STRATOS INITIATIVE

STRengthening Analytical Thinking for Observational Studies

Accessible and Accurate Guidance in the Design and Analysis of Observational Studies

On some contributions of STRATOS Topic Group 5 on Study Design: Guidance for the Design of Observational Studies to Estimate the Effects of Long-term Drug Exposures on Safety Outcomes

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Joint Statistical Meetings

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STRATOS INITIATIVE Topic Group 5

https://tg5.stratosinit.org/home

Website

Aim

To provide accessible and accurate guidance in the design of observational studies.

Key Principles

There already exist several guidelines for **reporting** the findings of observational research, notably the STROBE Statement and various extensions, e.g. when using routinely collected data (RECORD), or when examining genetic associations (STREGA).

TG5 focus is on developing guidance for **planning** observational studies. Key steps are: 1) define study objectives, 2) select the best design that minimizes threats to validity while acknowledging practical constraints, and 3) outline the main analytical approaches to ensure analyses are in accord with study aims.

Topic group 5 is a member of the STRATOS Initiative (STRengthening Analytical Thinking for Observational Studies) which is a large collaboration of experts in many different areas of biostatistical research. Ongoing research, discussions and activities within STRATOS are conducted in nine topic groups and several cross-cutting panels.

Members

Co-Chairs:

- Mitch Gail
- Suzanne Cadaratte

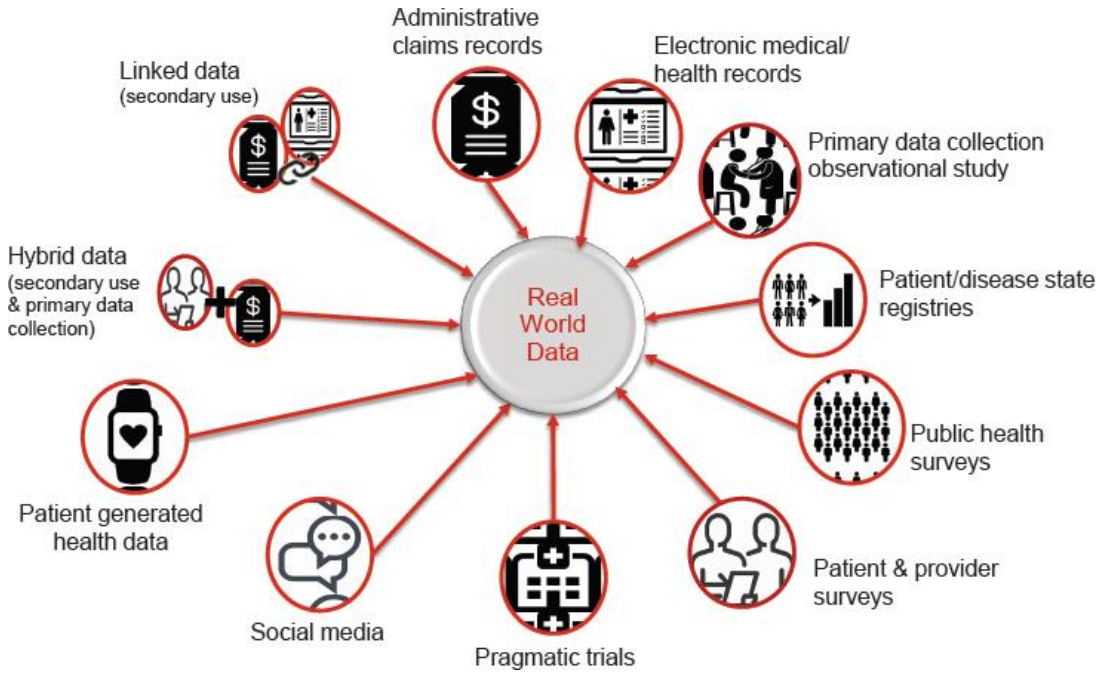
Members:

- Nicholas Bakewell (early career)
- Gary Collins
- Susan Halabi
- Rima Izem
- Thomas Lumley
- Paola Rebora
- Peggy Sekula
- Neus Valveny

Introduction

- Observational studies using real-world data have a vital role in quantifying the comparative safety of long-term treatments.

