



Pharmacoepidemiology: What, why, how?

Prof. Dr. Andrea Burden

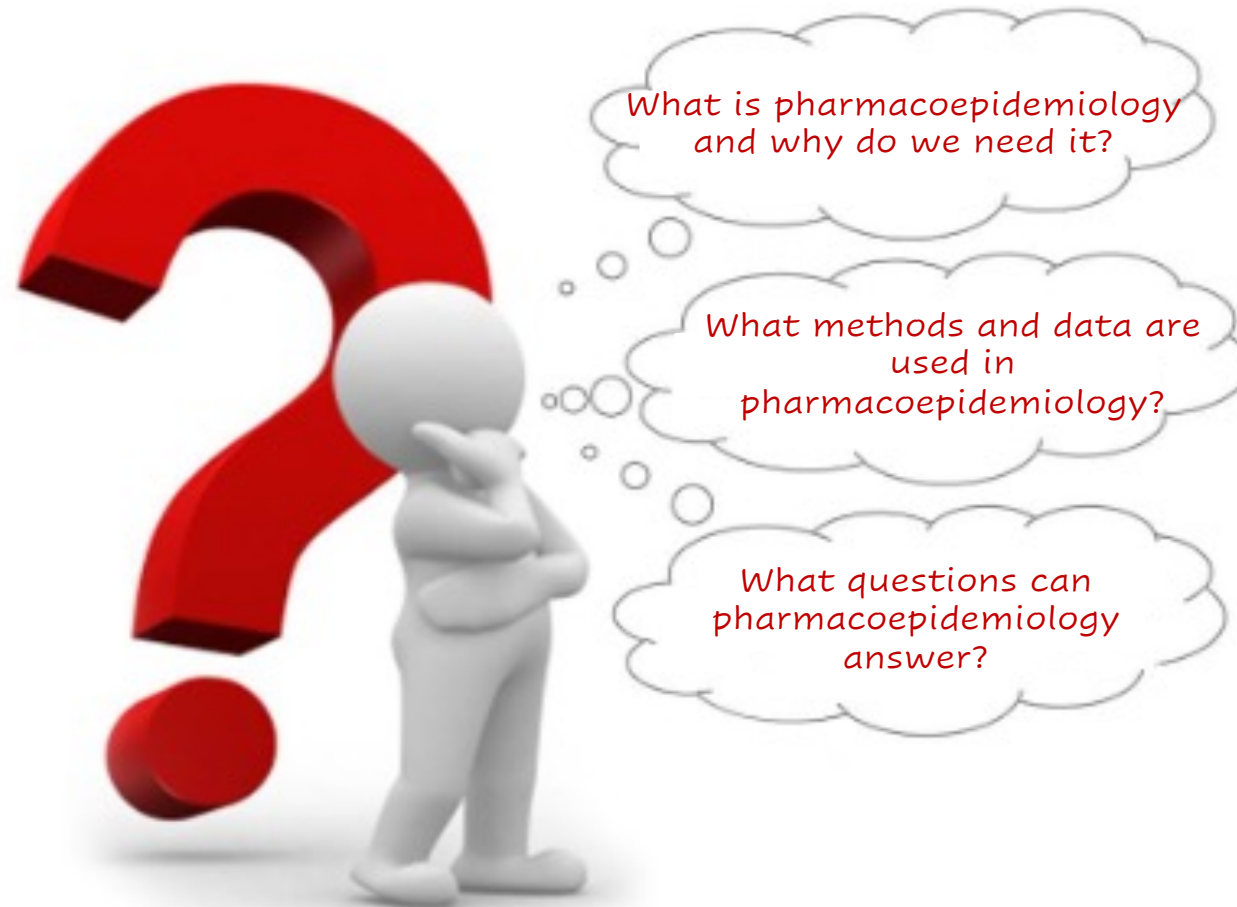
Institute of Pharmaceutical Sciences

Department of Chemistry and Applied Biosciences

Disclaimer

- Today's lecture will provide a “crash course” in pharmacoepidemiology.
- We will not get into the details, but rather provide a broad overview of the field
- If you are intrigued and want to learn more, go to the following resources:
 - International society of pharmacoepidemiology (<https://www.pharmacoepi.org>)
 - European network of centres of pharmacoepidemiology and pharmacovigilance (<https://www.encepp.eu/Training.shtml>)

Today's aim is to fall in love with pharmacoepidemiology!



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Epidemiology



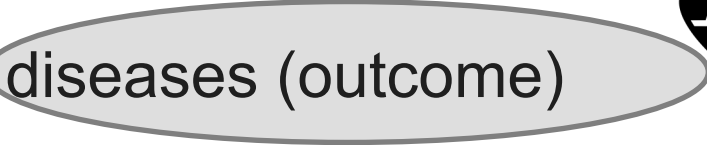



The study of the **distribution** of **diseases (outcome)**

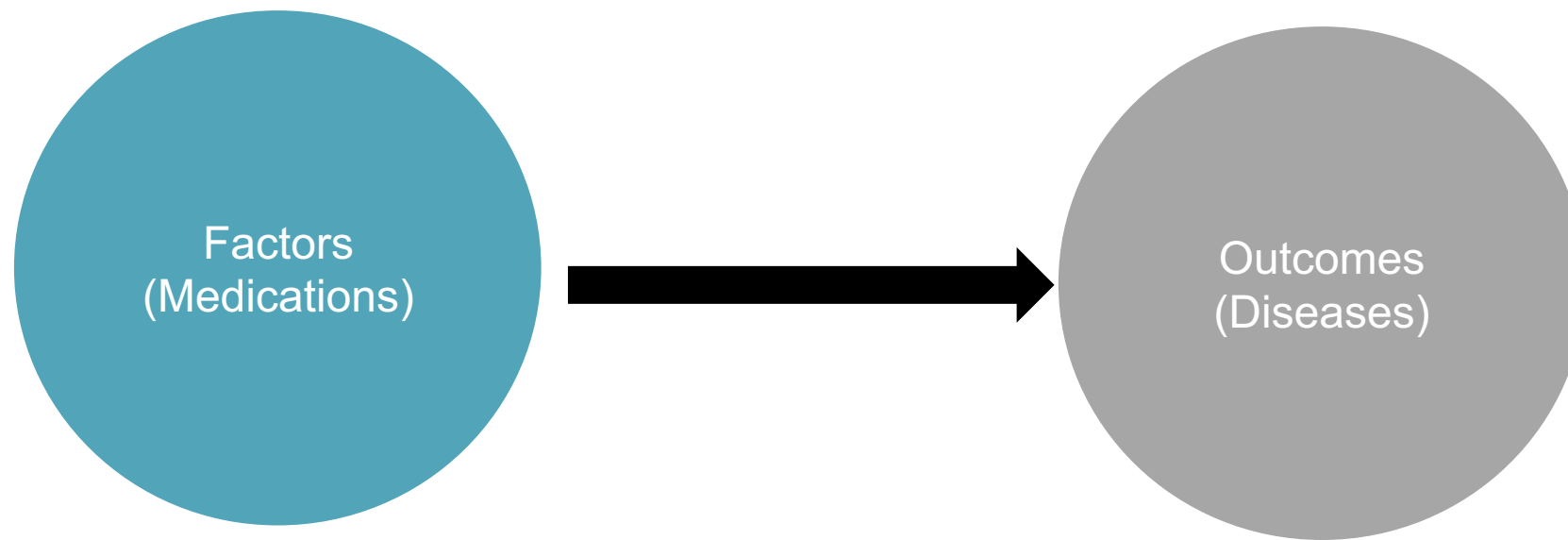


And the factors that influence a disease in the population

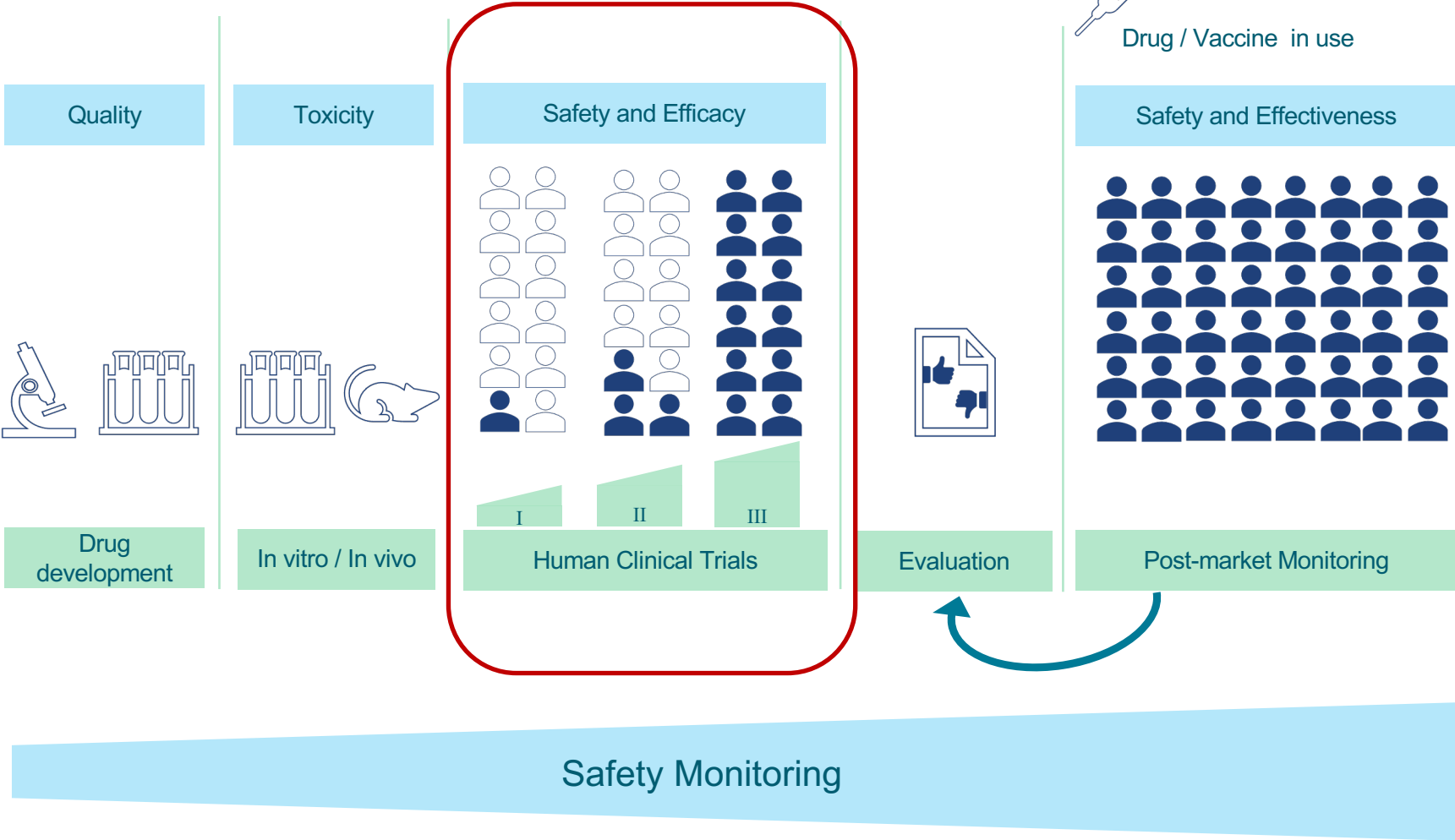
PharmacoEpidemiology

The study of the  distribution  of  diseases (outcome) 

And the  factors  that influence a disease in the population



Drug approval and monitoring



Adapted from www.ema.europa.eu

Pyramid of evidence in medical research



Lower Hospitalization Rates In Epilepsy Patients Treated With Adjunctive FYCOMPA® (perampanel) CIII

Statins May Cut Glaucoma Risk

Long-term use of cholesterol-lowering statin drugs cut the risk of a leading cause of blindness.

