From Certain Uncertainties to Certain Decisions:
Pragmatic Study Designs in Pandemic Response

Lars G Hemkens

The Pandemic Evidence Collaboration 2025 conference, Banff, 15 May 2025

UNIVERSITÄT BERN

PRAGMATIC EVIDENCE LAB

RC2NB

Certain uncertainties

“Women have fewer teeth than men“

Aristoteles; HA II 3, 501b19

“Pneumonia is one of the diseases in which a timely venesection may save life“

Sir William Osler; Principles and Practice of Medicine;1892

- **Bloodletting** for pneumonia
- **Mercury** for syphilis
- **Lobotomy** for psychiatric diseases
- **Heroin** for cough
- **Bedrest** in myocardial infarction
- **Low-fiber diet** in diverticulosis
- **Surgery** for peptic ulcers
- **Intensive glucose lowering** in type 2 diabetes
- **Hormone replacement therapy** in women
- **Vitamine E** in cardiac diseases
- **Antiarrhythmic** in myocardial infarction
- **Stents** in stable CVD

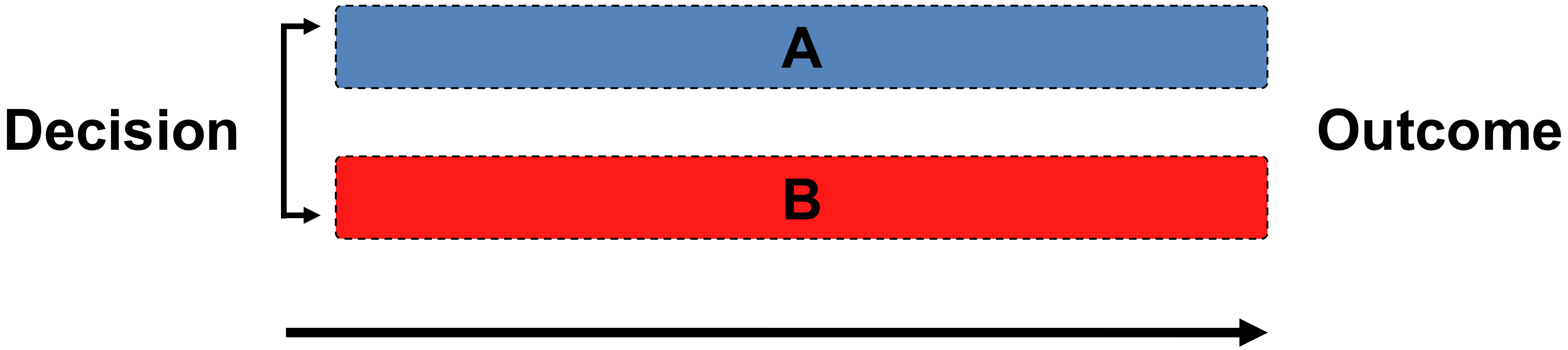
„Approximately **90% of new drugs** entered into clinical development on **promising** preclinical findings **fail** to yield sufficient **efficacy** and **safety** to receive …(FDA) license“

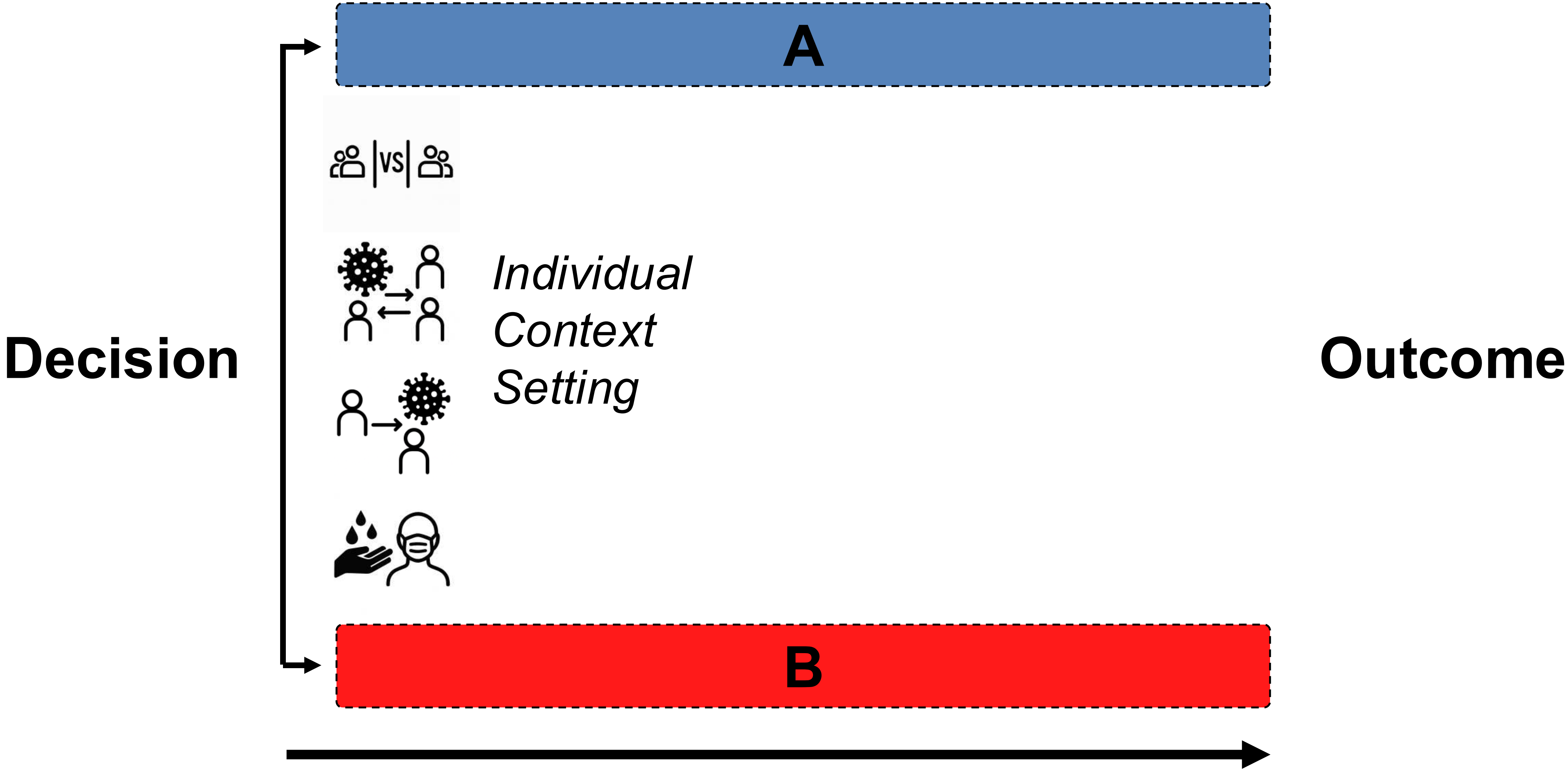
Benjamin et al. PLoS Biol 2017 (citing Hay et al. Nature Biotech 2014; 32: 40-51).

