Making recommendations based on limited or uncertain evidence

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Disclosure

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- No financial disclosures
- Member: GRADE Working Group, Guideline International Network, & Cochrane Public Health Group
- Co-founder: US GRADE Network & Evidence Foundation
- Methodologist for several national and international associations/governmental organizations

Overview of the Presentation

- Making recommendations useful
- Factors considered during decision-making
- Formulating recommendations
- Decision-making based on low certainty or insufficient evidence

Creating trustworthy guidelines

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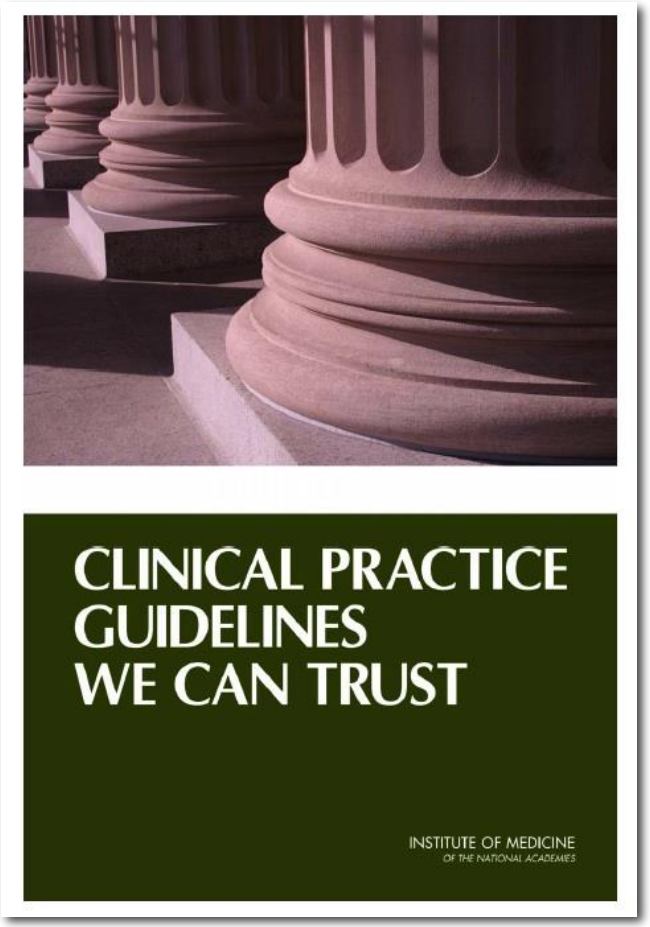
- Establishing transparency
- Management of conflict of interest
- Guideline development group composition
- Evidence based on systematic reviews
- Method for rating strength of recommendations
- Articulation of recommendations
- External review
- Updating



Guidelines and Questions

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Guidelines are a way of answering questions about clinical, communication, organisational or policy interventions, in the hope of improving health care or health policy.

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It is therefore helpful to structure a guideline in terms of answerable questions with a focus on relevant outcomes.

Questions ➡ Recommendations

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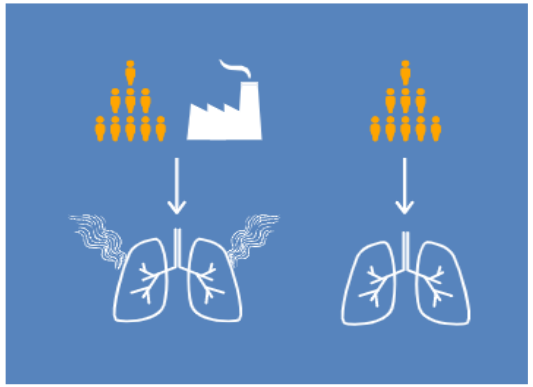
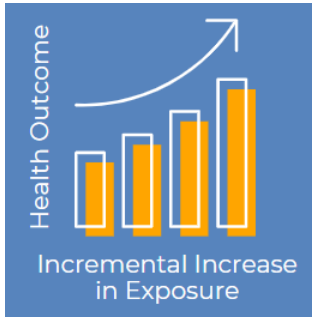


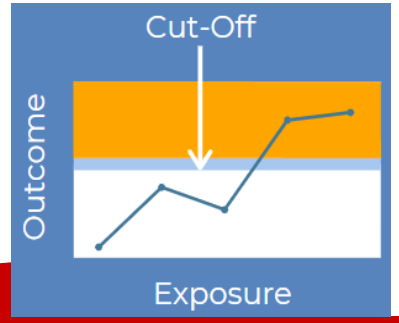
Evaluate the effect achieved by an intervention and comparison on health outcomes



Describe the nature of the relationship between the exposure and outcome

Compare the association between a known exposure cut-off and a known comparison cut-off.