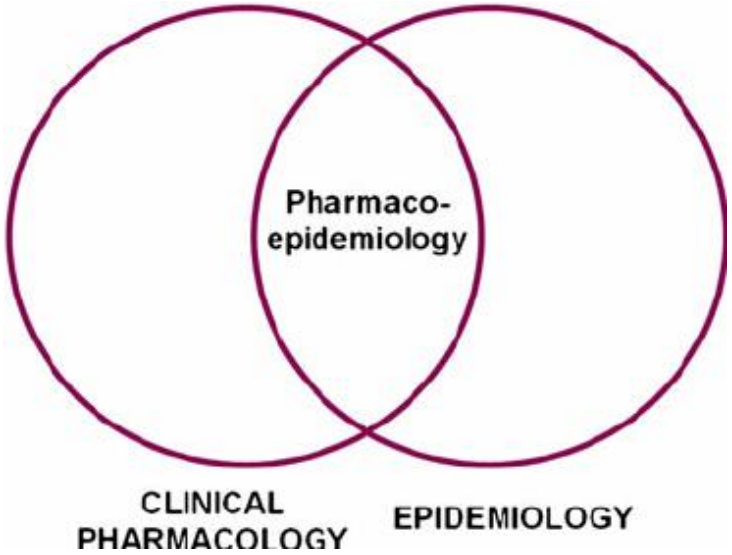
- Study design is critical - statistical methods alone are not enough.



Source: https://nap.nationalacademies.org/read/25352/chapter/7#72

Objectives

- Leveraging results from a scoping review of studies using real-world data to estimate the effects of antidiabetic medications on fracture risk, we:
  - establish purposeful connections between clinical pharmacology foundations and principles of pharmacoepidemiology; and
  - demonstrate how to consider study design aspects when designing aiming to estimate the long-term safety of antidiabetic medications on hip fracture.



Source: Wettermark, 2013

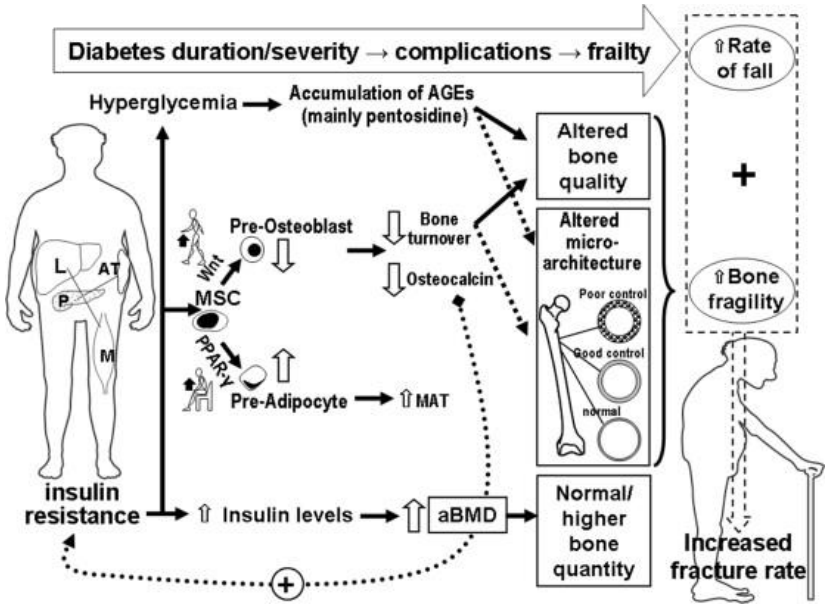
Key Consideration 1:

PATHOPHYSIOLOGY OF THE CHRONIC DISEASE BEING TREATED

PATHOPHYSIOLOGY OF THE CHRONIC DISEASE BEING TREATED

- Start with substantive knowledge - use **pathophysiology** to develop biologically plausible hypotheses before data analysis.

