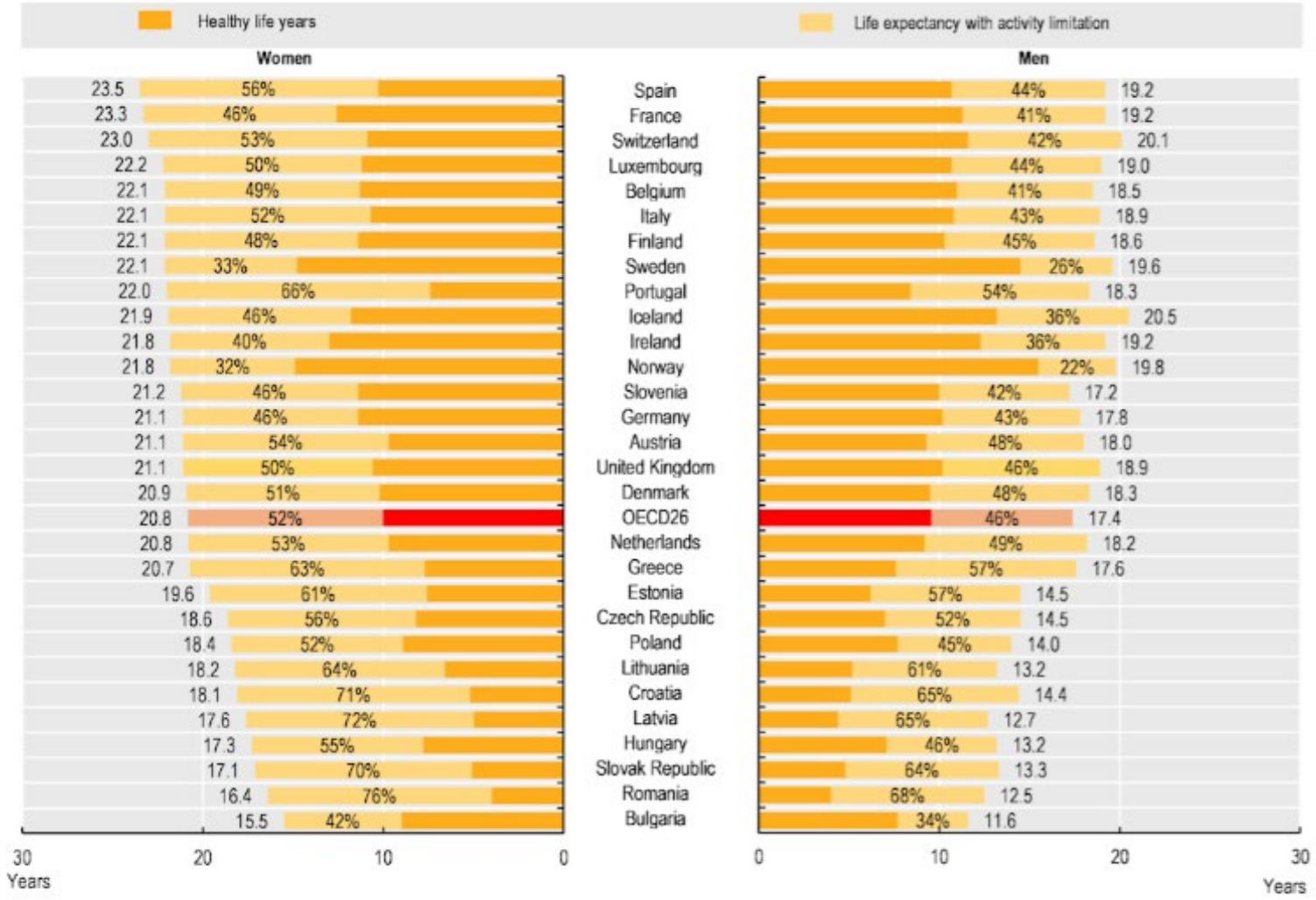
The Marmot Review (UK)

Marmot, M. et al., 2010. *Fair Society, Healthy Lives: The Marmot Review (Strategic Review of Health Inequalities in England Post-2010)*, UCL Institute of Health Inequality. United Kingdom.