Analyze health effects at different exposure levels when naturally occurring exposure levels or cut-off points are unknown.



Identify exposure and comparator cut-offs with an established dose-response relationship with the outcome.

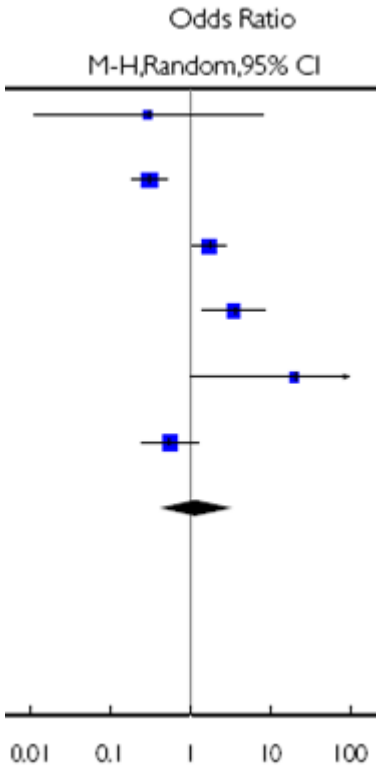
Factor that decrease our certainty in the evidence

Methodological limitations

Risk of bias:

- Allocation concealment
- Blinding
- Intention-to-treat
- Follow-up
- Stopped early

Inconsistency of results

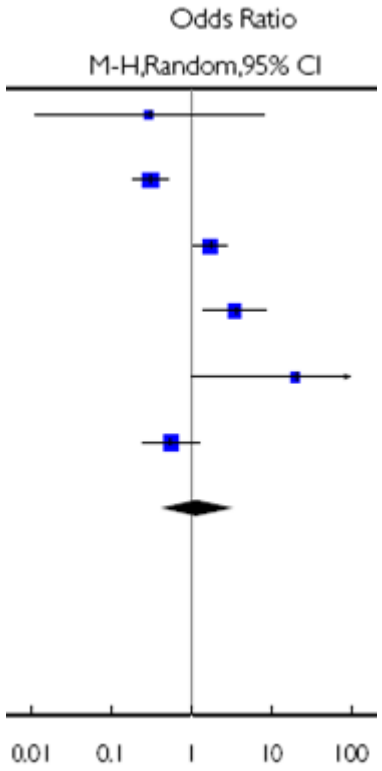


Indirectness of evidence

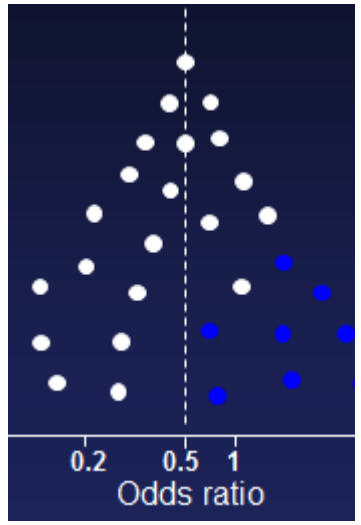
Sources of indirectness:

- Indirect comparisons
- Patients
- Interventions
- Comparators
- Outcomes

Imprecision of results



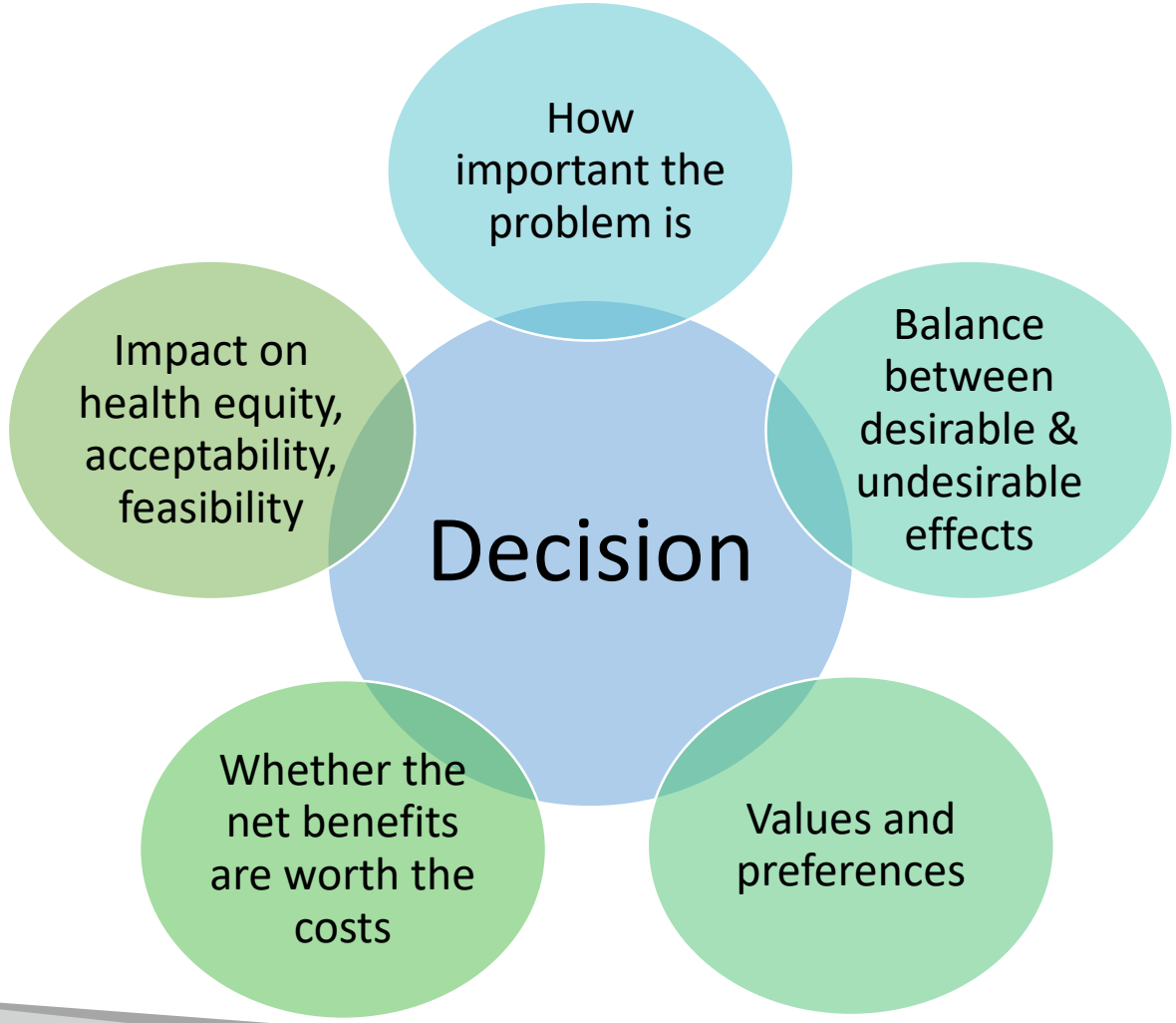
Publication bias



Conceptualizing certainty in the evidence

High	We are **very confident** that the true effect lies close to that of the estimate of the effect.	⨁⨁⨁⨁
Moderate	We are **moderately confident** in the estimate of effect: The true effect is likely to be close to the estimate of effect , but possibility to be substantially different.	⨁⨁⨁◯
Low	Our **confidence** in the effect **is limited**: The true effect may be substantially different from the estimate of the effect.	⨁⨁◯◯
Very low	We have **very little confidence** in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.	⨁◯◯◯

Healthcare decisions are complex



Strength of recommendation

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"The strength of a recommendation reflects the extent to which we can,

across the range of persons for whom the recommendations are intended,

be confident that desirable effects of a management strategy outweigh undesirable effects."