The New York Times

After a Hip Fracture, Reducing the Risk of a Recurrence

[home](#) / [arthritis center](#) / [arthritis a-z list](#) / [painkiller vioxx pulled from market alert article](#)

Painkiller Vioxx® Pulled from Market Alert

Last Editorial Review: 9/30/2004

Withdrawal of pain medicine flupirtine endorsed

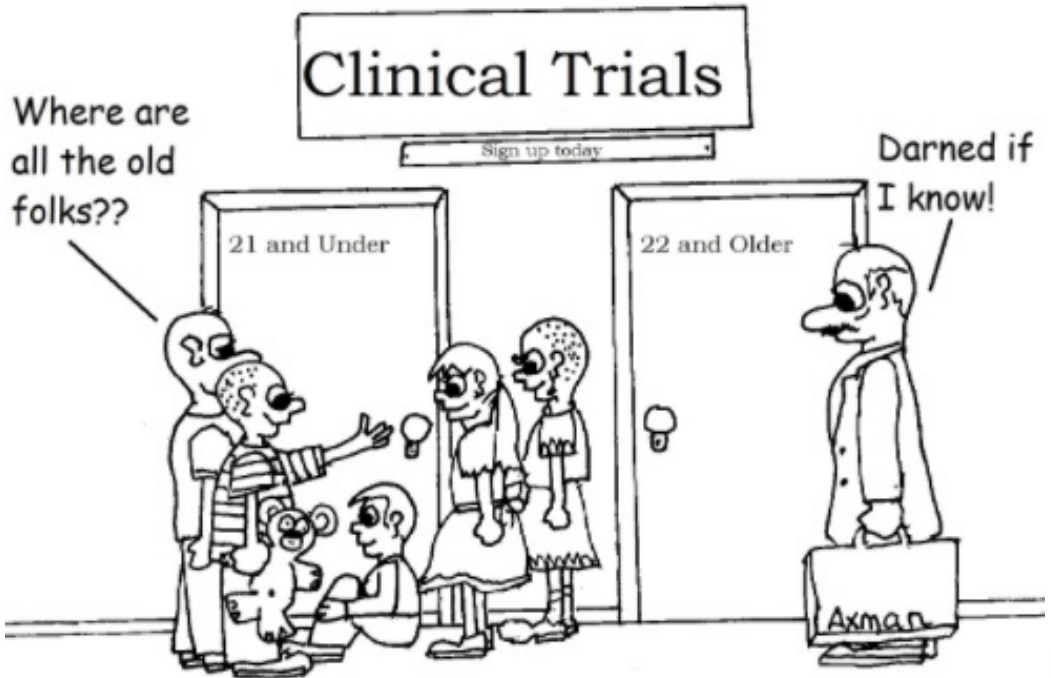
Press release 23/03/2018

Serious liver problems continued to be reported despite previous restrictions in use

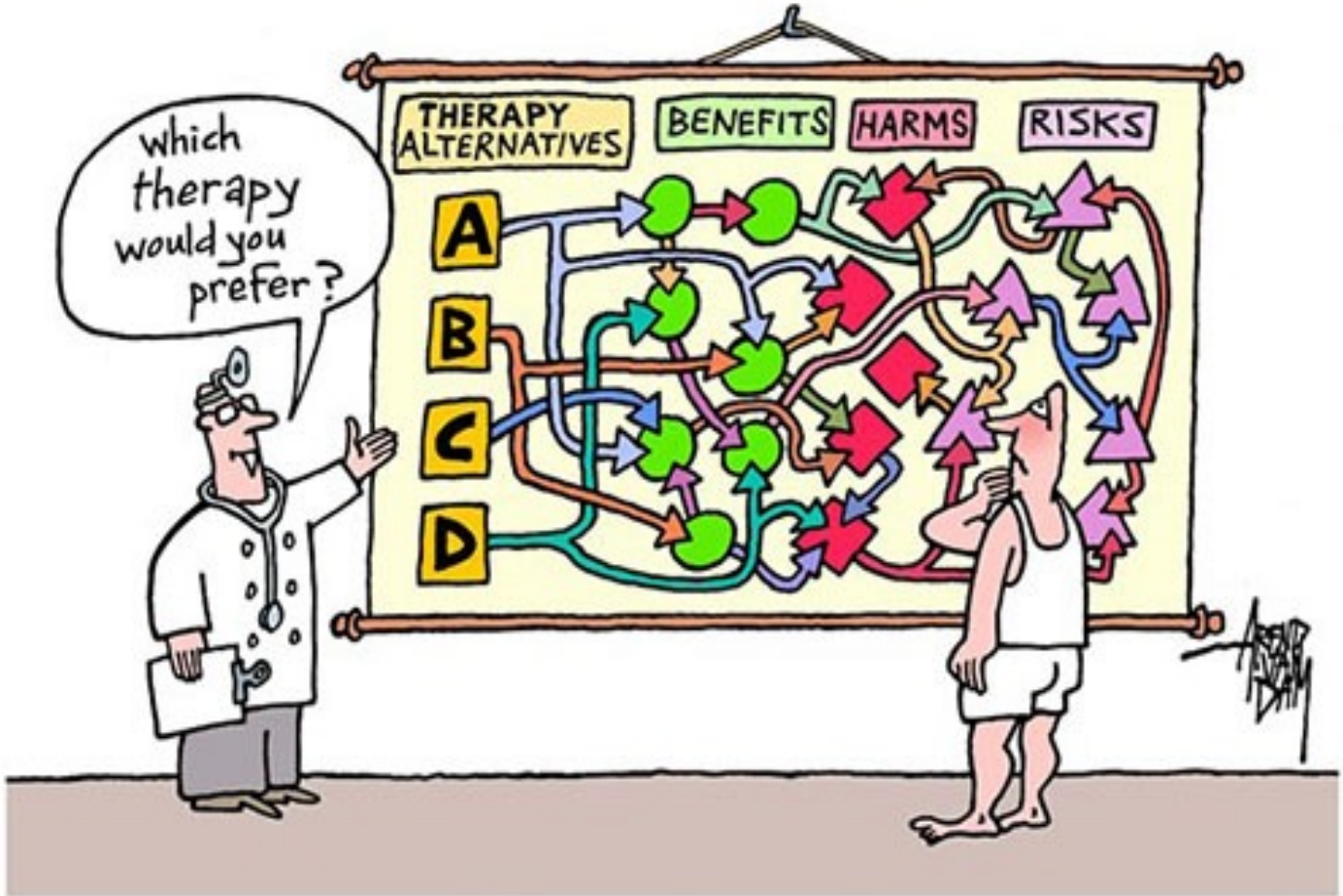
Why study safety after market approval?

- No drug or vaccine is 100% safe (...or effective)
- At the time of market approval we know the benefits outweigh the risks, but...





“Unknown factors”



“Human factors”

The Promise of Pharmacoepidemiology

Promise (strengths)	Challenges (weaknesses)
• Sample size	• Uncertainty re: causality
• Generalizability	• Susceptible to confounding
• Lengthy follow-up	• Black-box analyses limit interpretation
• Real-world clinical data	• Past-mistakes
• Rare events	• Methodological challenges = bias
• Use active comparators	

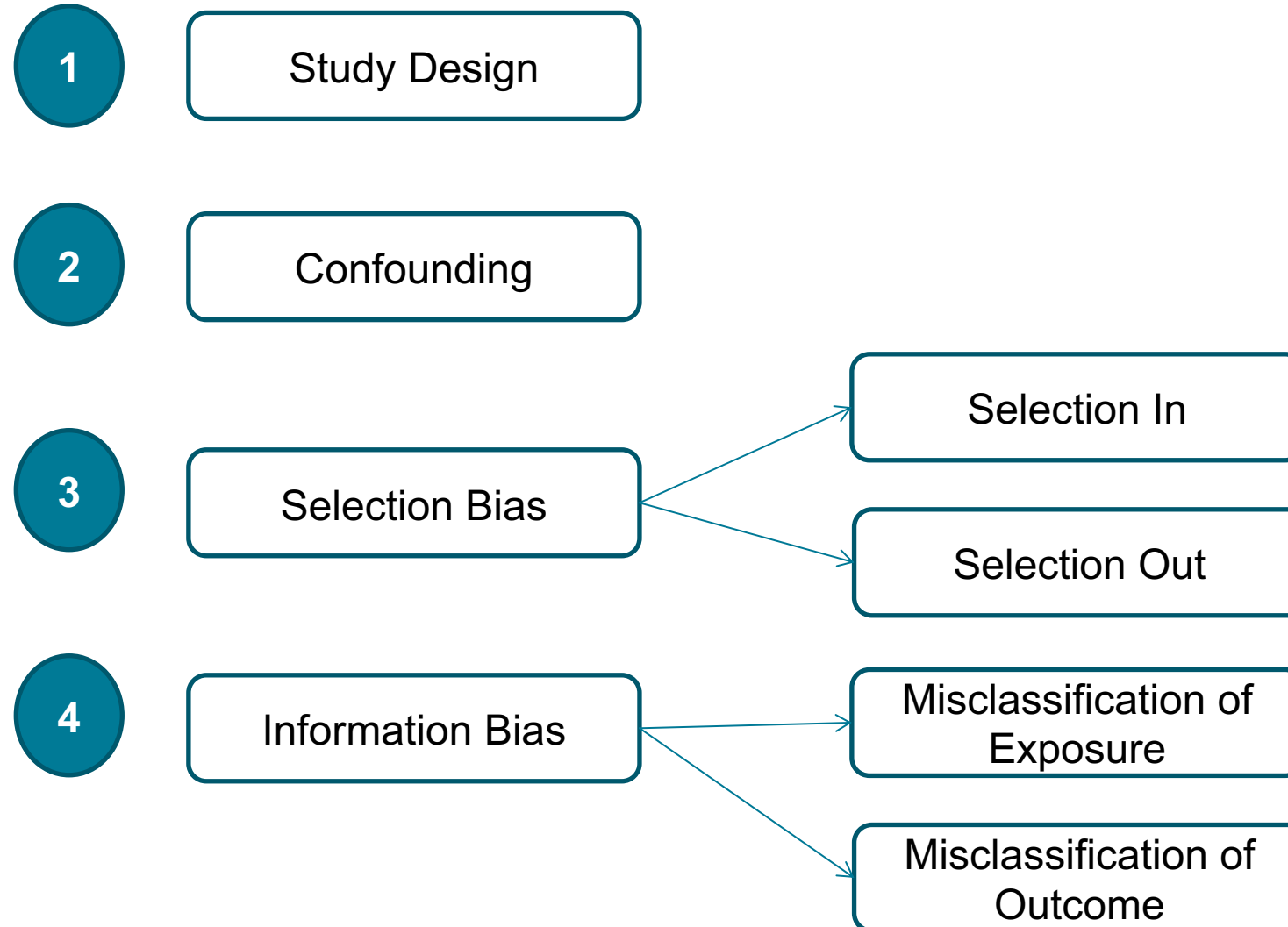


The Promise of Pharmacoepidemiology

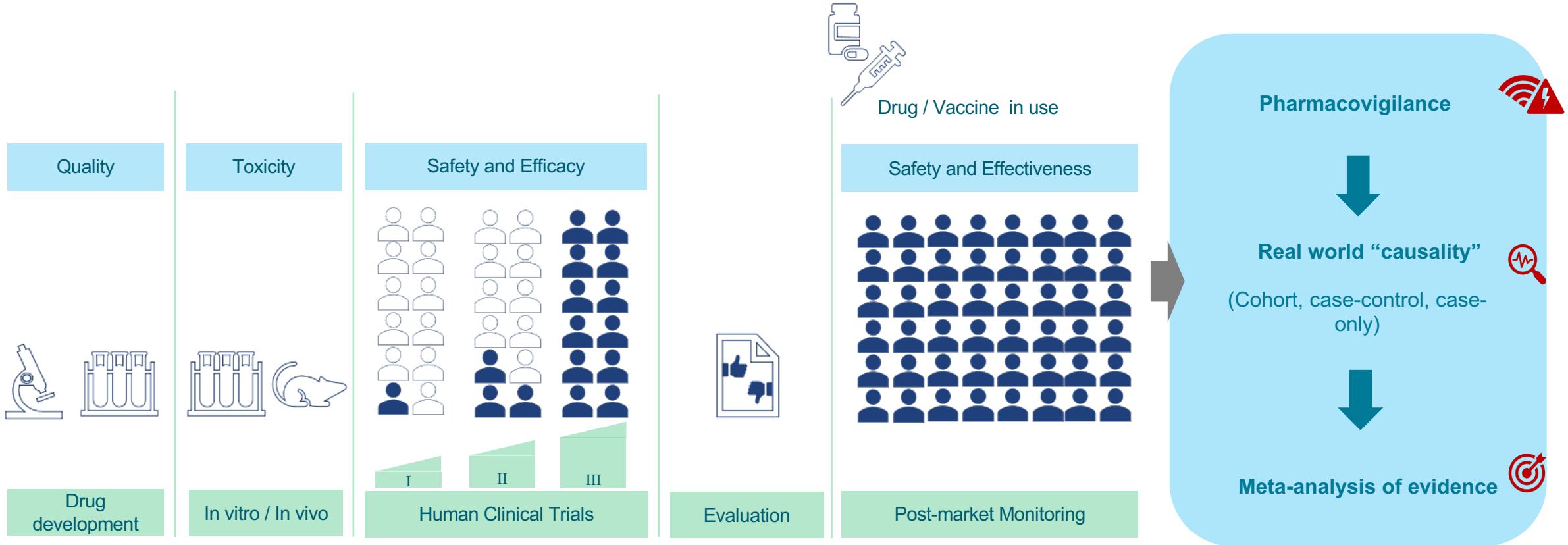
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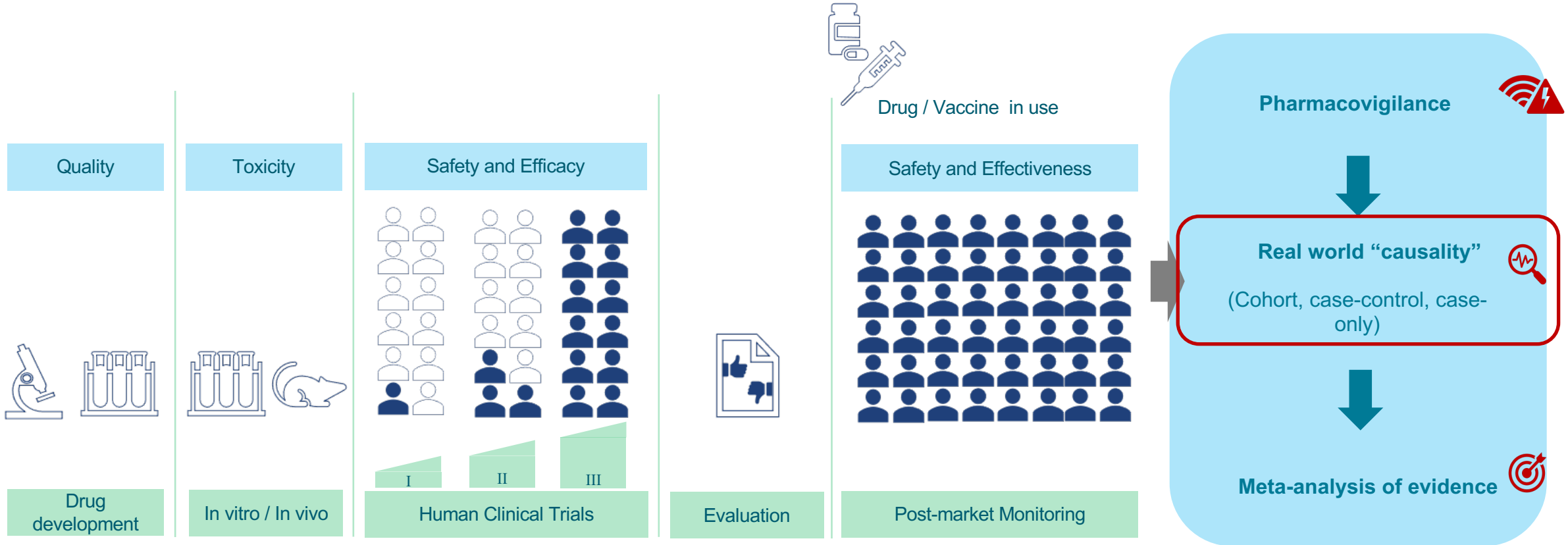
Sources of bias in Pharmacoepidemiology