“Only one third of the **ideas** tested at **Microsoft** improved **the metric(s)** they were designed to improve”

Kohavi, R. et al. 2013 Online Controlled Experiments at Large Scale. Retrieved from http://bit.ly/ExPScale

Certain uncertainties in pandemic research


Decision
A
B
Outcome


A
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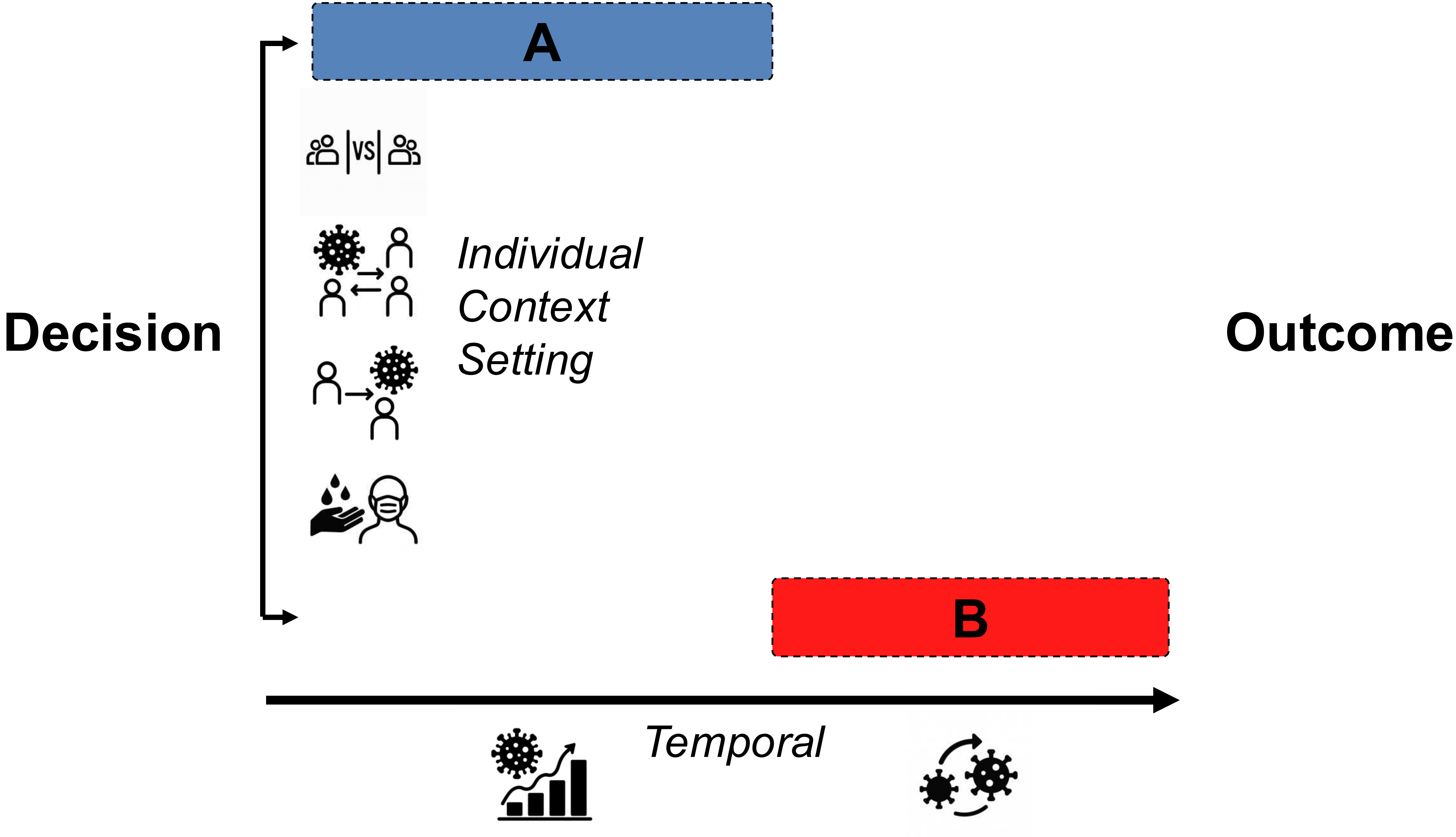
Individual
Context
Setting
Outcome
B