Considering the strength of a recommendation

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Factors that can weaken the strength of a recommendation	Explanation
❑ Lower certainty evidence	The lower the certainty of evidence, the more likely a conditional recommendation.
❑ Uncertainty about the balance of benefits versus harms and burdens	The smaller the net benefit and the lower certainty for that benefit, the more likely is a conditional recommendation warranted.
❑ Uncertainty or differences in patients' values	The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely conditional recommendation warranted.
❑ Uncertainty about whether the net benefits are worth the costs	The higher the costs of an intervention the less likely is a strong recommendation warranted.

Balance of benefits & harms

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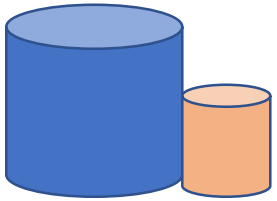
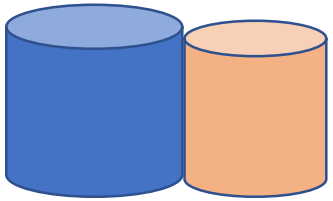


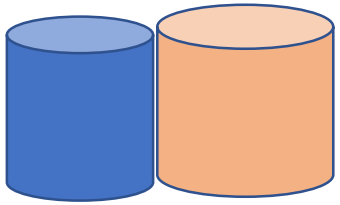
Benefits clearly outweighs the downsides

Strong recommendation for an action



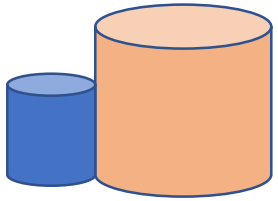
Benefits probably still outweighs the downsides

Conditional recommendation for an action



Harms probably outweighs the benefits

Conditional recommendation against an action



Harms clearly outweighs the benefits

Strong recommendation against an action

Formulating Recommendations

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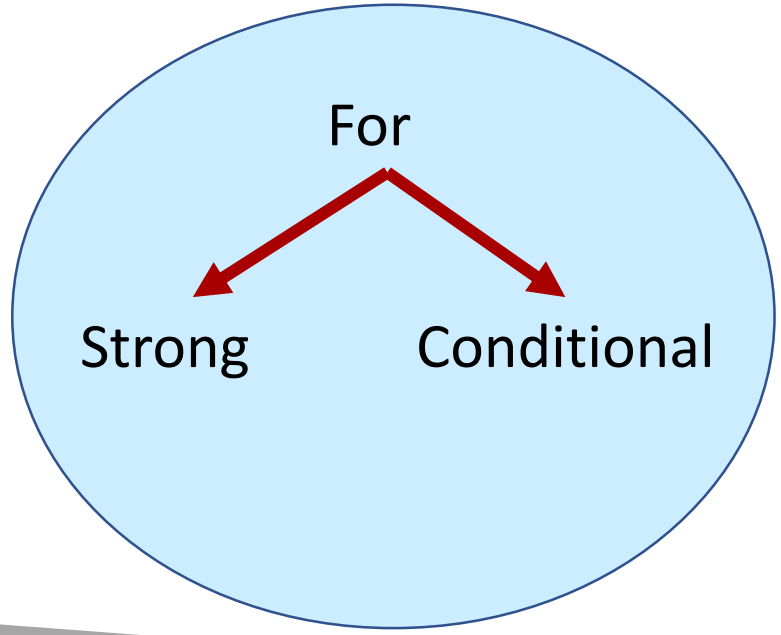
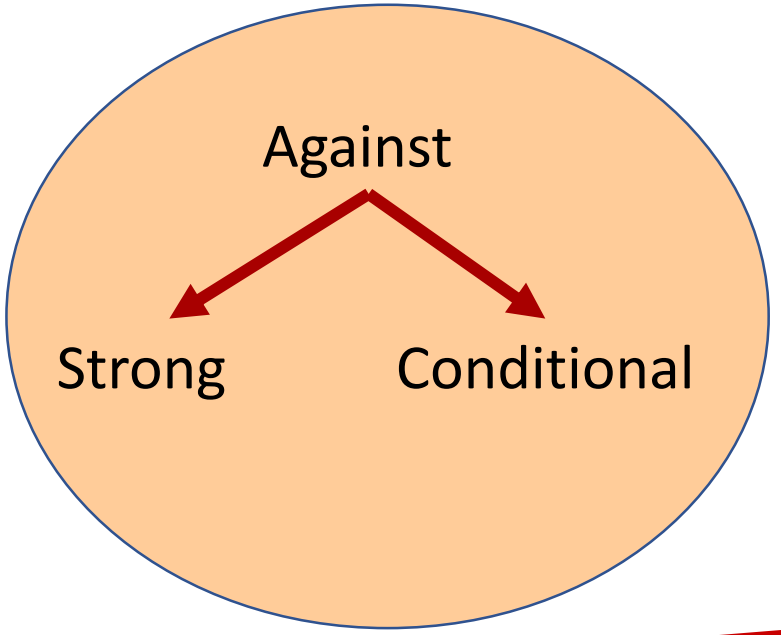
- Standardized wording to convey meaning clearly
- For each recommendation determine: Direction & Strength