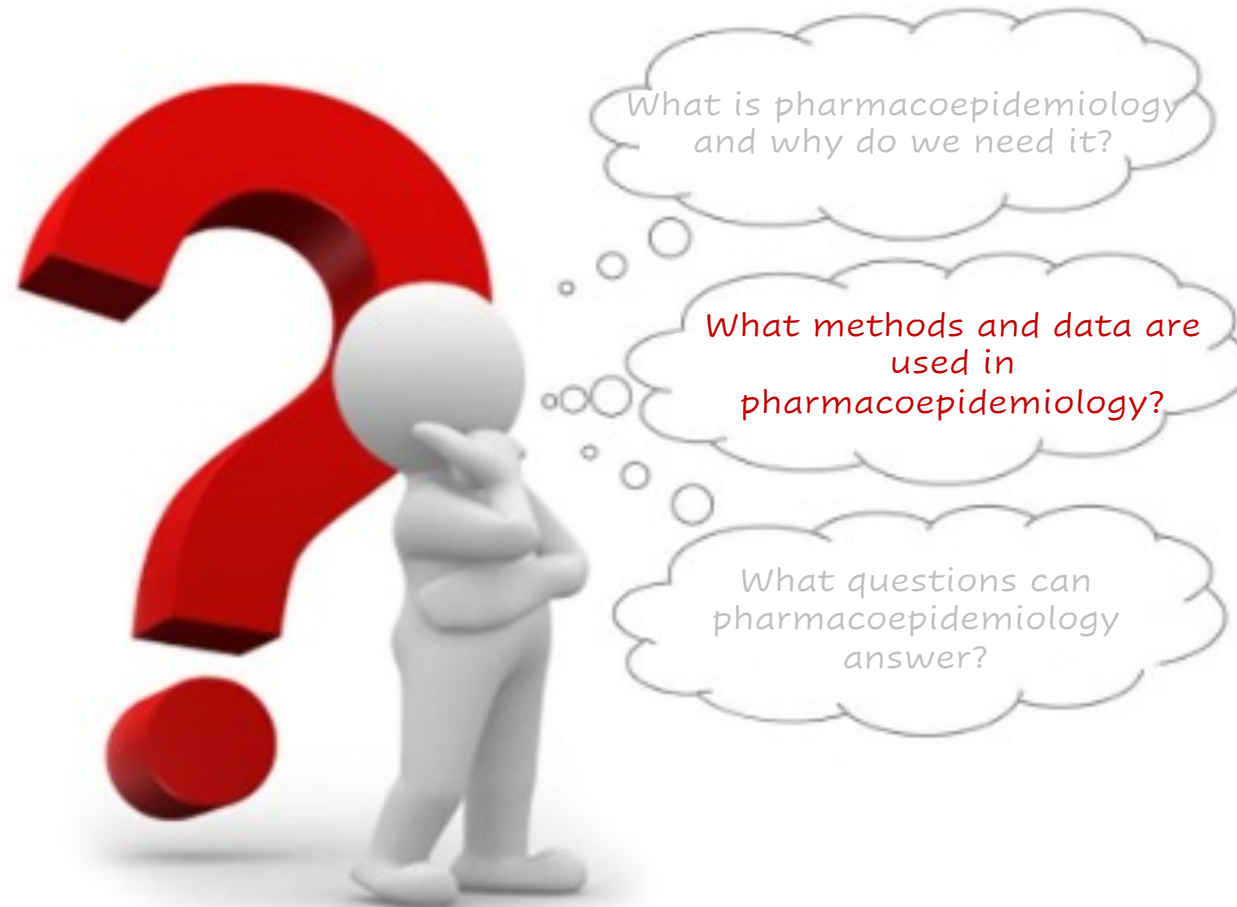
Post-market safety assessment



Post-market safety assessment



Today's aim is to fall in love with pharmacoepidemiology!



How do we conduct epidemiologic research?

- Routinely collected healthcare data for observational study designs







Data that is collected for non-research purposes.





Reimbursement, digital (electronic) health records or surveillance data.

Large population-based and anonymized.




What kind of data can we use?

- **Pharmacovigilance/safety data** 
 - Individual case safety reports reported to a centralized source
 - Only reports where the adverse event was suspected to be related to a drug
- **Administrative claims data** 
 - Insurance data that describe the billable interactions of patients
 - Only includes information that relates to the exchange of money
- **Electronic medical records** 
 - Paperless, digital versions of patient charts
 - Includes information important for the physician in patient care (i.e., what did they prescribe and why)
- **Registry data** 
 - Special purpose databases – usually prospectively collected
 - Smaller in size but richer in data collection for disease or drug specific monitoring

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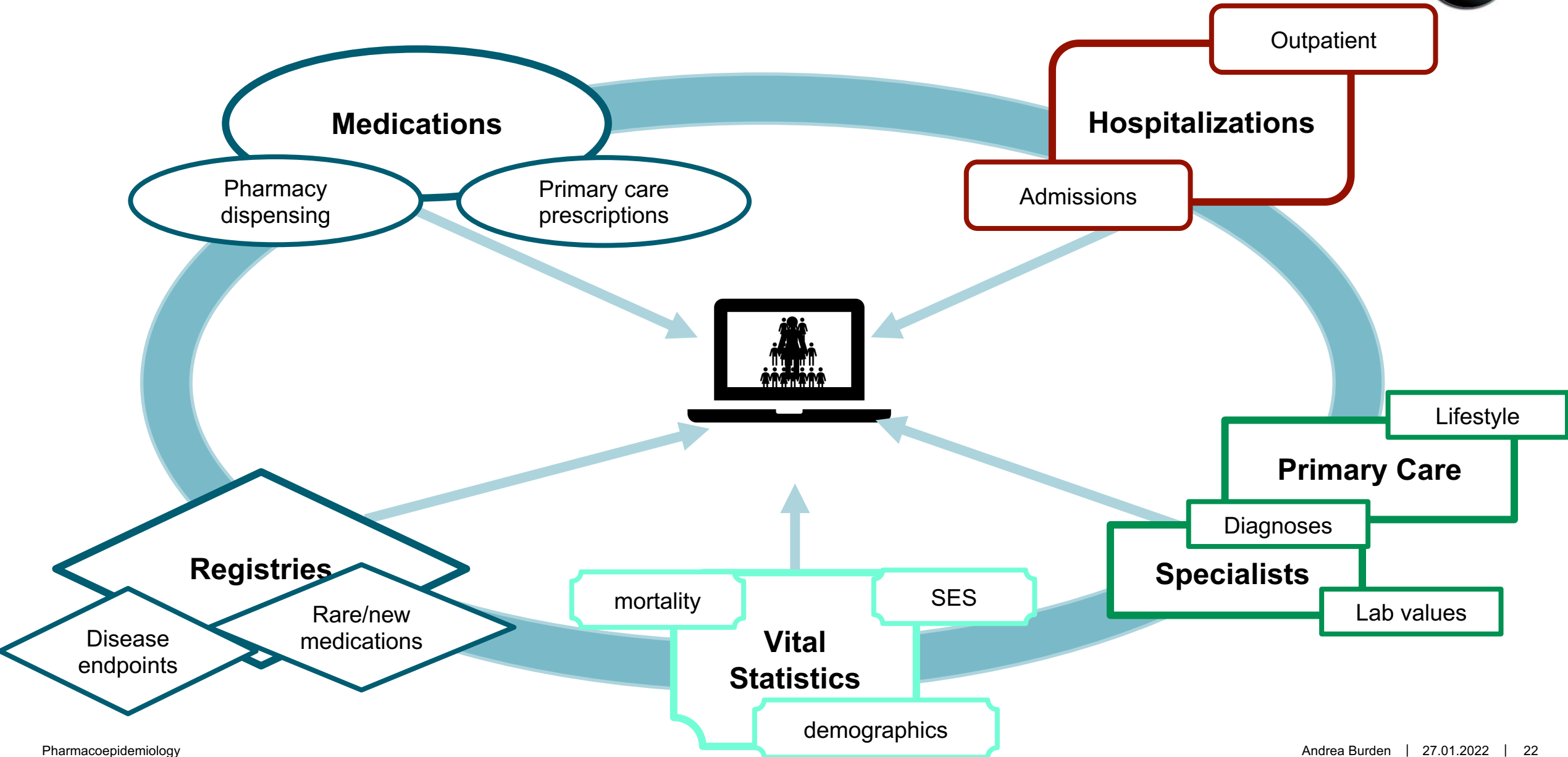
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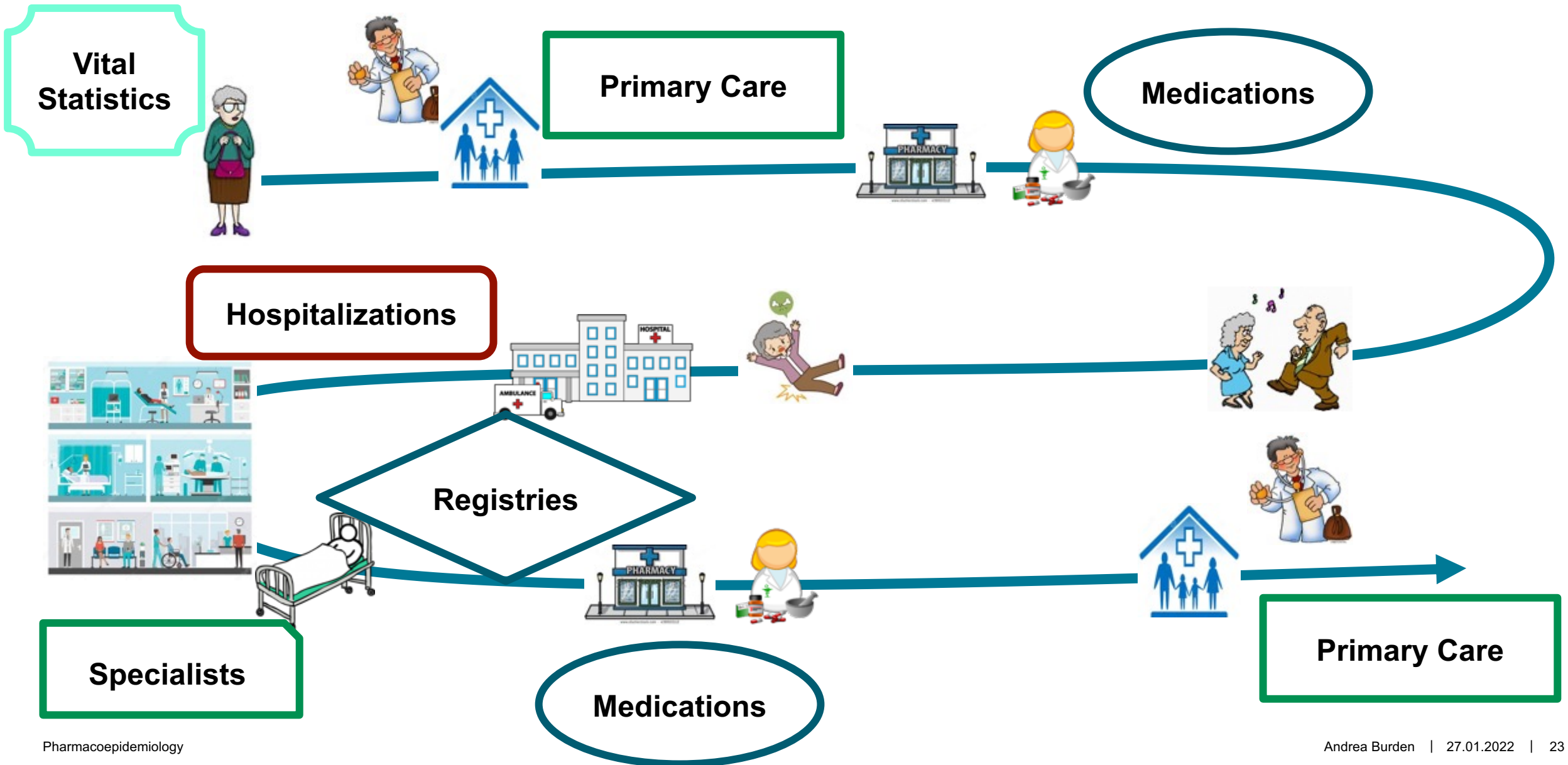
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Take home message:
Collected for purposes other than research