A
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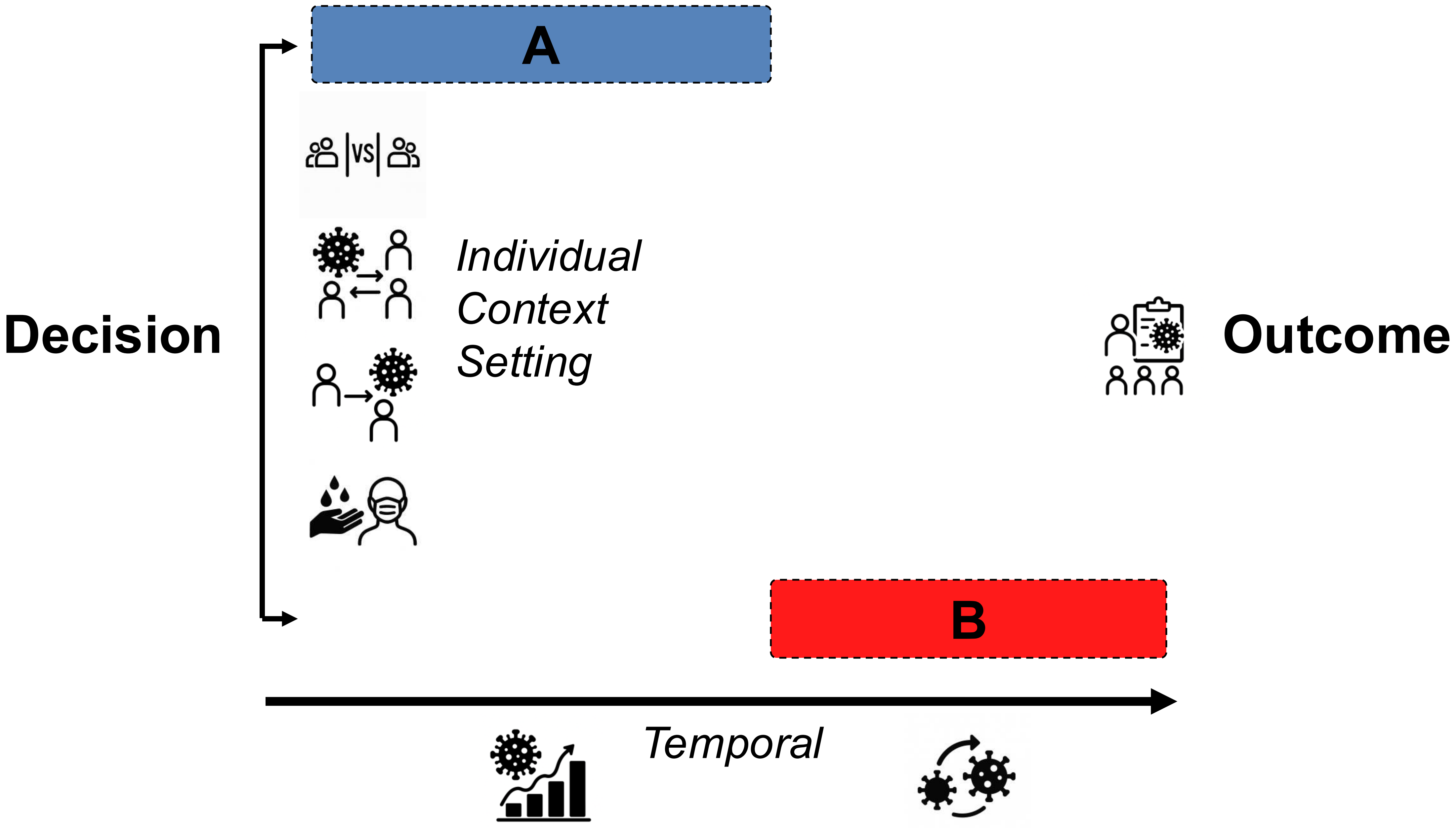
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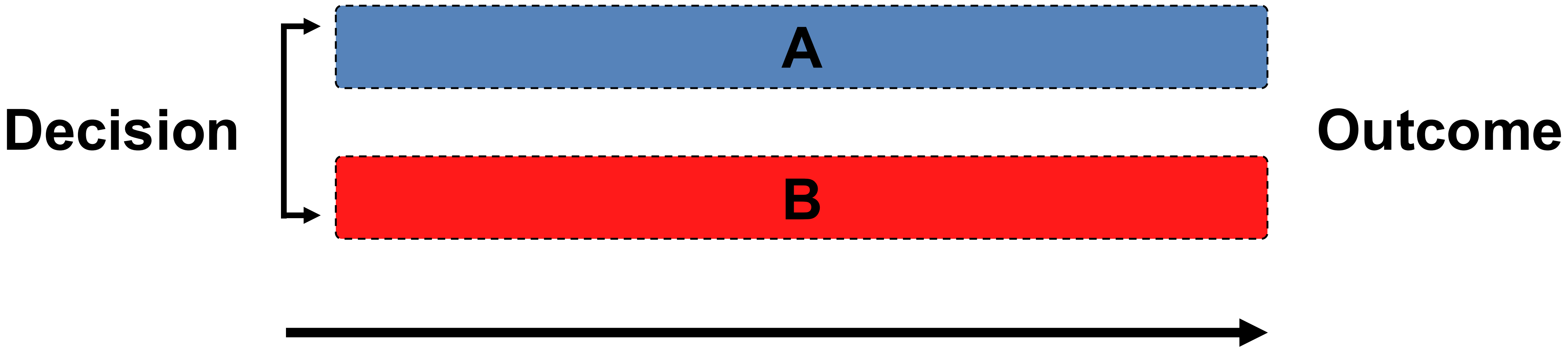
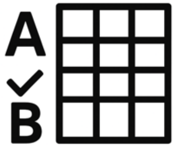