- fundamentally changed how governments and public health organizations approach public health
- **Focus shifts on the "social determinants of health"**—the fundamental conditions in which people are born, grow, live, work, and age
- A **social gradient** exists across the population - as socioeconomic status drops, health and life expectancy drop steadily across the entire population → applies to CVD, too
- early childhood education, fair employment, housing, and community environments play a much larger role in dictating lifelong health
- Requires **action across the gradient**, '*proportionate universalism*'

OECD: Life expectancy at 65 yrs and healthy life expectancy at 65 yrs

Figure 10.4. Life expectancy and healthy life-years at age 65, by sex, 2021 (or nearest year)

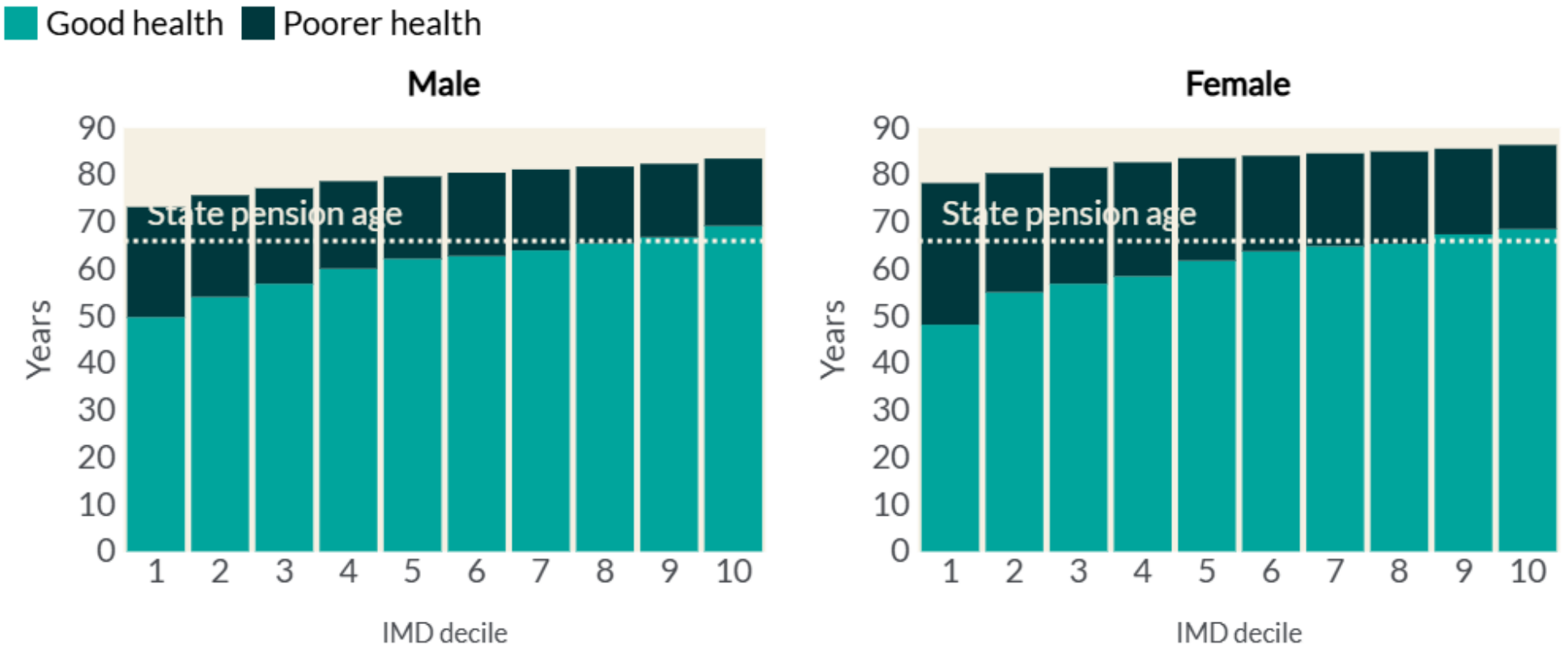


Note: Data comparability is limited because of cultural factors and different formulations of the GALI question in the EU-SILC survey. 1. Data for Iceland and the United Kingdom refer to 2018 2. Data for Norway refer to 2020.