Wording of Recommendations

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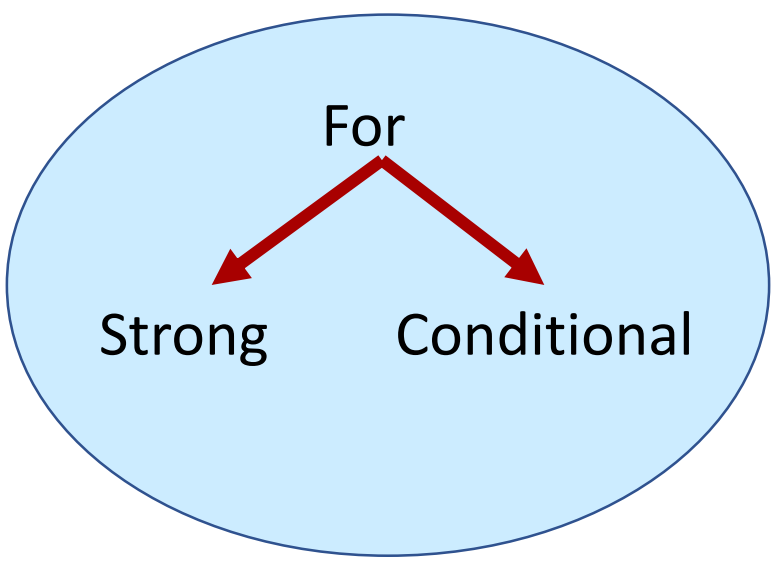

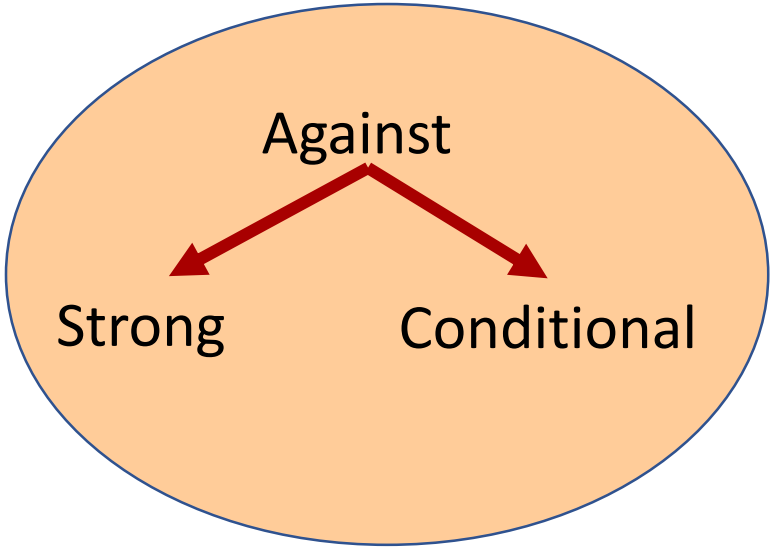

Strong recommendation	Weak/conditional recommendation
We **recommend … vs. …**	We **suggest … vs. …**
We ***recommend against***… vs. …	We ***suggest against***… vs. …