Decision
A
B
Outcome

Assumptions that need certainty

1. Data for A vs B correct
2. Data for Outcome correct and measured identically in both groups



3. A) All differences between A and B are known

   B) All differences between A and B are measured

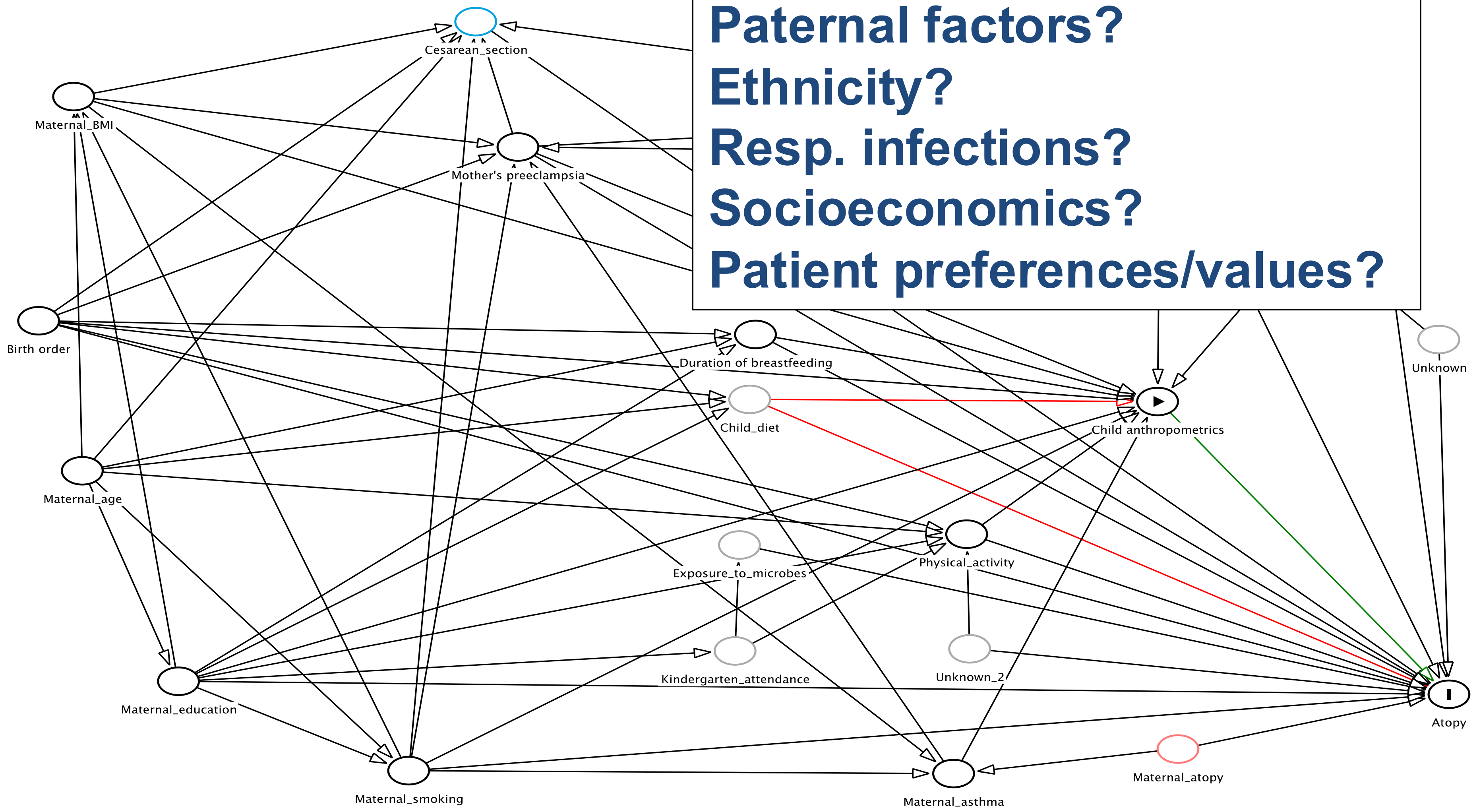
   C) All differences between A and B are statistically adequately controlled