What does real-world data include?



Real-World Healthcare Data



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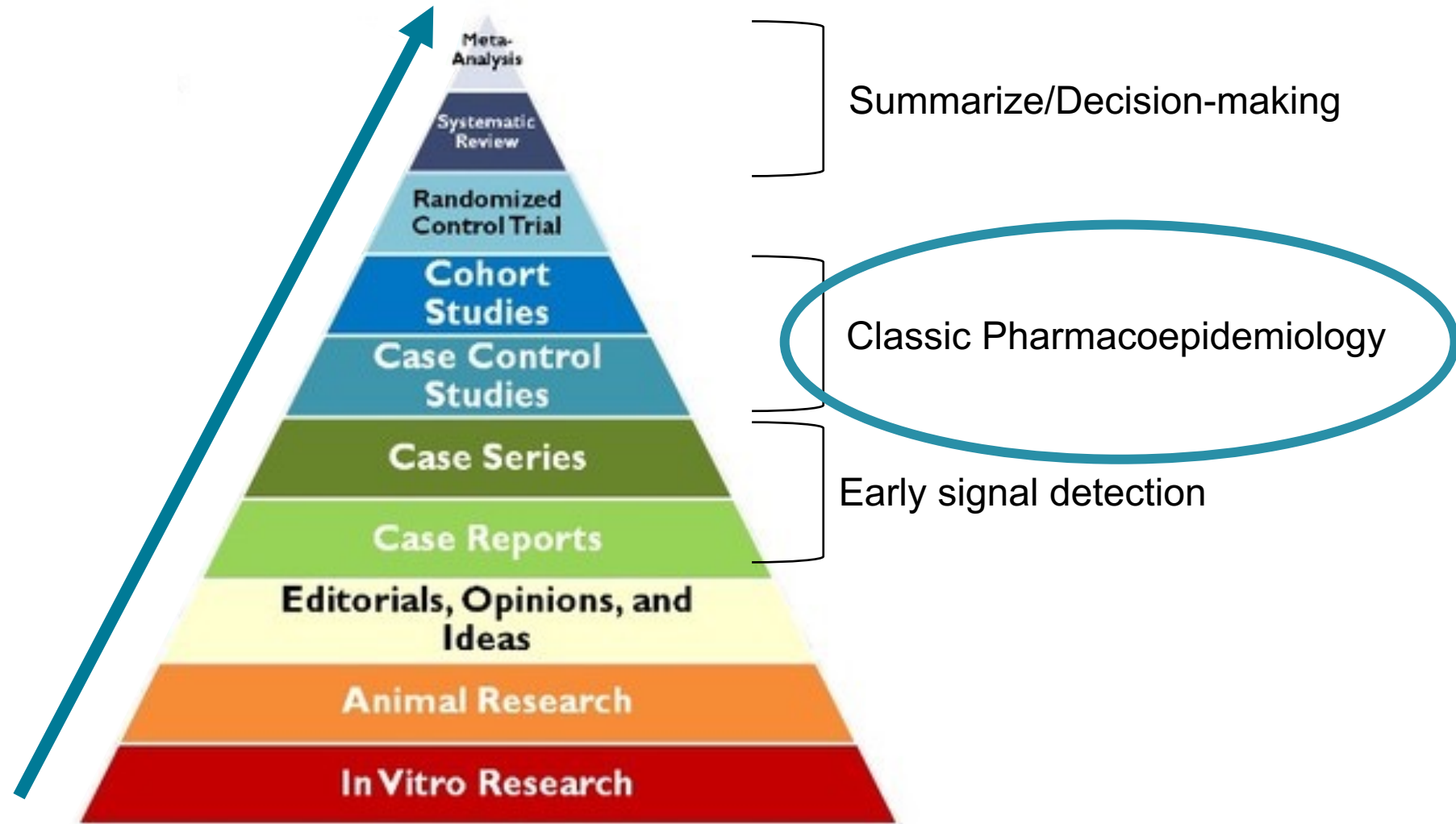
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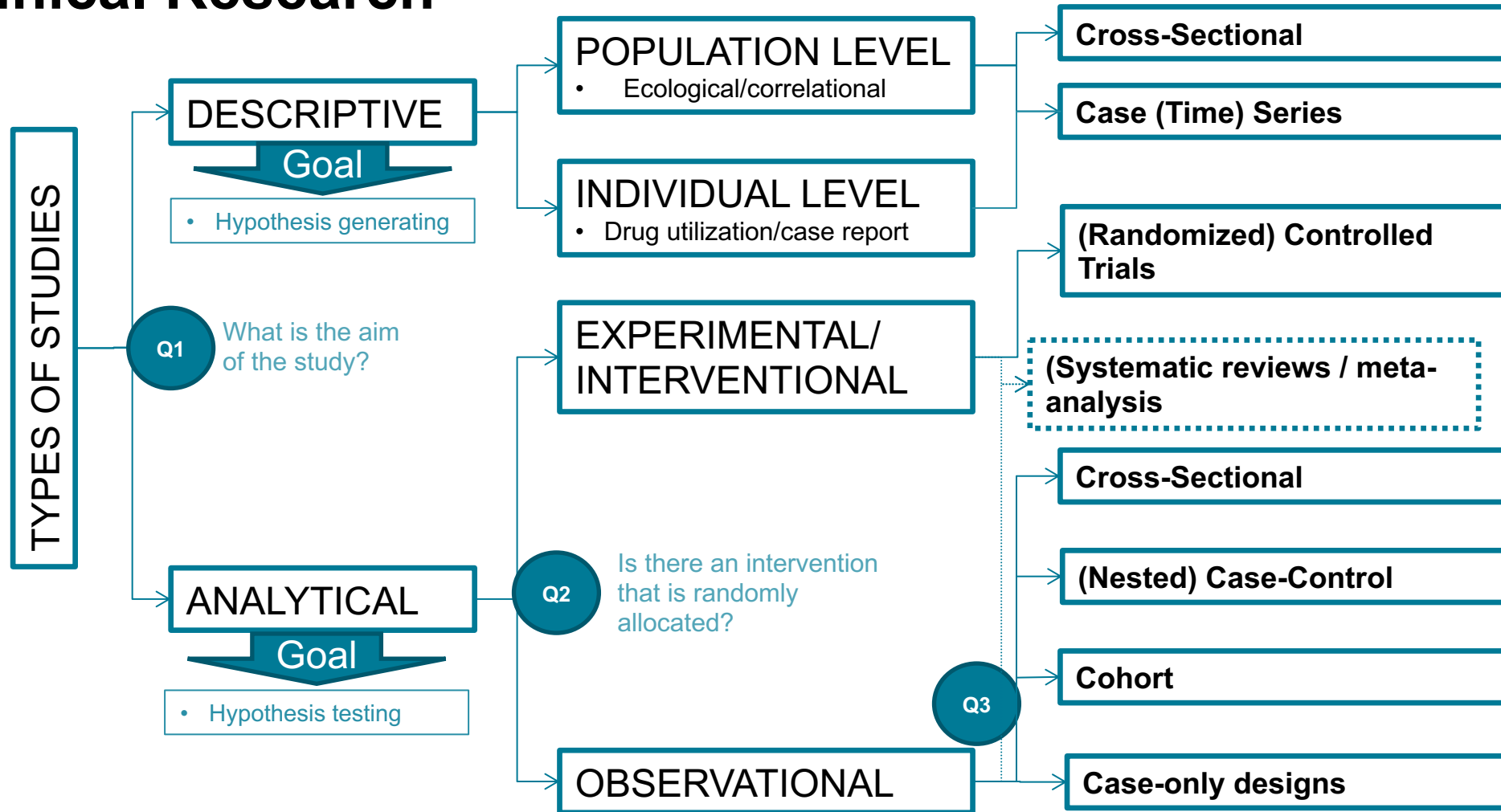
Non-experimental.

Researchers do not determine the exposure. They observe what is already happening in real-world settings.

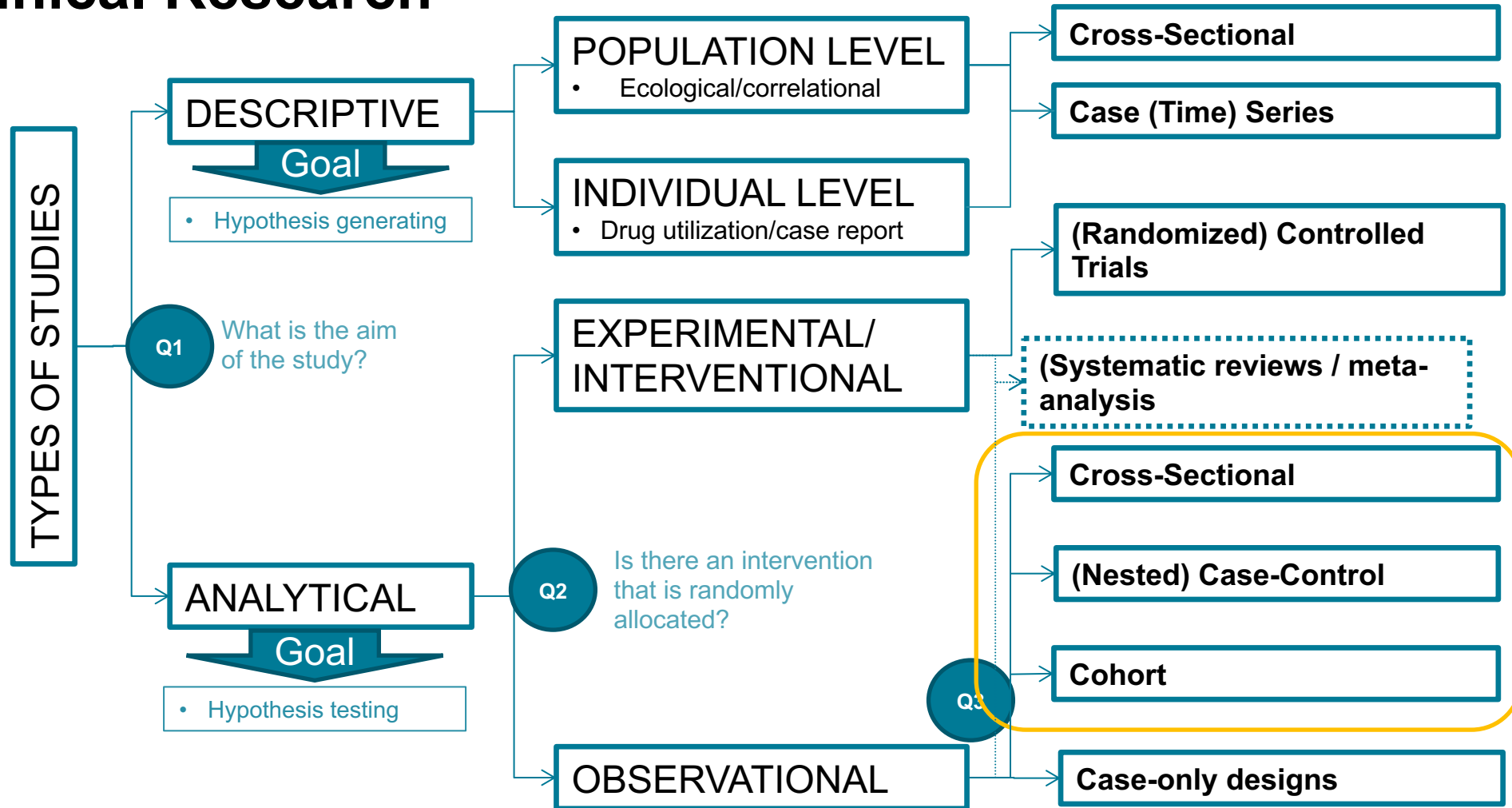
Pharmacoepidemiology in medical evidence