Source: Eurostat Database.

Healthy life expectancy is almost 20 years lower in the most deprived areas compared to the least deprived

Years spent in good health and poorer health by deprivation decile, England, 2022-24



Source: Office for National Statistics (2026)
IMD is Index of Multiple Deprivation (1 = most deprived, 10 = least deprived). Current state pension age is 66 years, but will rise to 67 by March 2028.

https://www.kingsfund.org.uk/insight-and-analysis/data-and-charts/health-inequalities-nutshell

Randomized Controlled Trials (RCTs)

- RCTs are the gold standard for efficacy + safety and authorisation of individual medicines
- 1990s–2010s – Landmark CV RCTs: Established causal treatment benefits
  - Statins (4S, HPS) - First clear mortality reduction with statins
  - ACE inhibitors (HOPE) - Reduced CV death, MI, stroke in high-risk patients (not just HTN) → from BP drugs → vascular protection agents
  - RE-LY (2009, dabigatran) - first DOAC to show non-inferiority/superiority vs warfarin in AF

    →Proof that oral anticoagulation could be done without INR monitoring → DOACs become default anticoagulants (RWE later confirms broad population effectiveness and safety)
  - And other classes followed …

→ evidence-based medicine and guidelines

Rosiglitazone

- First-in-class PPAR-γ agonist (thiazolidinedione)
- Robust HbA1c reductions (glycaemic control as surrogate for outcome benefits)
- targets insulin resistance (considered the root cause of type 2 diabetes)
- Unmet medical need - limited options beyond: Metformin, Sulfonylureas, Insulin
- Low risk of hypoglycaemia
- Oral treatment

- Graham DJ et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA doi:10.1001/jama.2010.920;
- → early "real-world evidence" approach, RSG vs pioglitazone (real world, comorbidities, longer FU); more confounding
- ↑ MI risk, ↑ heart failure
  ↑ mortality (in some analyses)

- Nissen 2007 and
- Nissen SE et al. Rosiglitazone revisited. An updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med doi:10.1001/archinternmed.2010.207.
- → classic evidence hierarchy; but selected patients (RCTs), trials not designed for CV outcomes; focus on MI; lower power

Signal:

↑ MI risk

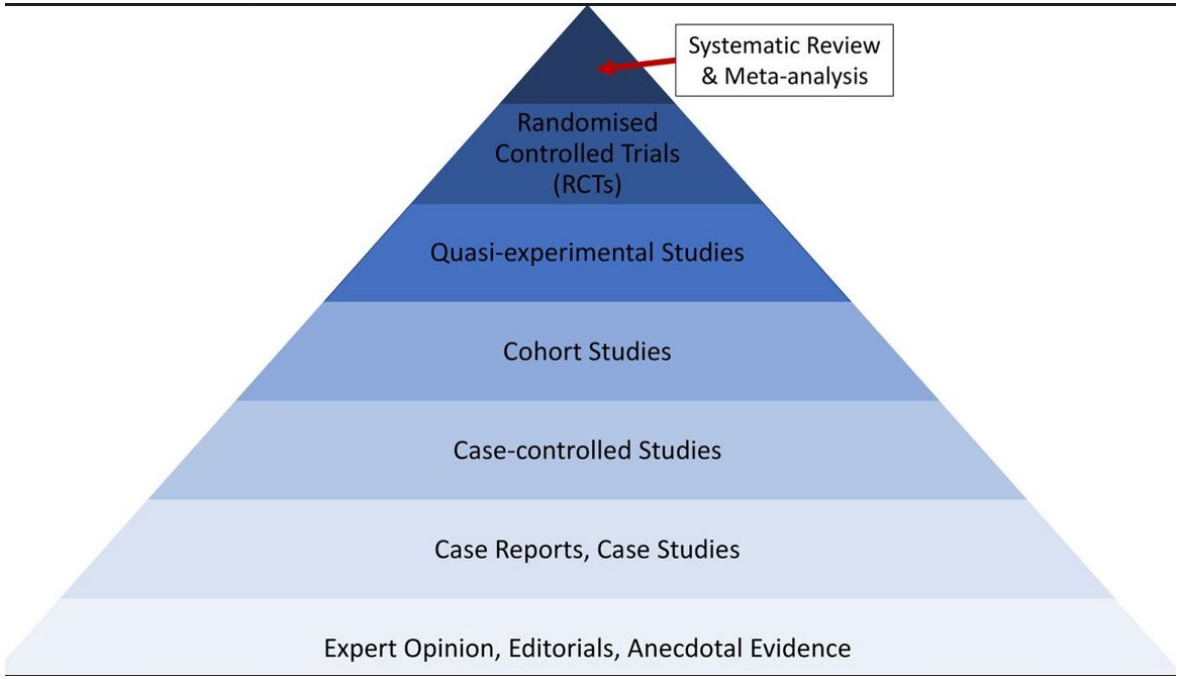
✓And a CVOT is born – to rule out CV risk
Then the goal posts changed