Some essential data required for unbiased assessments

Domain	Category	Examples
Key Information	▪ **Exposure**	**A/B assignment**
	▪ **Outcome**	**Symptoms, hospitalization, death**
Individual-Level	▪ Risk of exposure	Household density, occupation, social interactions
	▪ Behavioral/Psychological	Risk perception, mental health, social support, adherence
	▪ Risk of outcome (if infected)	Age, comorbidities/medications, care access, genetics, vaccination, immunity
	▪ Outcome detection	Health literacy, testing access, healthcare-seeking behavior
Contextual/Systemic	▪ Environment	Urban/rural, ventilation, public space density
	▪ Community	Social networks, institutions (e.g., schools, nursing homes)
	▪ Social norms	Culture, stigma, mask-wearing norms
	▪ Healthsystem capacity	ICU availability, staff, diagnostic infrastructure
	▪ Occupational	Workplace, transportation dependence, remote work possible
	▪ Digital infrastructure	Telehealth, contact tracing apps, online education access
	▪ Information	Health communication, media exposure, misinformation
Specific Temporal	▪ Pandemic and policy	Early outbreak, variants, vaccination waves, lockdowns, mandates

Some Confounder Relationships

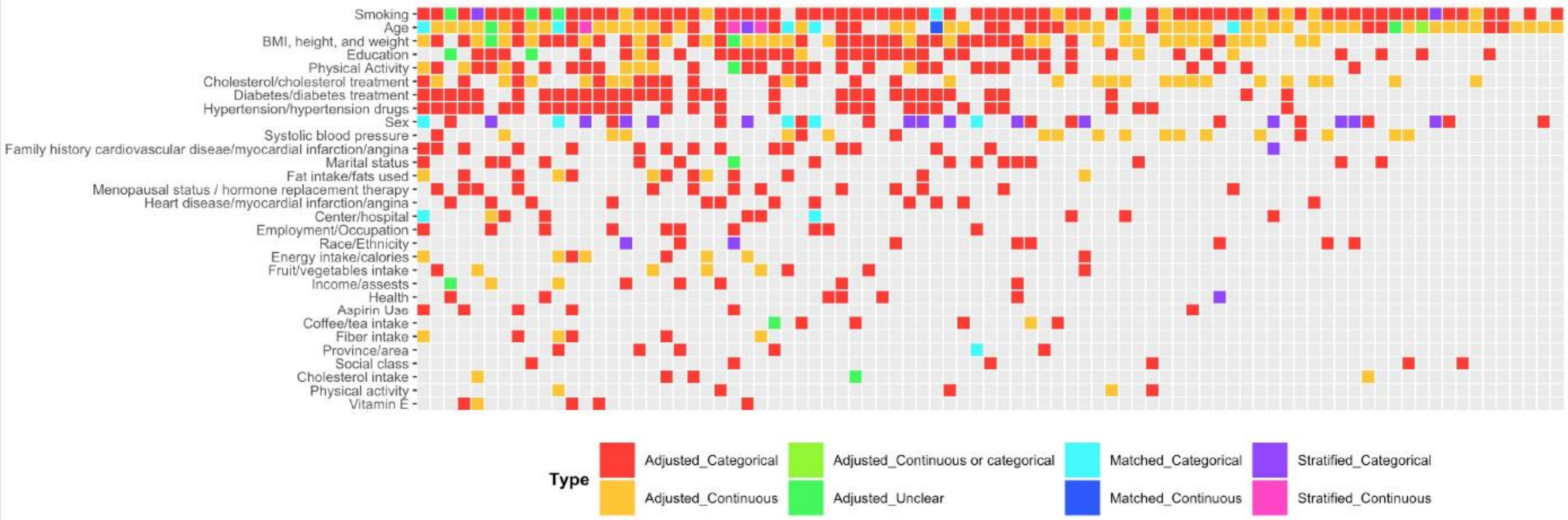
BMI and physical activity in early childhood with atopy



Paternal factors?
Ethnicity?
Resp. infections?
Socioeconomics?
Patient preferences/values?

Some Confounder Relationships

Alcohol and Cardiovascular disease



Wallach et al. BMC Medical Research Methodology 2020; 20:64
URL: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-020-0914-6

> J Clin Epidemiol. 2018 Jan;93:94-102. doi: 10.1016/j.jclinepi.2017.09.013. Epub 2017 Sep 21.