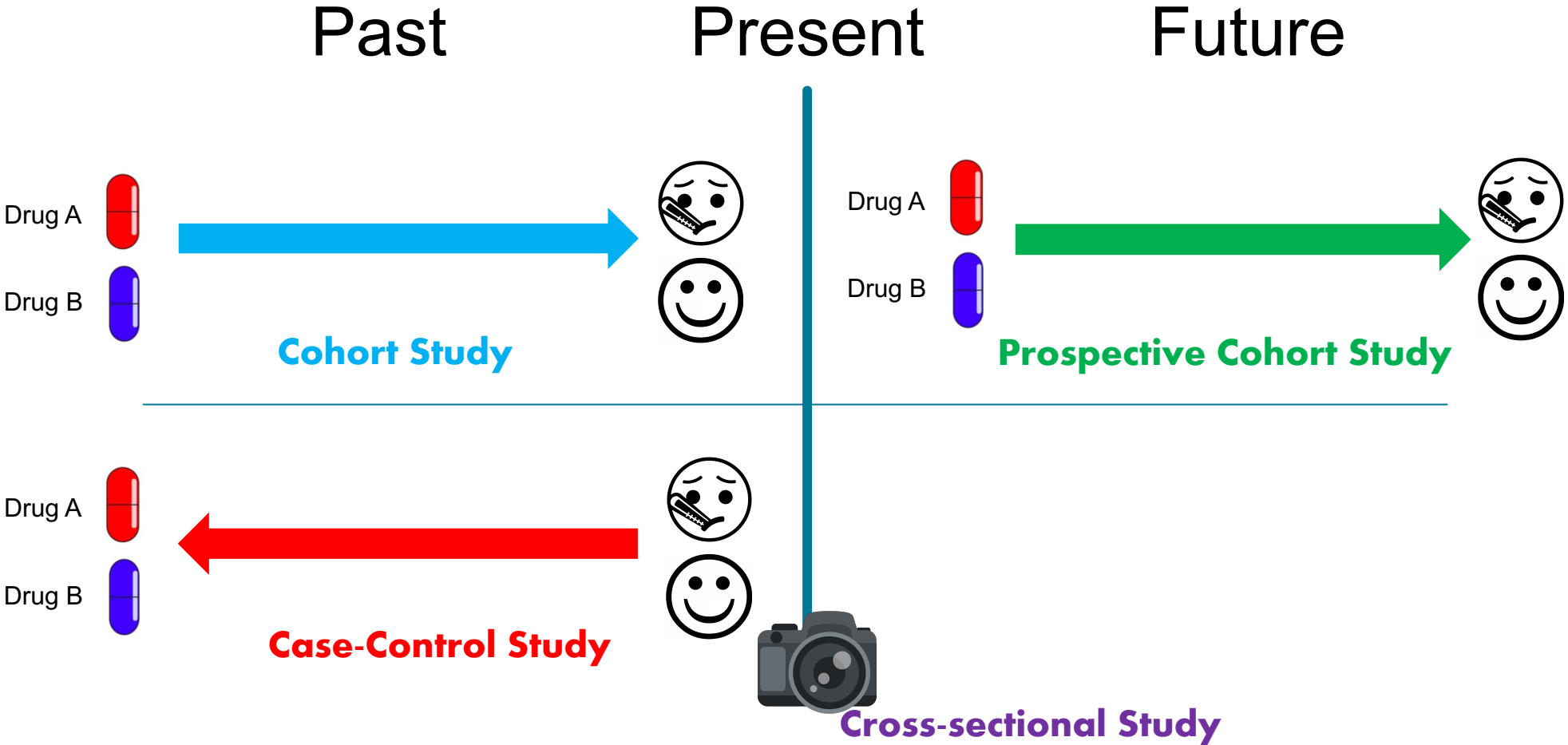


Clinical Research

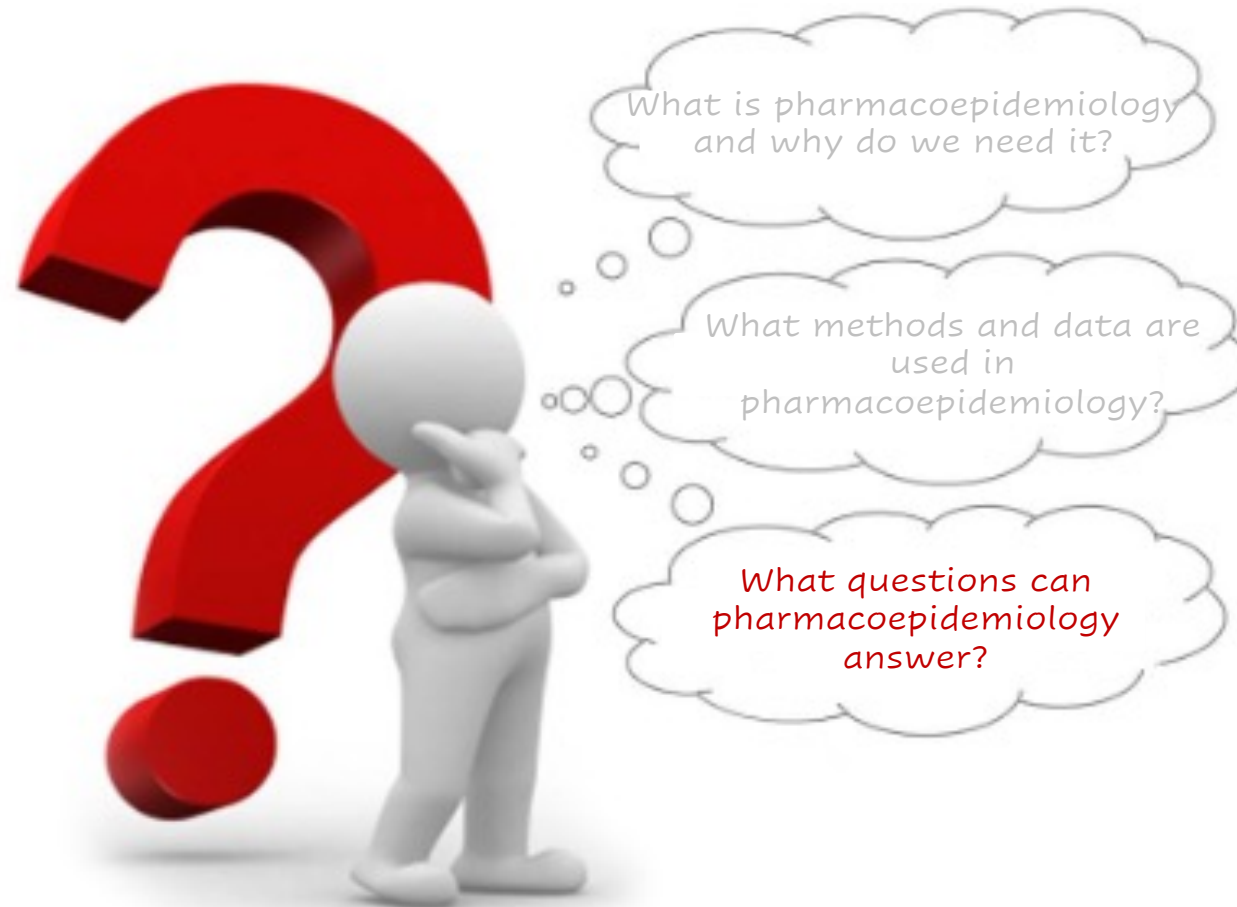


Clinical Research





Today's aim is to fall in love with pharmacoepidemiology!



Common Use of Real-World Data

- Three applications of observational studies with real-world data:
 - Characterization
 - Assess causality
 - Prediction

Public Health Policy



Clinical Practice



Precision Medicine

Common Use of Real-World Data

- Three applications of observational studies with real-world data:

- **Characterization**
 - Pain medication utilization in Switzerland
- **Assess causality**
 - Glucocorticoids and fractures – intervention thresholds

- **Prediction**

Public Health Policy



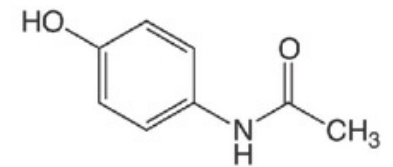
Clinical Practice



Precision Medicine

Public Health: Paracetamol poisonings in Switzerland


- Paracetamol is one of the most commonly used pain medications worldwide
- Indicated for short-term pain and fever relief
- Limited evidence of effectiveness
- High doses can have serious and potentially fatal effects
- Maximum daily dose is 4,000 mg / 24 hours



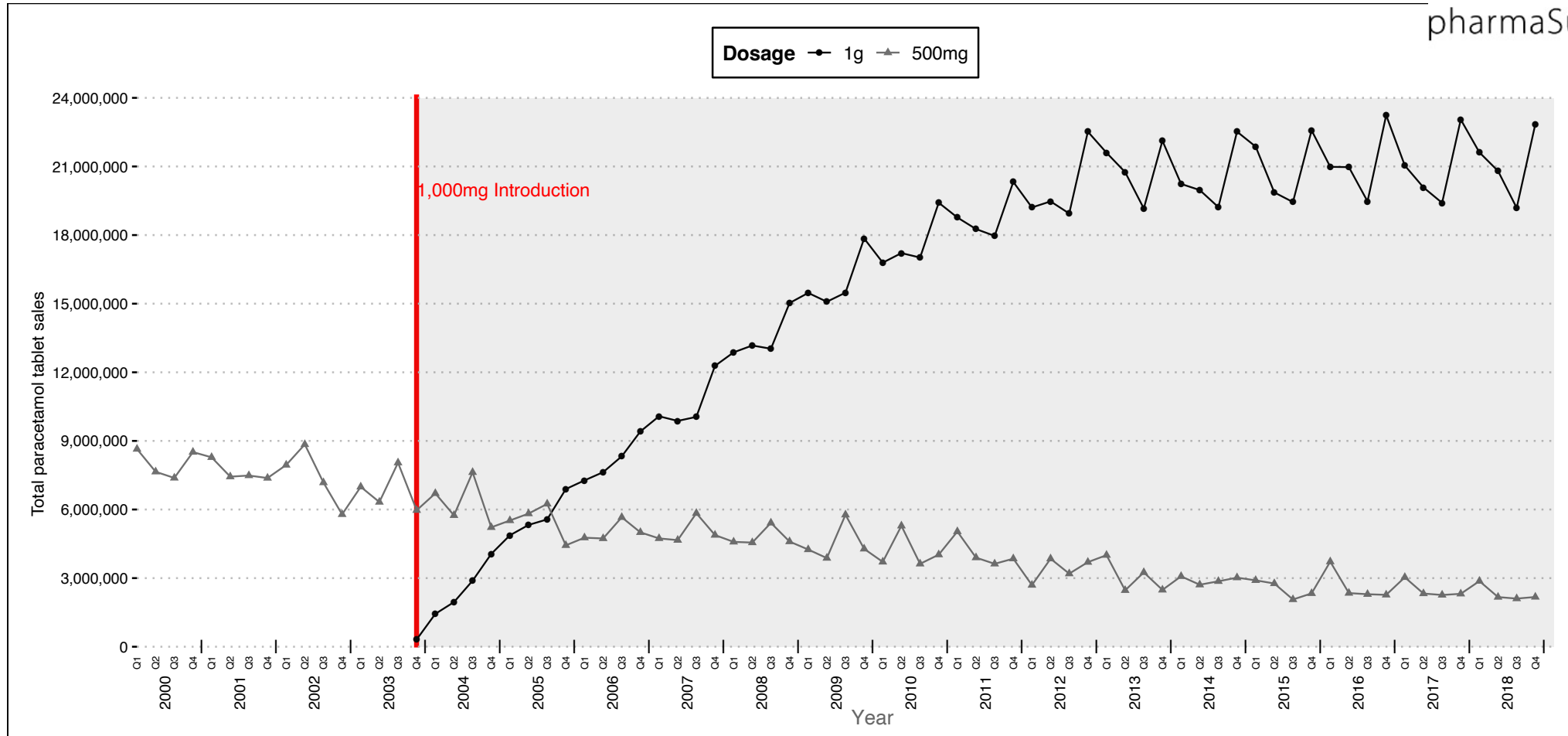
Acetaminophen (APAP, Paracetamol)

Research Question: Did the introduction of the 1,000mg paracetamol tablets increase the number of paracetamol poisonings in Switzerland?