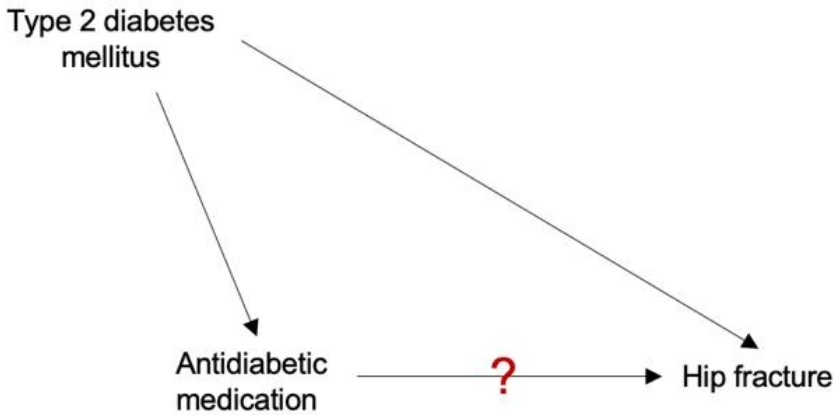
- **Use causal diagrams** (like directed acyclic graphs (DAGs)) early in the design stage to visualize relationships.

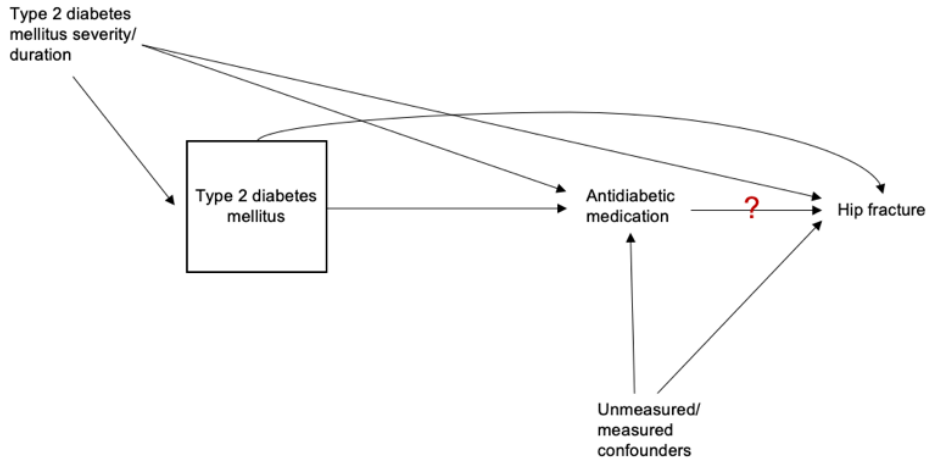


Source: Carnevale et al., 2014

PATHOPHYSIOLOGY OF THE CHRONIC DISEASE BEING TREATED

- Pathophysiology of T2DM has been linked to hip fracture risk.
  - Includes pathways that reduce BMD and increase falls risk.
- Key challenge to highlight: mitigating confounders like T2DM severity and confounding by indication.