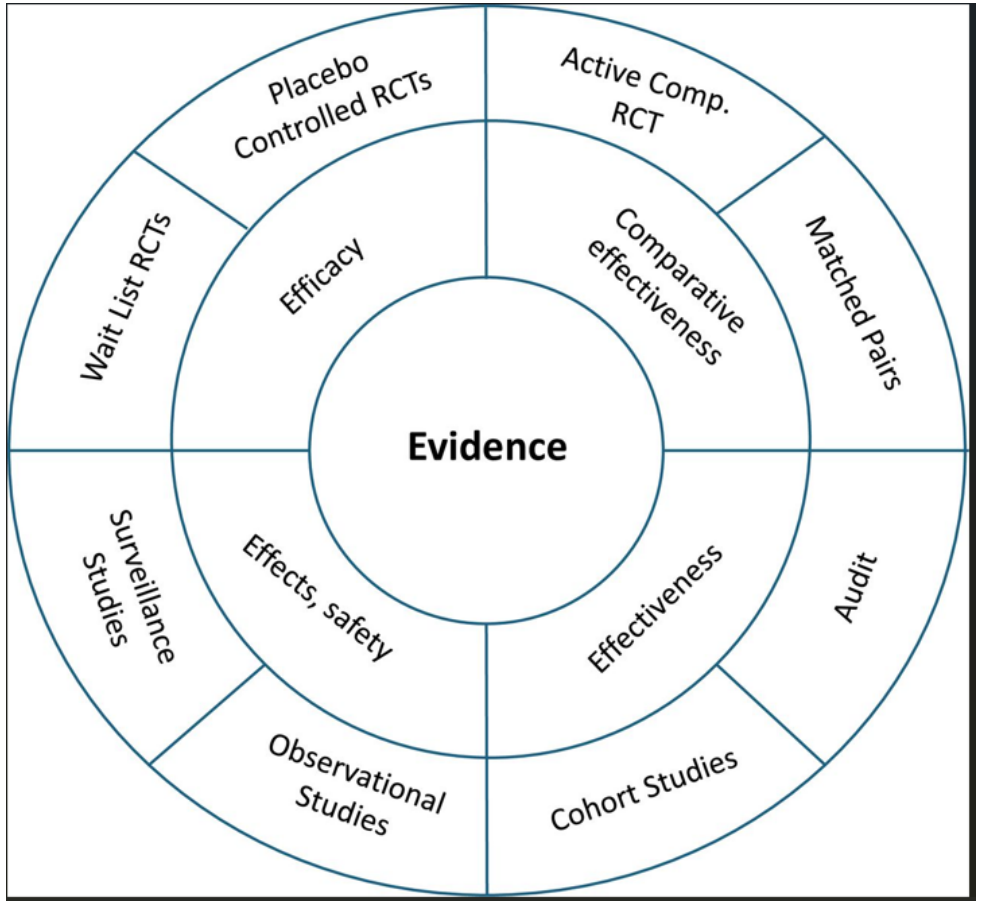
- 2015 – EMPA-REG OUTCOME (empagliflozin)
  - First CVOT showing mortality benefit in T2D
  - ↓ CV death, ↓ heart failure hospitalization
  - Shift to cardiorenal protection paradigm
  - Triggered extension of **SGLT2** inhibitors use in HF
- 2016 - LEADER (liraglutide)
- ↓ MACE (atherosclerotic outcomes)
- GLP1s class boom