Paracetamol poisonings in Switzerland – study methods

- National prescription Data  pharmaSuisse
 - All paracetamol dispensed in Switzerland community pharmacies (2000-2018)
 - Number of packages sold per quarter tabulated and plotted
- Swiss National Poison Centre Data  **tox** info suisse
 - All suspected paracetamol poisonings reported to the Swiss poison centre (2000-2018)
 - ITS analysis to assess change in poisonings following introduction of 1,000mg tablets
 - Intervention date October 2003 (corresponds to Quarter [Q] 4 2003)
 - Descriptively assess poison reports with 500mg vs. 1,000mg tablets

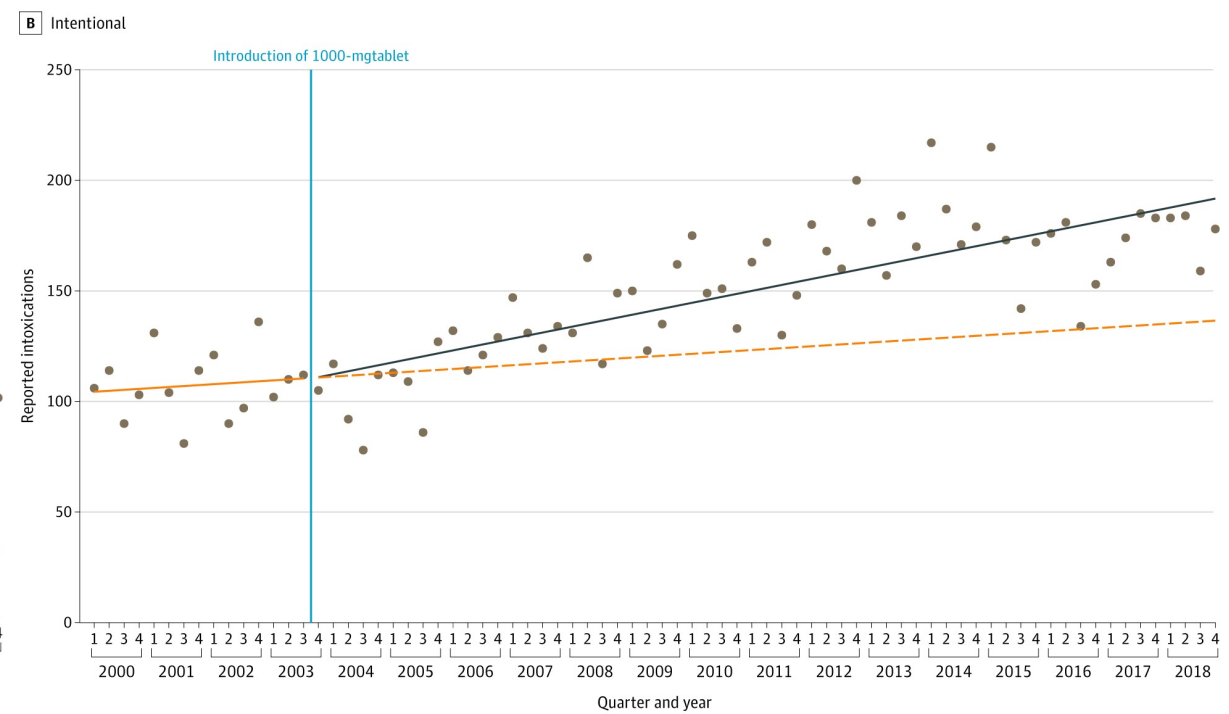
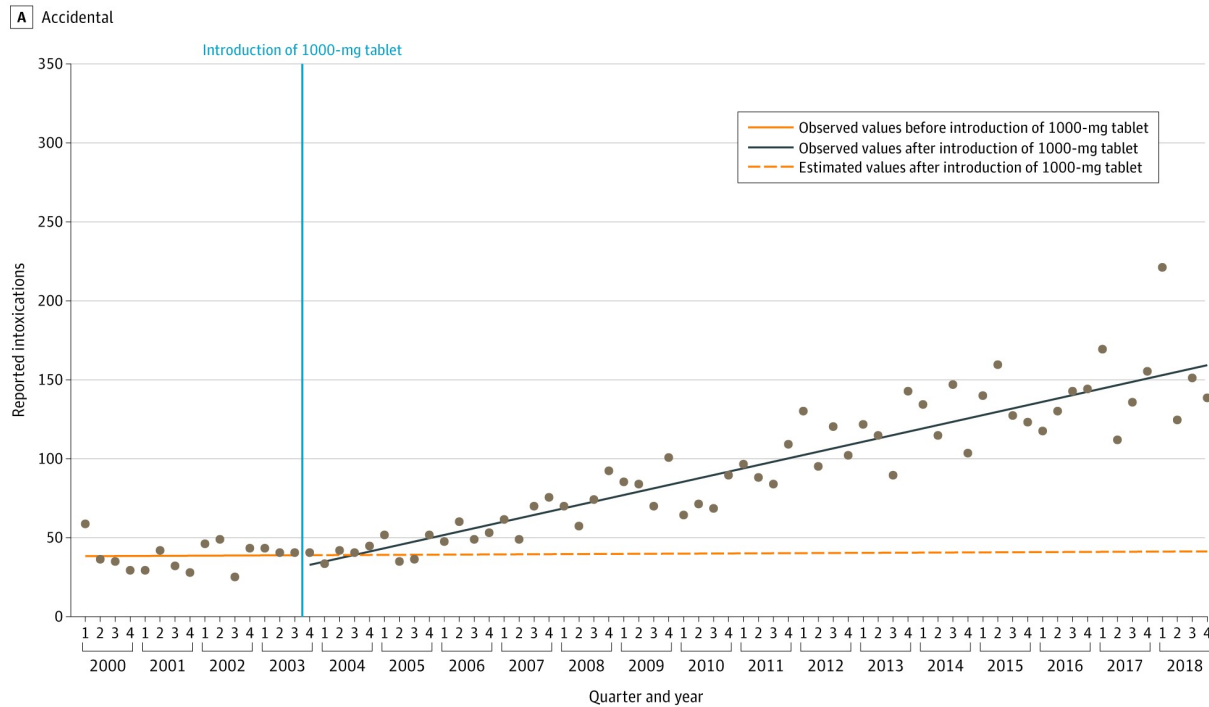
Total Paracetamol Sales in Switzerland by formulation



pharmaSuisse

Martinez de la Torre A et al. JAMA Network Open (2020)

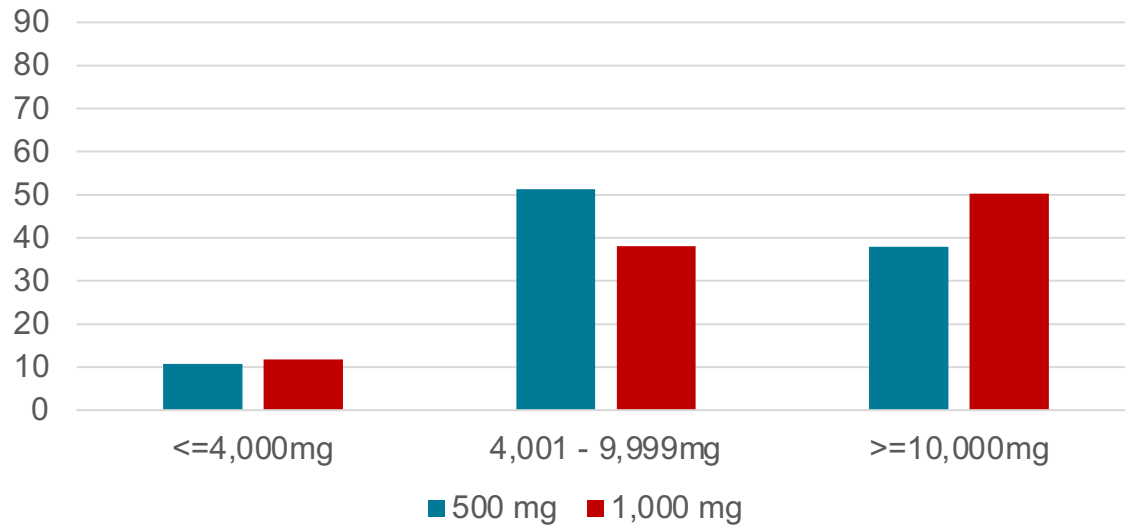
Impact of 1,00mg tablets on paracetamol-related poisonings



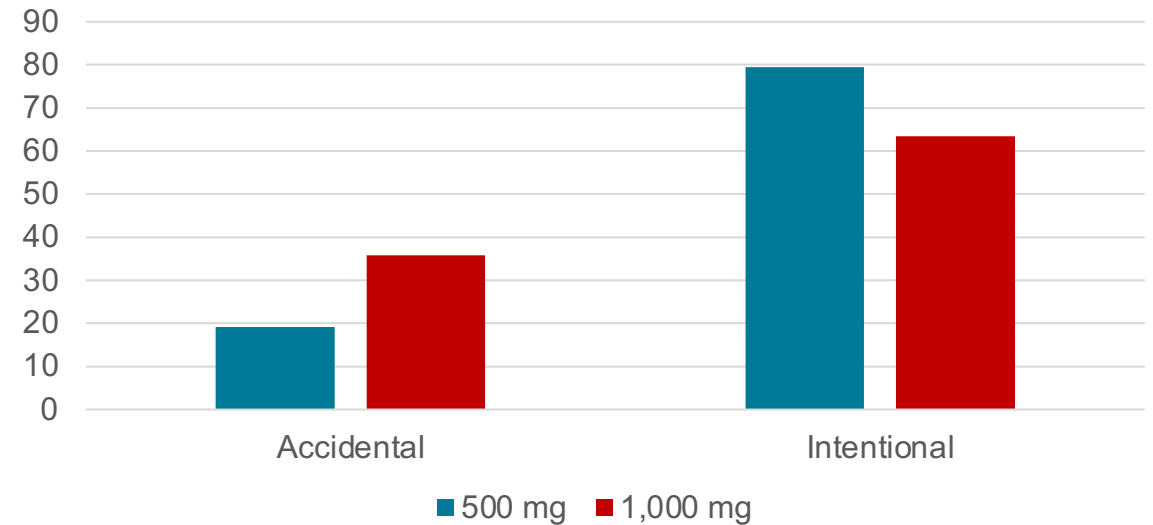
Martinez de la Torre A et al. JAMA Network Open (2020)

Impact of 1,000mg paracetamol on harmful poisonings

Proportion of toxic doses by paracetamol formulation



Proportion of accidental or intentional by paracetamol formulation



Martinez de la Torre A et al. JAMA Network Open (2020)