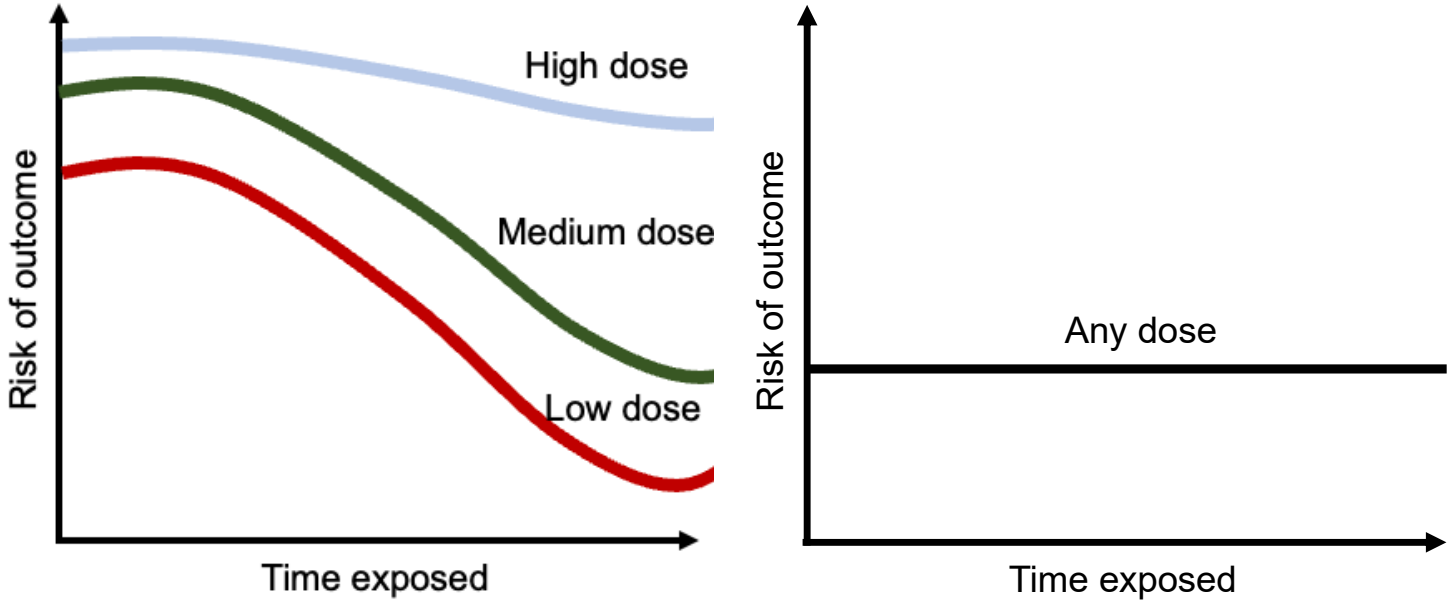


Key Consideration 2:

CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY

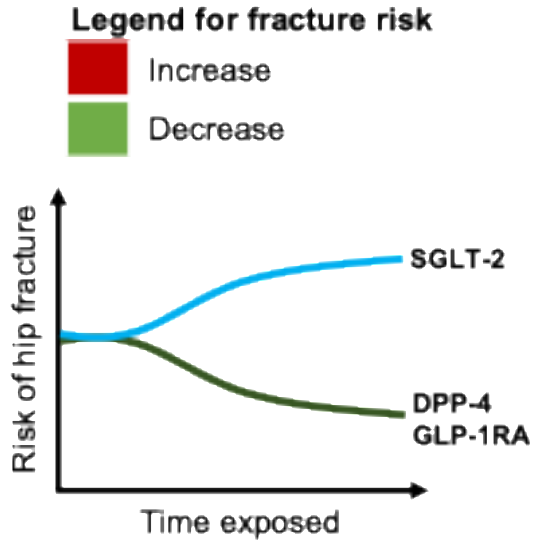
- **Clinical pharmacology** is key to understanding how drug exposures (dose, duration) relate to outcomes and effects in humans.
- **Provides information** on several study design parameters (e.g., comparator selection).
- **Plausible effects:** It also helps define the plausible functional form and direction of the treatment's effects.



CLINICAL PHARMACOLOGY

- The table below summarizes the the clinical pharmacology of select antidiabetic medications.

Antidiabetic Medication	Year of approval of first agent in the United States	First agent approved in the United States (route of administration)	Fracture risk	Primary biological mechanism	Length of plausible risk window
SGLT-2	2006	Sitagliptin (oral)	↑	BMD	months
DPP-4	2013	Canagliflozin (oral)	↓	BMD	months
GLP-1RA	2005	Exenatide (injection)	?	BMD	months



Key Consideration 3:

[DRUG EXPOSURE] TIME TRENDS

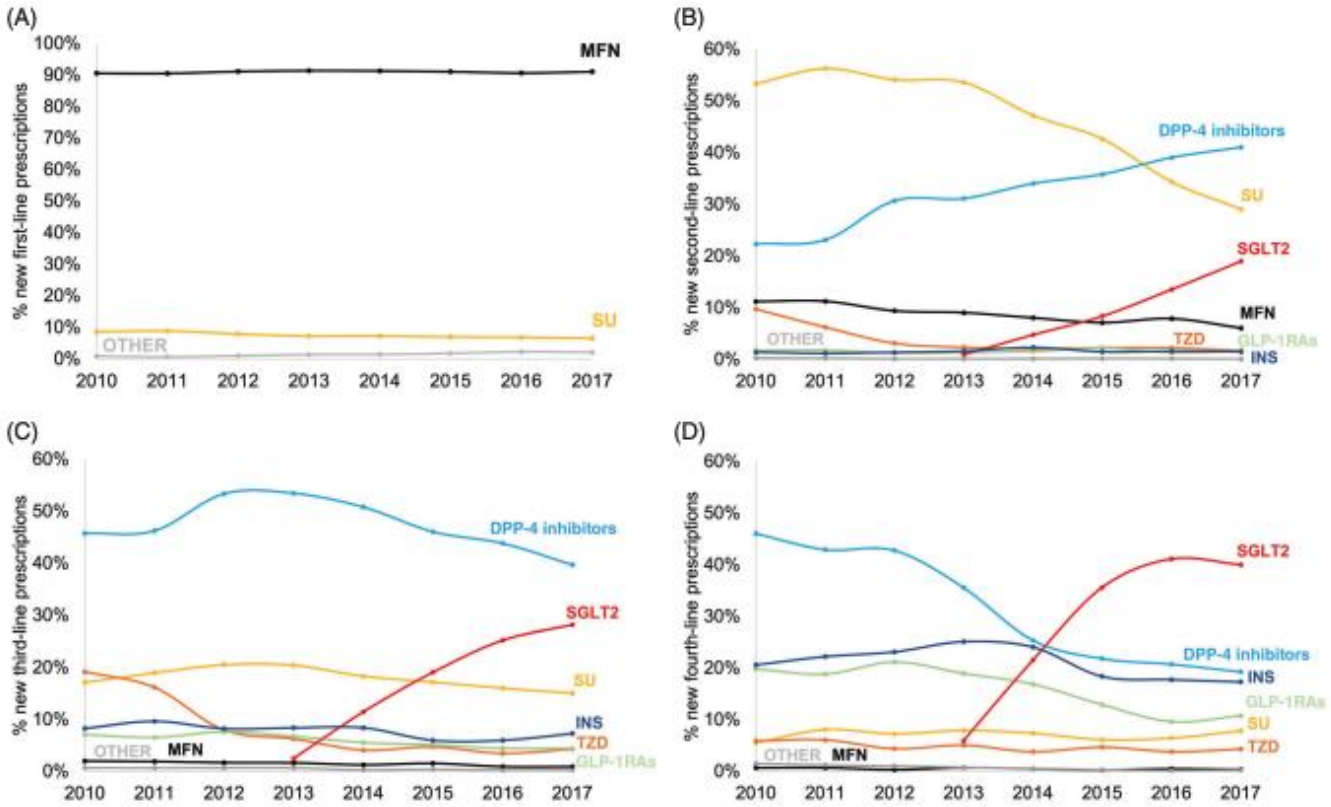
DRUG EXPOSURE TIME TRENDS: POPULATION-LEVEL

- **Population-level** trends are driven by changes in drug policies, clinical guidelines, and newly marketed drugs.
- These trends can introduce biases (confounding, selection, information) in both observational studies and RCTs.
- Mitigation strategies include:
  - account for calendar time: Use adjustment, matching, or stratification; and
  - account for changes over time in drug prescribing and the coding of outcomes.
- **Key takeaway:** Knowledge of population-level time trends at the **study design stage** ensures the most appropriate approach is chosen.

DRUG EXPOSURE TIME TRENDS: POPULATION-LEVEL

- Specific to antidiabetic medications, below are graphs of time trends of different lines of therapy in the UK.

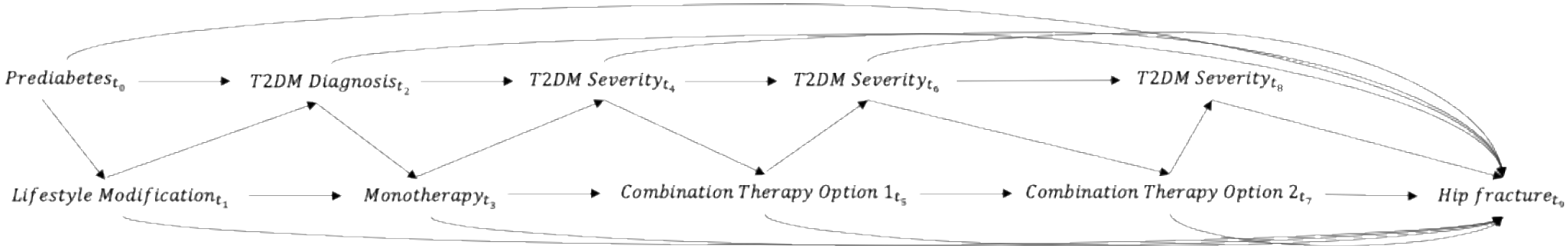
Time trends in new drug prescriptions for A, first-line, B, second-line, C, third-line and D, fourth-line therapy