LEADER trial replicated as TTE RWD study (FDA RCT DUPLICATE*)

→shifting diabetes care from glucose-centric to cardiovascular and renal risk reduction

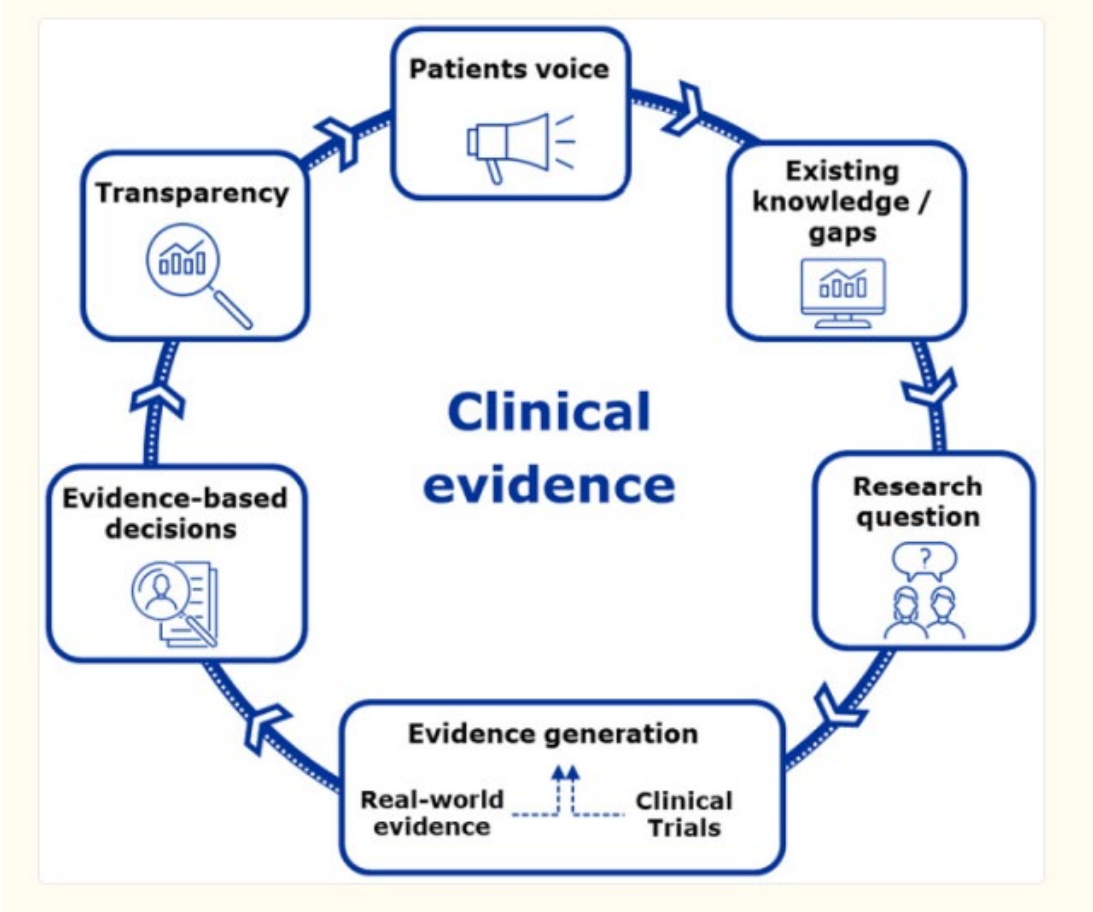
It’s not an evidence competition! From ‘pyramids’ to ‘amphitheatres’





Source: Shakir and Lane, 2025. https://doi.org/10.1136/bmjopen-2025-103538

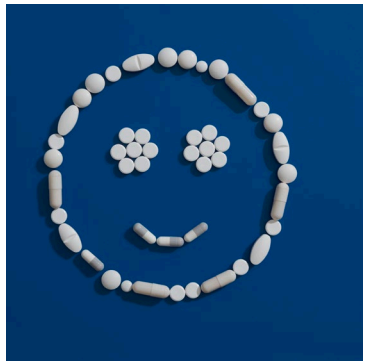
The totality of evidence, and the right evidence for the right research question



"The **full spectrum of data and methods** is embraced, **with better, smarter, and faster clinical trials remaining at the core** of clinical evidence, **complemented by real-world evidence** for which evidentiary value is established across the full spectrum of research questions"

Arlett et al. Clin Pharmacol Ther. 2025 Feb 14;117(4):884–886.
doi: 10.1002/cpt.3596

What innovations and changes on the horizon?