Interpretation of epidemiologic studies very often lacked adequate consideration of confounding

Lars G Hemkens [1], Hannah Ewald [2], Florian Naudet [3], Aviv Ladanie [2], Jonathan G Shaw [4], Gautam Sajeev [5], John P A Ioannidis [6]

Affiliations + expand

PMID: 28943377 DOI: 10.1016/j.jclinepi.2017.09.013

Abstract

Background and objective: Confounding bias is a most pervasive
observational epidemiologic research. We assessed whether auth
epidemiologic studies consider confounding bias when interpretin

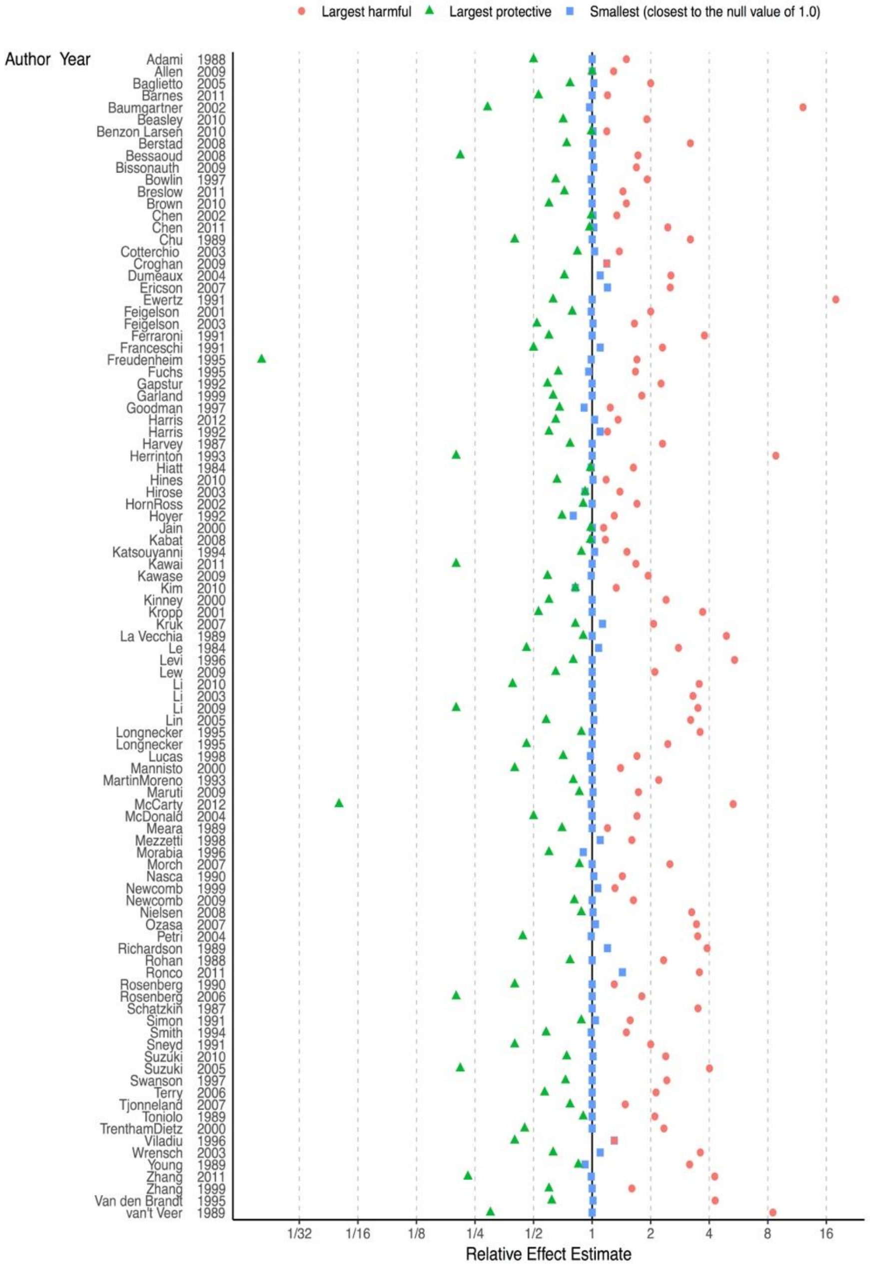
Study design and setting: We randomly selected 120 cohort or case-control studies published in 2011 and 2012 by the general medical, epidemiologic, and specialty journals with the highest impact factors. We used Web of Science to assess citation metrics through January 2017.

Results: Sixty-eight studies (56.7%, 95% confidence interval: 47.8-65.5%) mentioned "confounding" in the Abstract or Discussion sections, another 20 (16.7%; 10.0-23.3%) alluded to it, and there was no mention or allusion at all in 32 studies (26.7%; 18.8-34.6%). Authors often acknowledged that for specific confounders, there was no adjustment (34 studies; 28.3%) or deem it possible or likely that confounding affected their main findings (29 studies; 24.2%). However, only two studies (1.7%; 0-4.0%) specifically used the words "caution" or "cautious" for the interpretation because of confounding-related reasons and eventually only four studies (3.3%; 0.1-6.5%) had limitations related to confounding or any other bias in their Conclusions. Studies mentioning that the findings were possibly or likely affected by confounding were more frequently cited than studies with a statement that findings were unlikely affected (median 6.3 vs. 4.0 citations per year, P = 0.04).