Source: Dennis et al., 2019

DRUG EXPOSURE TIME TRENDS: INDIVIDUAL-LEVEL

- **Individual-level** trends are driven by changes in an individual's health status and responses to drug exposures.



- These trends can introduce biases such as time-dependent confounding, overadjustment, and selection bias.

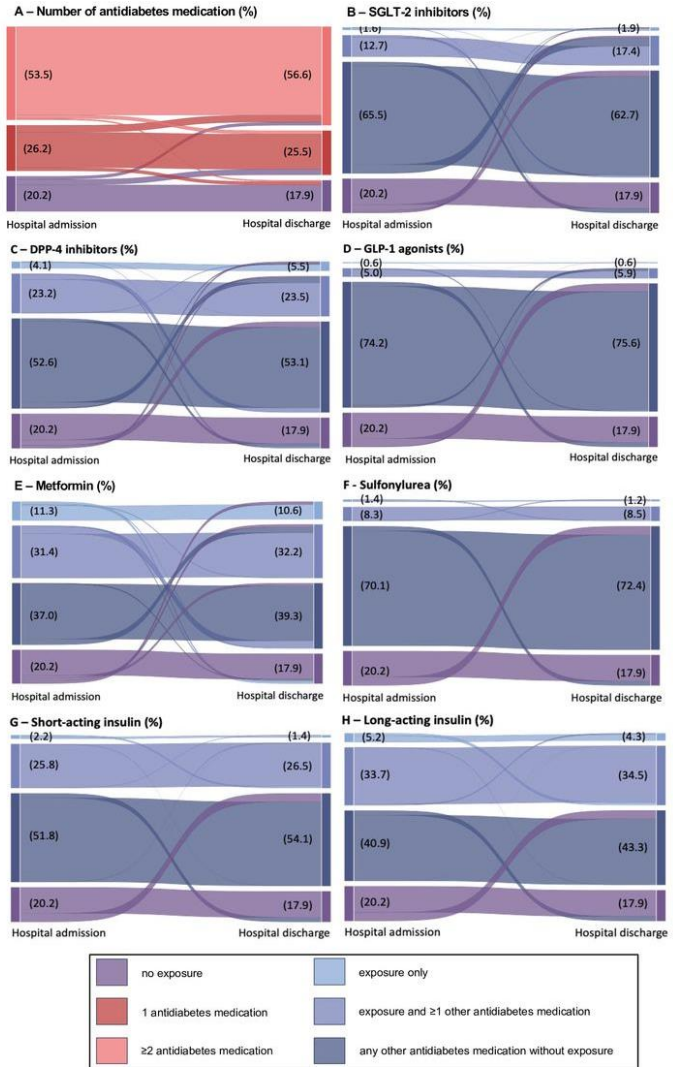
- Mitigation strategies are primarily analytical.

  - Inverse-probability of treatment/censoring weighting.

- **Key takeaway:** Knowledge of individual-level trends at the **study design** stage is essential for choosing the most appropriate approach.

DRUG EXPOSURE TIME TRENDS: INDIVIDUAL-LEVEL

Longitudinal patterns in use of antidiabetic medication classes among patients with type 2 diabetes from admission to discharge



Source: Meier et al., 2024

CONCLUSIONS

- **Focus on causal thinking:** Encourage formal causal thinking at the study design stage to build a plausible conceptual model and focus on real-world problems.
- **Transparent reporting:** Strongly recommend transparent reporting of all study design implementations.
- **Clarity of assumptions:** Transparent reporting ensures assumptions are clearly stated by the authors, not inferred by the reader.

REFERENCES

- Carnevale, V., et al. "Bone damage in type 2 diabetes mellitus." Nutrition, Metabolism and Cardiovascular Diseases 24.11 (2014): 1151-1157.
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