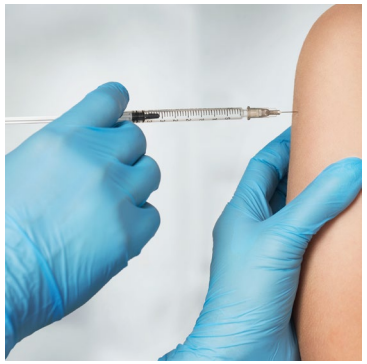


Polypill

~20 years

Modelled based on individual RCTs → now confirmation from individual pills' RCTs

Broad, simple public health intervention which could ~halve CVD burden (1)



Vaccination

Lower risk of CV outcomes after vaccination against influenza, COVID-19 (+others) (2)

Attractive preventive intervention

Self-monitoring, 'biohacking'

Pulse, SpO2%, steps, glucose, arrhythmias, genetic testing

Data sharing with HCPs?

Petabytes of data points

Overdiagnosis?

Wearables + AI

Widely taken up – 1B globally; 35% US, 25% EU adults;

observation > ECG/Holter (can diagnose Afib)

Data ownership, sharing with HCP? (in CV specialty, seems higher)

Validation?

Registries, networks, JA, biobanks

R-RCTs

New biomarkers (eg Lp(a))

Genetics, PRS (3)

→updated risk scores, better prevention + optimal treatment

Registries, networks, joint actions, biobanks

- **EuroHeart**: European Unified Registries On Heart care Evaluation And Randomized Trials
- National registry programmes with common EuroHeart structure for common CVDs (ACS, PCI, HF, Afib, valve disease)
- →collaborative research (R-RCTs, safety surveillance for drugs and devices)

- Building on existing experience such as SwedeHeart (~dozen R-RCTs)
- Many national and international collaborations and networks

- **Jacardi** 2023-2027 (Joint Action on CARdiovascular diseases and DIabetes): 143 evidence-based projects in 18 EU countries

- **IHI GREG**, 2025 onwards
- practical, evidence-based guidance and tools to help generate and use RWE → regulators and HTAs

- UK Biobank, Estonian Biobank – participate in DARWIN EU
- **Our Future Health** (UK)

DARWIN EU

The Netherlands
Integrated Primary Care Information
Netherlands Cancer Registry

Belgium
IQVIA Longitudinal Patient Database Belgium
UZA Antwerpen
Belgian Cancer Registry

United Kingdom
UK BioBank
Clinical Practice Research Datalink GOLD
Clinical Practice Research Datalink AURUM
National Neonatal Research Database

France
Bordeaux University Hospital
Système National des Données de Santé
Health Data Warehouse of Assistance Publique
French National Registry of Rare Diseases

Germany
IQVIA Disease Analyzer Germany
InGef Research Database
Dresden University Hospital

Portugal
ULSM-RT
Egas Moniz Health Alliance DataBase
IPO Porto

Spain
SIDIAP
BIFAP
IMASIS and IMIM
Valencia Health System Integrated Database
H12O
Health Data Research Platform of the Balearic Islands
Hospital Universitario Virgen Macarena

Norway
Norwegian Linked Health Registry
Cancer Registry of Norway

Sweden
Health Impact

Finland
FinOMOP

Estonia
Estonian Biobank

Lithuania
Lithuanian Health Data

Denmark
Danish Health Data Registries

Poland
Children's Memorial Health Institute Database

Hungary
Semmelweis University Clinical Data

Croatia
National Public Health Information System

Greece
Papageorgiou General Hospital

Italy
POLIMI
Pedianet

United States of America
IQVIA US Ambulatory EMR, PharMetrics, Oncology

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EU PAS number: EUPAS1000000430

First published: 04/01/2025 **Last updated:** 14/05/2025

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Thank you

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