Recommending against an exposure/intervention

- Avoid: “we do not recommend…”
- Instead use: “we recommend against…”
- Decide whether to recommend for the intervention or against the alternative
- Always include the comparator in the recommendation (“use X rather than Y…”)

Implications of a strong recommendation

Population: Most people in this situation would want the recommended course of action and only a small proportion would not

Health care workers: Most people should receive the recommended course of action

Policy makers: The recommendation can be adapted as a policy in most situations

Implications of a conditional recommendation

Population: The majority of people in this situation would want the recommended course of action, but many would not

Health care workers: Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision making

Policy makers: There is a need for substantial debate and involvement of stakeholders

Make recommendation actionable

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- Avoid statement of facts
  - "Exercise training (or regular physical activity) is recommended as safe and effective for patients with heart failure who are able to participate to improve functional status. (Level of Evidence: A)" (AHA 2013)
- Use of "there is insufficient evidence"
  - "Current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults" (Grade I) (USPSTF 2015)
  - Often overused
  - Most of the time not helpful for clinicians
  - Instead recommend as part of study
- Keep the actual recommendation concise

“What if there is no evidence?”

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- If there is a question, then there is evidence
- Lack of RCTs does not mean no evidence
- All evidence may be examined
  - Special challenges:
    - Animal data
    - Laboratory data
- Higher certainty indirect data may be preferable to low certainty direct data

Strategies for improving evidence synthesis with insufficient evidence

- Reconsider eligible study designs
- Summarize indirect evidence
- Summarize contextual and implementation evidence
- Consider modelling
- Incorporate unpublished health system data in the evidence synthesis

Special situation: Research recommendation

- Insufficient evidence supporting an intervention for a panel to recommend its use
- Further research has a large potential for reducing uncertainty about the effects of the intervention
- Further research is deemed good value for the anticipated costs

- Example:
  - Among ambulatory patients with mild-to-moderate COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma only in the context of a clinical trial. (Knowledge gap) (IDSA 2021)

Discordant Recommendations

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Be cautious of discordant recommendations

5 scenarios exists in which a strong recommendation may be warranted based on low/very low certainty of evidence

1. Life-threatening situation, high baseline risk
2. Uncertain benefit, certain harm
3. One option clearly less harmful or costly
4. One option clearly more harmful or costly
5. Potential catastrophic harm

Uncertain benefit/Certain harm

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- Low/Very low CoE for possible/uncertain benefits
- Moderate/High CoE of harm
- Higher value placed on avoidance of harm
- High incremental cost
- Strong recommendation against the intervention

Ex. CT screening for early detection of cancer

Summary

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- Consider alternative direct or indirect evidence
- The certainty of evidence is not the only factor that drives the strength of recommendations
- Create standardized, clear, concise recommendation statements
- Assess the appropriateness of research recommendations
- Avoid discordant recommendations

References

- Andrews, J., Guyatt, G., Oxman, A. D., Alderson, P., Dahm, P., Falck-Ytter, Y., ... & Schünemann, H. J. (2013). GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *Journal of clinical epidemiology*, *66*(7), 719-725.
- Andrews, J. C., Schünemann, H. J., Oxman, A. D., Pottie, K., Meerpohl, J. J., Coello, P. A., ... & Guyatt, G. (2013). GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *Journal of clinical epidemiology*, *66*(7), 726-735.
- Morgan, R. L., Whaley, P., Thayer, K. A., & Schünemann, H. J. (2018). Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environment international*, *121*(Pt 1), 1027.
- Murad, M. H., Chang, S. M., Fiordalisi, C. V., Lin, J. S., Wilt, T. J., Tsou, A. Y., ... & Viswanathan, M. (2021). Improving the Utility of Evidence Synthesis for Decisionmakers in the Face of Insufficient Evidence. *Journal of Clinical Epidemiology*.
- Steinberg, E., Greenfield, S., Wolman, D. M., Mancher, M., & Graham, R. (Eds.). (2011). *Clinical practice guidelines we can trust*. National Academies Press.

Thank You. Questions?

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