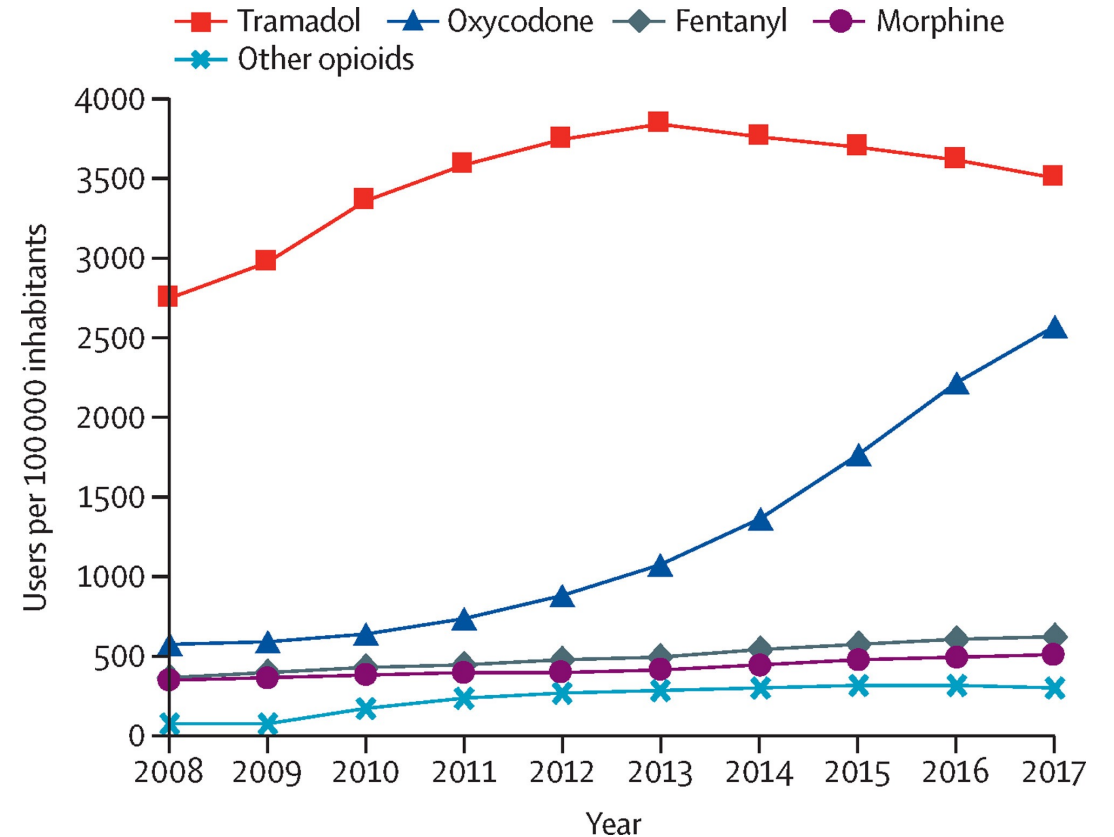
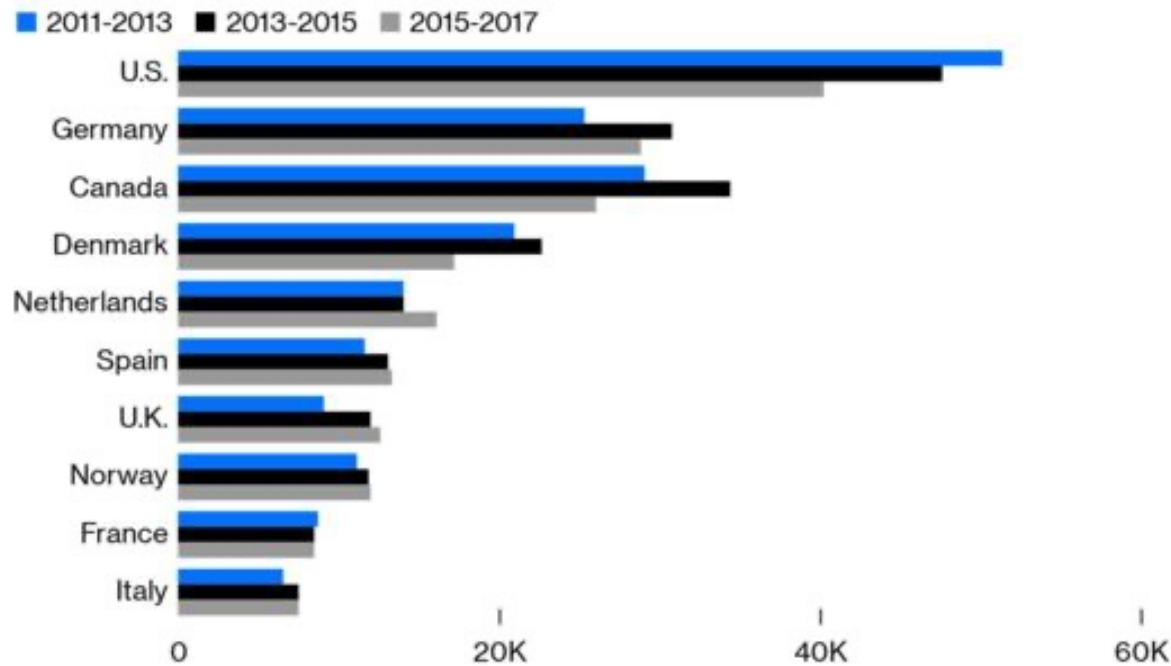
Take Home Message - Paracetamol poisonings in Switzerland

- Significant **increase in the number poisonings**, mirrors increase in use
 - Significant increase in accidental poisonings, but not intentional
 - Increase in the proportion of patients with toxic or lethal doses (>4g or >10g)
 - Proportion with >10,000 mg paracetamol was higher among those with 1,000mg tablets
- The **high number of accidental poisonings** suggests greater care in prescribing information should be taken
- **Benefit-risk** should be considered before giving paracetamol in high doses
 - No evidence of efficacy in chronic pain

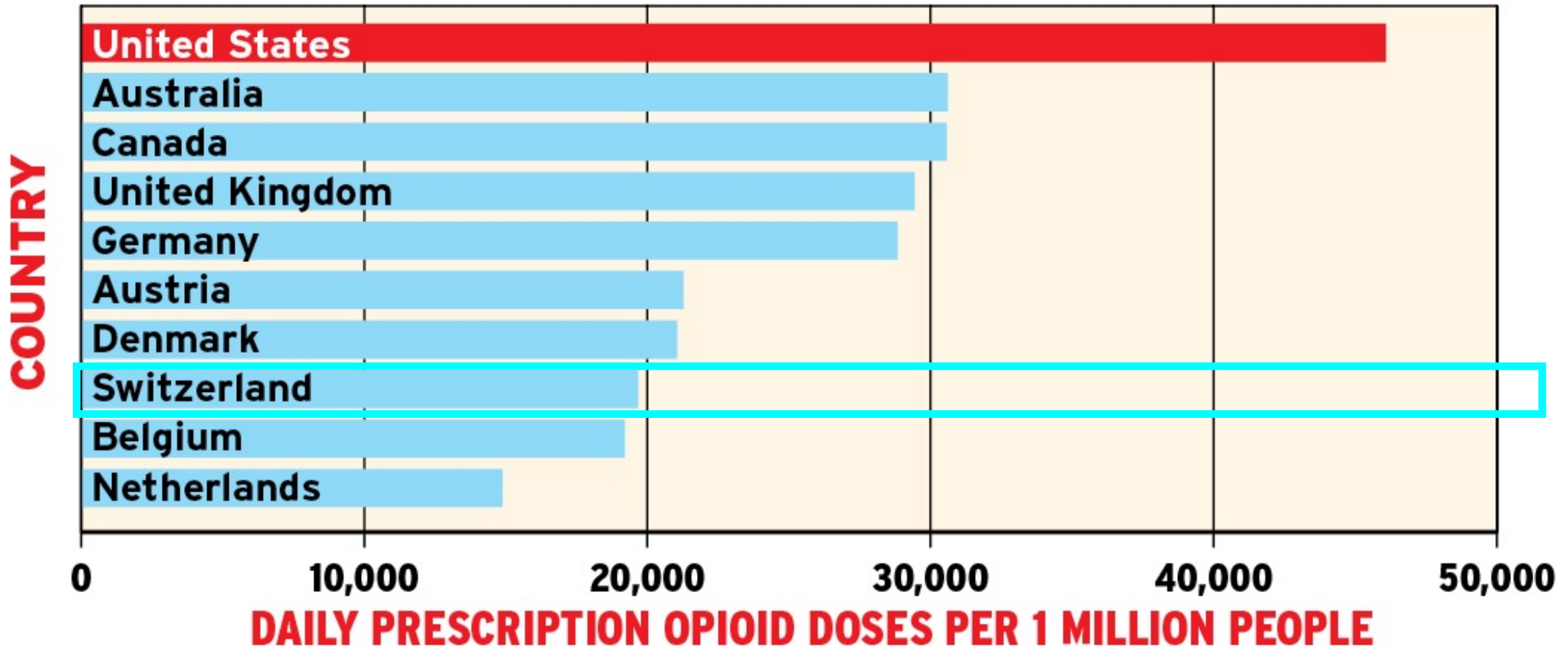
Drug Utilization Study: Opioid use and overdose in Europe

- Opioid epidemic in the US is well known, but there is **increasing use in Europe** [1]

Prescription opioid consumption in defined daily doses per million inhabitants per day



Use of legal prescription opioids – positioning Switzerland



SOURCE: UNITED NATIONS INTERNATIONAL NARCOTICS CONTROL BOARD, 2016 DATA

Research objectives



- With growing use of opioids across Europe in the last decade, we sought to:
 - To evaluate 20-years of sales and overdoses associated with opioids in Switzerland
 - To assess differences between potency and type

Conclusions

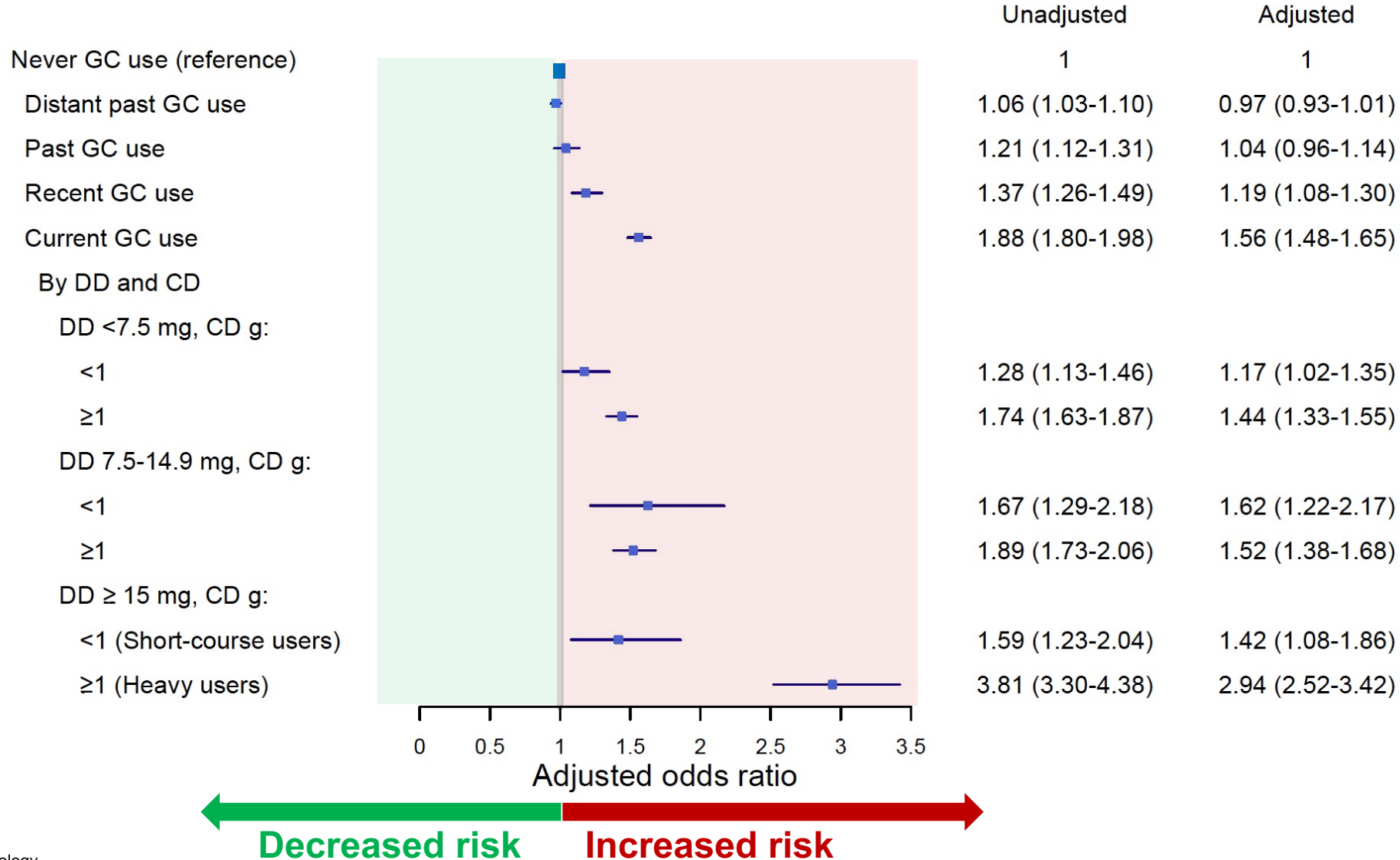
- Increasing trends in Swiss opioid sales and poisonings
 - Most pronounced increase in **strong opioids**
 - Substantial increase in **oxycodone** sales and poisonings - particularly since 2008
- High per capita sales of strong opioids to community-dwelling inhabitants suggests opioids are **not restricted to palliative cancer pain management**
- While the Swiss rates of sales and poisonings remain below those in North America - **National monitoring is warranted**
- Swiss guidelines on pain management should be reviewed to avoid an opioid crisis