Conclusions: Many observational studies lack satisfactory discussion of confounding bias. Even when confounding bias is mentioned, authors are typically confident that it is rather irrelevant to their findings and they rarely call for cautious interpretation. More careful acknowledgment of possible impact of confounding is not associated with lower citation impact.

- **57%** discuss confounding
- **3%** limit conclusions in any way

Hemkens et al. J Clin Epi 2018



Analytical choices

"Most observational studies evaluating the impact of alcohol on breast cancer report relative effect estimates for the same associations that diverge by **>2-fold**."

Wallach et al. (Figure from OSF)
Peer-reviewed paper: Int J Epidemiol. 2020 Apr 1;49(2):608-618.

A certain assumption in a pandemic is that most others are uncertain

Pragmatic Evidence

Πρᾶγμα

“What difference
would it practically make ...
if this notion rather than that notion
were true?

If no practical difference
whatever can be traced, then the
alternatives mean practically the same thing,
and all dispute is idle”

What pragmatism means; In William James „Pragmatism“

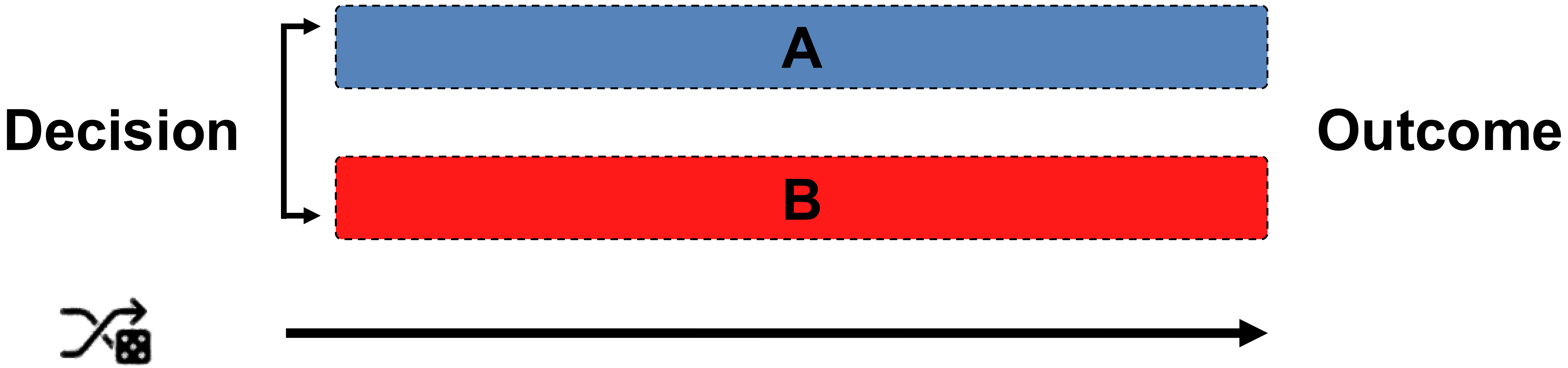
Pragmatic trials

Assumptions in randomized trials

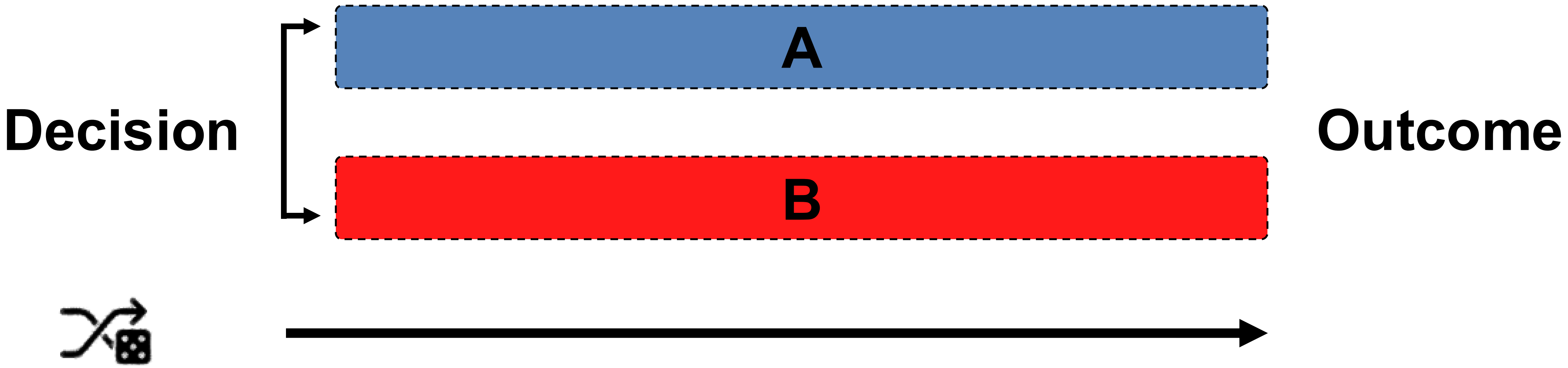
1. Data for A vs B correct
2. Data for Outcome correct and measured identically in both groups

3. Decision for A and B randomly

The nature of a randomized trial



The nature of a pragmatic randomized trial



A / B are real choices
Outcome matters in practice

A randomized trial
that helps to
make a better decision
about which treatment strategy
to use in practice is
pragmatic

Janiaud P, Hemkens LG. J Clin Epi 2024

Not a pragmatic randomized trial

- **Population:** Selected only, not the real target
- **Intervention:** Artificial (e.g., supervised by researchers, blinded)
- **Follow-up:** Artificial (e.g., in research centers)
- **Adherence**: Optimized / non-adherent excluded
- **Outcomes**: Matter for researchers - not for decision makers

All essential data required for pragmatic trials

Domain	Category	Examples
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Comparisons that matter

Decisions

- A vs B are **true actionable** decisions public health leaders can make
- No randomization without true uncertainty
- If the answer is clear: **act, don’t experiment**

Interventions

- Must be **feasible** in the actual setting
- Require **no unrealistic or extra** (research) **resources**
- All compared strategies must be **implementable post-trial**

Outcomes that matter

General

- **Stages: Direct→ Infection → Disease → Societal/Population Impact**
- **Objective where possible**
- **Blinded where possible**

Outcome Types

- **Direct** (e.g., missed school, financial loss)
- **Infection-related** (e.g., asymptomatic infections)
- **Disease-related** (e.g., symptoms, hospitalization, death)
- **Societal/Population-level** (e.g., health system burden, economic impact)

Populations

- Individuals directly affected
- **Close contacts (!)**
- **Society/population at large (!)**
- Special Subgroups, e.g., vulnerable household members, essential workers (e.g., police, ICU staff)

Rapid setup and Scalability

1. Solid Data Infrastructure

- Outcome data essential – randomized or not
- Standardized formats and interoperability

2. Use What Exists

- Leverage routine public health data (no added burden)
- Digital surveillance (e.g., standardized contact tracing)

3. Enhance When Needed

- Add research elements via contact tracing teams:
    - Trial participant? (individual or part of cluster)
    - Contact of participant? (e.g., grandparents of child in trial schools)

Rapid setup and Scalability

4. Prepare in Advance

- Pre-approved, tested protocols
- Train public health staff in research
- Collaborate early: health authorities, regulators, communities
- Ethical and legal preparedness

5. Keep Designs Simple

- Avoid complexity that delays or risks failure

WHAT before WHY approach

- **Prioritize decisions**: What works first. Why it works later.

- Tom Chalmers' "Randomize the first patient!" ➔ **Randomize the first decision!**

- **Adherence is a critical effect modifier** – **but observe not control**

- **Combine Pragmatic (WHAT) and Explanatory (WHY) Research:**
  - **Observational analyses** using routine health data
  - **Decentralization / Remote interviews** (e.g. via phone, mobile apps)
  - **Blood sampling** (e.g., immune markers)
  - **Subgroup analyses** (e.g., high-adherence groups like health workers)

- **Leverage modern technology** as digital biomarkers to monitor adherence, for example
  - **Air quality sensors** (ventilation)
  - **Hand-sanitizer sensors** (usage tracking)

- **Advanced stat. approaches (causal modeling, estimands):** effect modifiers

More details:
Janiaud P, Hemkens LG. J Clin Epi 2024

Summary

- **Uncertainty** dominates decision-making and research in a pandemic
- Priority is not more data - **reliable data**, available fast
- Most **assumptions** are uncertain – and often wrong
- **Designs that reduce uncertainty** without uncertain assumptions.
- **Only randomization provides certainty** given strong/unrealistic assumptions
- **Pragmatic trials in pandemics are not only possible –
they are essential for evidence that matters when it matters most.**

Prof. Dr. med. Lars G. Hemkens MPH

Academic Director Clinical Trials
Department of Clinical Research
University of Bern | Bern | Switzerland

Lead of Pragmatic Trials and Real-World Evidence
RC2NB - Research Center for Clinical Neuroimmunology and Neuroscience Basel
University of Basel and University Hospital Basel | Basel | Switzerland

ORCiD: 0000-0002-3444-1432

Lars.Hemkens@unibe.ch

dcr.unibe.ch

www.pragmatic-evidence.org

www.rc2nb.unibas.ch

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Special Thanks

P Janiaud (U Bern)
J Hirt (U Basel)
A Schmitt (U Basel)
L Chabeaud (U Basel)
T Woelfle (U Basel)
F Naudet (U Rennes / INSERM)
O Fröbert (U Orebro)
HM Verkooijen (UMC Utrecht)
B Thombs (U McGill)
D Moher (U Ottawa)
A Fretheim (U Oslo)
S Goodman (U Stanford)
JPA Ioannidis (U Stanford)
D Contopoulus-Ioannidis (U Stanford)
B Djulbegovic (City of Hope)
G Guyatt (McMaster)
U Dirnagl (Charite / BIH / QUEST)
B Kasenda (U Basel)
J Kuhle (U Basel)
Ö Yaldizli (U Basel)
C Granziera (U Basel)
L Kappos (U Basel)
E Segelov (U Bern)