Clinical Impact: Safety of glucocorticoids – threshold effects

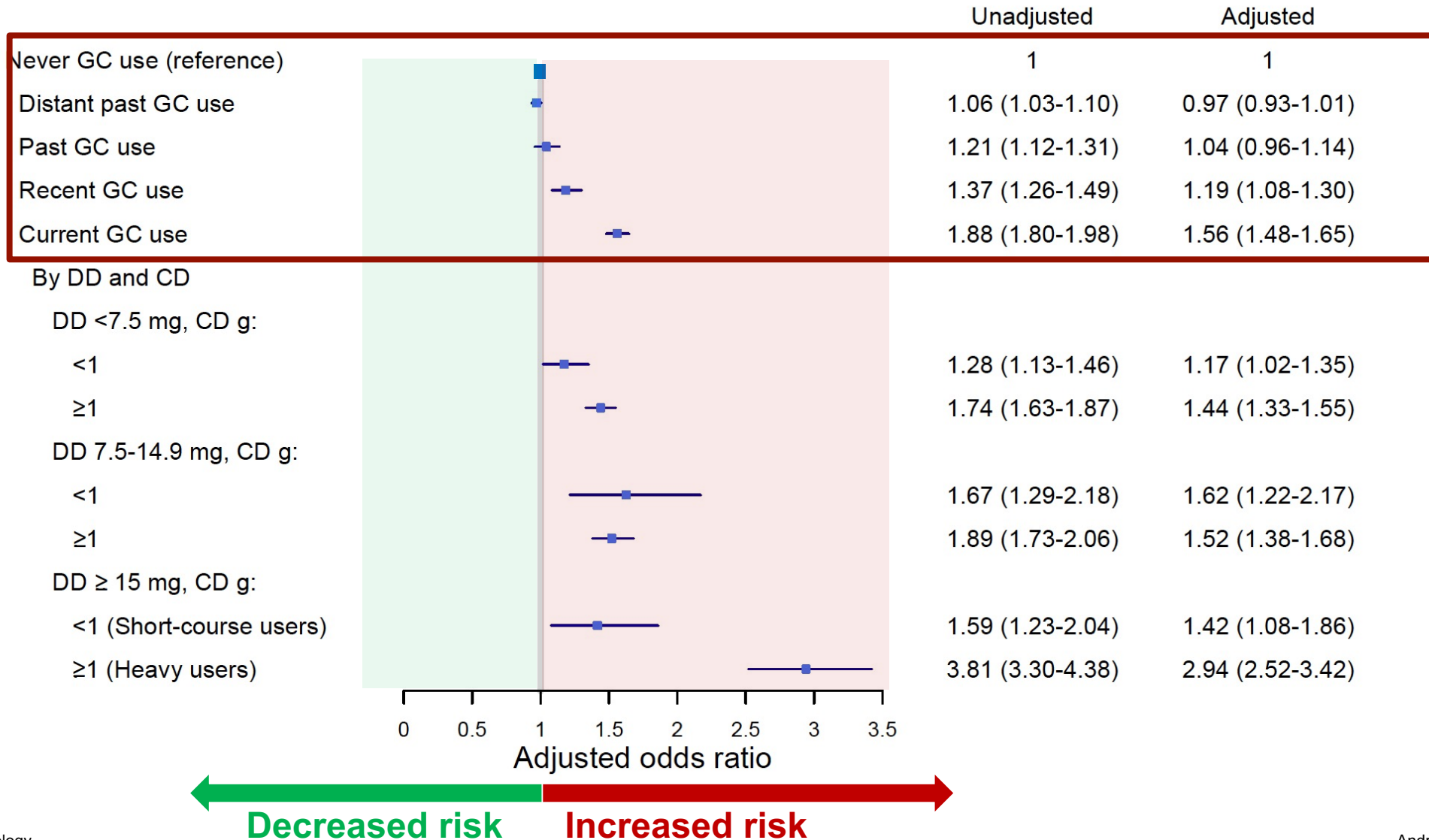
- Indications often have frequent short-courses or tapering regimens for symptom management
- Oral glucocorticoids are associated with an increased fracture risk
- Effect on fracture risk is dose dependent (≥ 15 mg day), but effect of cumulative exposure, and interaction with daily dose, is unclear

Research Question: To investigate the effect of intermittent vs. long-term glucocorticoid exposure on hip fracture risk

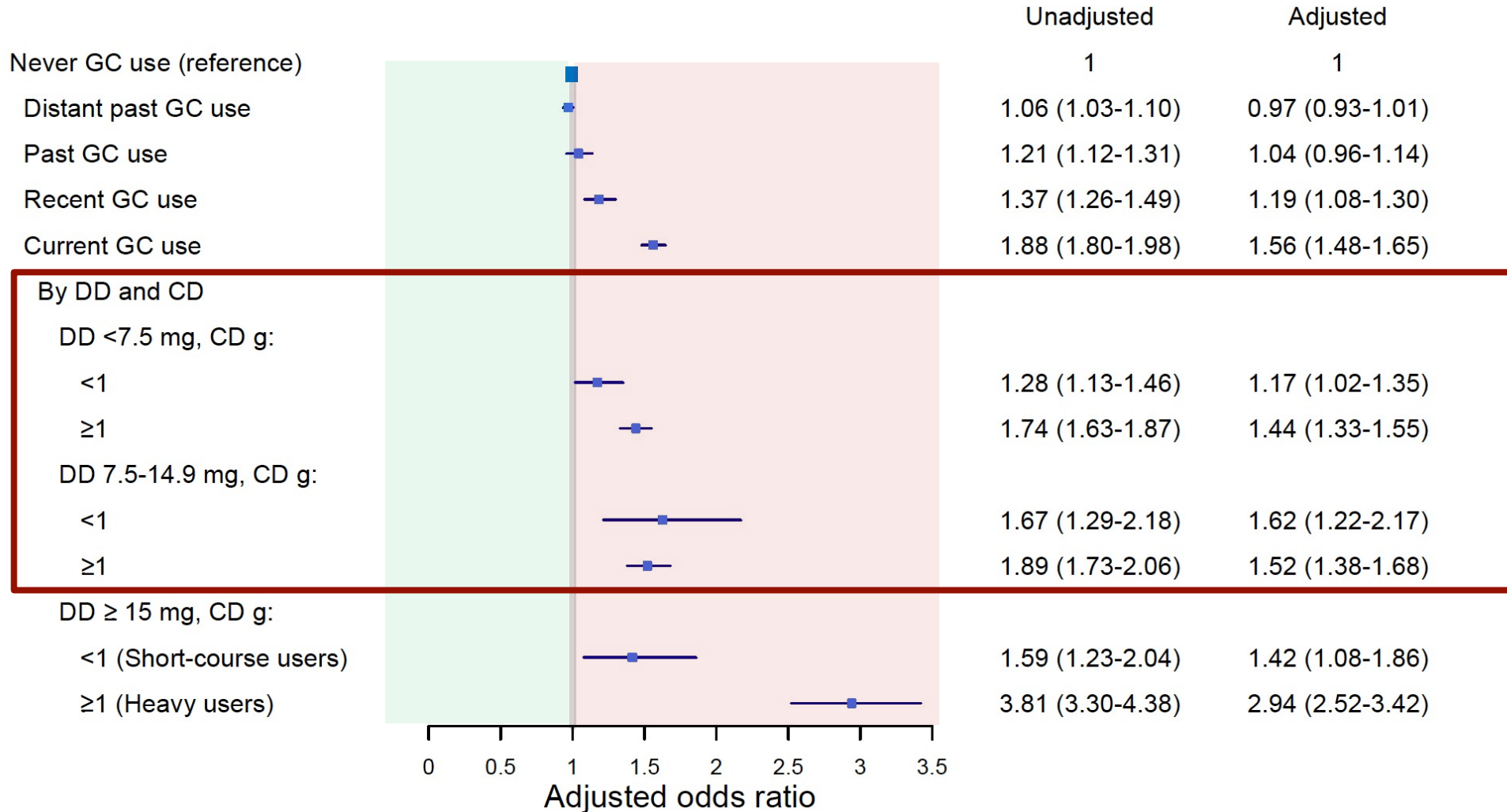
Glucocorticoid thresholds and hip fracture risk



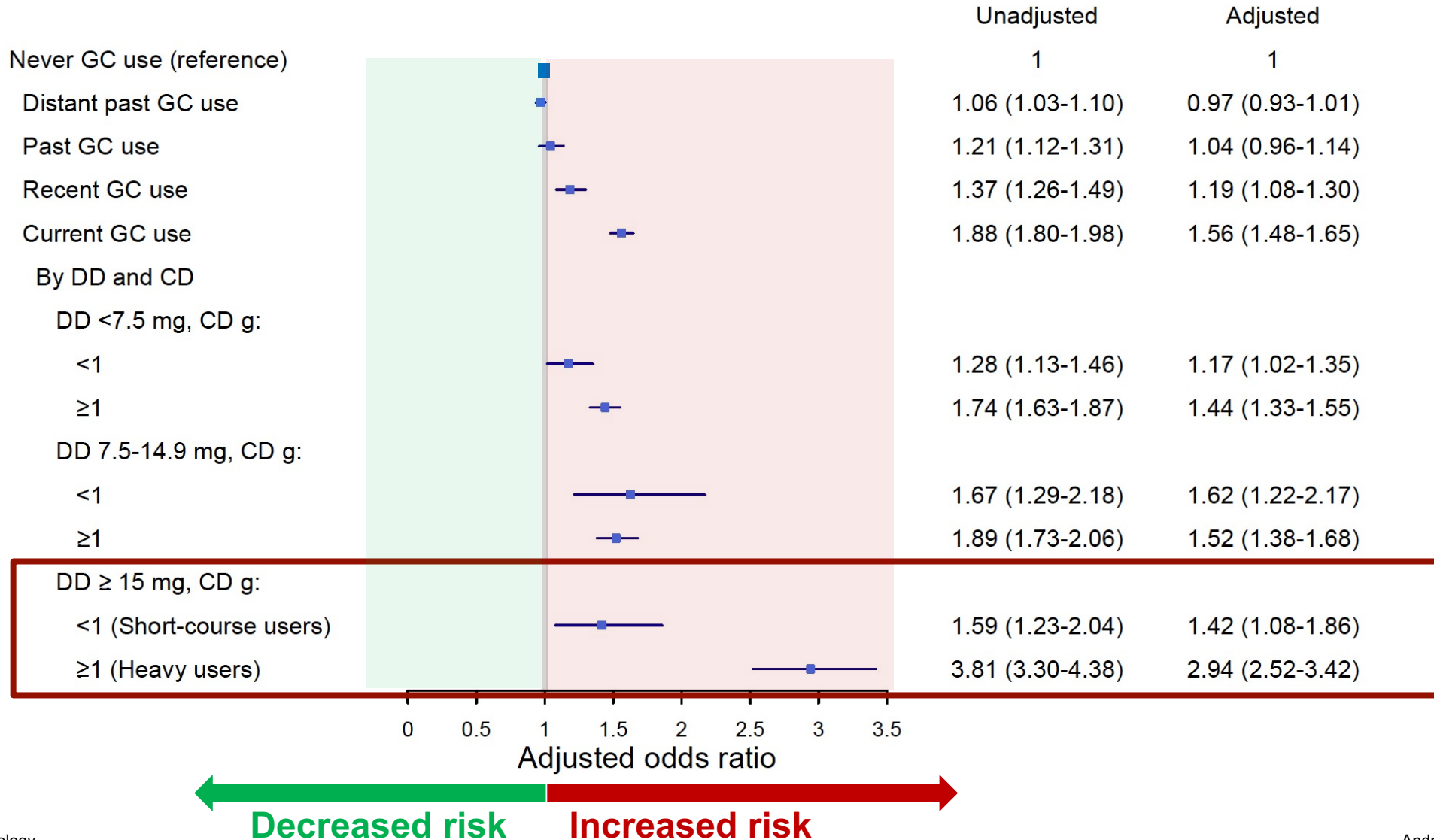
Glucocorticoid thresholds and hip fracture risk



Glucocorticoid thresholds and hip fracture risk



Glucocorticoid thresholds and hip fracture risk



Glucocorticoid thresholds - take home message

- Risk of hip fracture **increased 56%** given current use of glucocorticoids
- **High daily-dose** (≥ 15 mg) and **high-exposure** (≥ 1 gram) was associated with an almost **3-fold increase** in hip fracture risk
- The **threshold of 1-gram cumulative exposure among patients receiving ≥ 15 mg** prednisone equivalent daily can be used to **identify high risk** patients to be targeted for fracture prevention (e.g., initiate anti-osteoporosis drugs)

Closing Remarks

- Real-world studies can overcome common limitations in clinical trials
 - Restricted patient sample
 - Limited follow-up
 - Small sample sizes for rare adverse event detection
- Challenges can be overcome if researchers follow key principles:
 - Ensure the data source contains the needed information
 - Match the study design to the research question
 - Control for sources of bias and confounding
- Well conducted pharmacoepidemiology studies are essential to inform drug safety and clinical decision making

Critical thinking is essential medical evidence

“ It is easy to lie with statistics and graphs because few people take the time to look under the hood and see how they work.”

“We – each of us – need to **think critically and careful about the numbers and words** we encounter... This means checking the numbers, the reasoning, and the source for plausibility and rigor. It means **examining them as best we can before we repeat them or use them to form an opinion**. We want to avoid the extremes of gullibly accepting ever claim we encounter or cynically rejecting ever one. **Critical thinking doesn't mean we disparage everything, it means that we try to distinguish between claims with evidence and those without.**”

-Daniel Levitin, “Weaponized lies: how to think critically in the post-truth era”



**Thank you for your
attention!**

Questions?

Please connect with us!



<http://pharmacoepidemiology.ethz.ch/>



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