How to rate the certainty of evidence?
GRADE approach

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Contents

1. Introduction to GRADE
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Three principles of evidence-based medicine

1. Optimal clinical decision making requires awareness of the best available evidence
   • Ideally from best evidence summaries

2. Not all evidence is equal
   • A hierarchy of evidence guides clinical decision making

3. Evidence alone is never enough
   • Decision makers balance risks and benefits of alternative management strategies in the context of patient values and preferences

Users' guides to the medical literature, 3rd edition
Systems for grading the quality of evidence and the strength of recommendations

- Grading levels of evidence and the strength of recommendation
  - American College of Chest Physicians (ACCP)
  - Australian National Health and Medical Research Council (ANHMRC)
  - Oxford Centre for Evidence-Based Medicine (OCEBM)
  - Scottish Intercollegiate Guidelines Network (SIGN)
  - US Preventive Services Task Force (USPSTF)
  - US Task Force on Community Preventive Services (USTFCPS)
  - ......

Atkins et al., BMC Health Serv Res. 2004;4(1):38.
Detailed guidance on GRADE

- **2000**: Start to meet
- **2004 BMJ**: First description
- **2008 BMJ**: Introductory 6 part series
- **2008 Cochrane**: 2 chapters in Cochrane Handbook
- **2010 Allergy**: Examples with allergy field
- **From 2011 JCE**

https://gdt.gradepro.org/app/handbook/handbook.html
More than 110 organizations from 19 countries around the world have endorsed or are using GRADE
What are we grading?

- Two components:
  1. Quality/certainty/confidence in evidence
  2. Grading strength of recommendations

Grading strength of recommendations:

- Strong vs Weak

GRADE guidelines: 1
### Outcomes in example review

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Source of evidence</th>
<th>Evidence for 1,000 people</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>More red meat consumption</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>5 RCTs</td>
<td>10 more death</td>
</tr>
<tr>
<td>CVD</td>
<td>3 RCTs</td>
<td>7 more CVD</td>
</tr>
<tr>
<td>Quality of life</td>
<td>4 RCTs</td>
<td>10 points better (scale 0 to 100, better)</td>
</tr>
<tr>
<td>Satisfaction with diet</td>
<td>5 RCTs</td>
<td>3 points better (scale 0 to 10, better)</td>
</tr>
</tbody>
</table>
GRADE process

Research Question (PICO)

S1  S2  S3  S4  S5
Critical outcomes

OC1  OC2  OC3  OC4
Important outcomes

Systematic review

Summarize evidence (effect estimates) & Rate the certainty of evidence for each outcome, across studies

Guideline

Rate overall certainty of evidence across all critical outcomes Decide on the direction (for/against) and grade strength (strong/weak) of the recommendation

S, study
OC, outcome
Rating certainty of evidence for what?

GRADE addresses certainty of evidence:

- Impact of therapeutic interventions on outcomes
- Impact of screening interventions
- Impact of diagnostic strategies
- Diagnostic accuracy
- Prognosis
Questions about GRADE

- GRADE rating of certainty of evidence
  1. Address quality of individual studies
  2. Address quality of bodies of evidence
  3. Both individual studies and bodies of evidence

- Rating different outcomes (pain and all-cause mortality)
  1. Certainty of evidence always same across outcomes
  2. Certainty of evidence usually same across outcomes
  3. Certainty of evidence usually differs across outcomes

GRADE guidelines: 1
Quality?

Quality of body of evidence
Quality of overall evidence
Confidence of evidence
Certainty of evidence
Trustworthy of evidence
e.g. GRADE

Study quality
Study limitation
Internal validity
Quality of an individual study
e.g. Cochrane RoB tool
If you are interested in

What is the impact of general health screening on health outcomes in adults?

- P: adults
- I: screening
- C: no screening
- O: all-cause mortality, disease-specific mortality, etc.

- Pooled summary results showed that: RR=XX, 95% CI=XX to XX
- What makes the evidence more or less certain?
- What increases confidence in the evidence?
How certain are you?

- Well conducted 7 RCTs
- Consistent results across studies
- Different types of cancer
- About 1,500 people
- Comprehensive search

No confidence (0) ...................................................... Totally confident (100)
How certain are you?

- Moderate to high risk of bias
- Inconsistent results across studies
- Only prostate cancer

Total 105 people
Protocol published, but

No confidence (0) ______________________________________________________________________ Totally confident (100)
GRADE’s approach to rating certainty of evidence

- **Risk of bias**: Well conducted 7 RCTs *vs* Moderate to high risk of bias
- **Inconsistency**: Consistent *vs* Inconsistent results across studies
- **Indirectness**: Different types of cancer *vs* Only prostate cancer
- **Imprecision**: About 1,500 people *vs* Total 105 people
- **Publication bias**: Comprehensive search *vs* Protocol published, but...
GRADE’s approach to rating certainty of evidence

- Randomized trials
  - Risk of bias
  - Inconsistency
  - Indirectness
  - Imprecision
  - Publication bias
  - Low to very low certainty

- Observational studies
  - Large effect
  - Dose response
  - Opposing confounding
  - +1 or +2

GRADE guidelines: 1, 3

South Korea GRADE Network

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Evidence summary: Evidence profile

### Reduction of Unprocessed Red Meat Intake (3 Servings per Week) and Cancer Mortality and Incidence

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Baseline Risk</th>
<th>Relative Risk</th>
<th>Absolute Risk</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancer mortality (Up to: 5 to 28 years follow-up, 182,484 participants)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 observational studies</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>105/1000 (10.5%)</td>
<td>RR 0.93 (0.90 to 0.95)</td>
<td>7 fewer per 1,000 (from 5 fewer to 10 fewer)</td>
<td>⬤⬤◯◯ LOW</td>
</tr>
</tbody>
</table>

- **Esophageal cancer incidence (Mean: 11 years follow-up, 472,538 participants)**
  | 1 observational studies | serious b | not serious | not serious | not serious | none | 7/1000 (0.7%) | RR 1.00 (0.72 to 1.39) | 0 fewer per 1,000 (from 2 fewer to 3 more) | ⬤⬤⬤⬤ VERY LOW |

- **Colorectal cancer incidence (Up to: 3 to 15 years follow-up, 314,478 participants)**
  | 4 observational studies | not serious | not serious | not serious | not serious | none | 20/1000 (2.0%) | RR 0.99 (0.90 to 1.09) | 0 fewer per 1,000 (from 2 fewer to 2 more) | ⬤⬤⬤⬤ LOW |

GRADE guidelines: 1
## Evidence summary: Summary of findings

### Reduction of Unprocessed Red Meat Intake (3 Servings per Week) and Cancer Mortality and Incidence

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of studies (follow-up period, no of participants)</th>
<th>Relative risk (95% CI)</th>
<th>Estimated Lifetime Population Risk a</th>
<th>Risk difference</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cancer mortality</td>
<td>7 (Up to: 5 to 28 years follow-up, 875,291 participants)</td>
<td>RR 0.93 (0.91 to 0.94)</td>
<td>105 per 1,000</td>
<td>7 fewer per 1,000 (9 fewer to 6 fewer)</td>
<td>LOW Due to observational design</td>
<td>Reduction of unprocessed red meat may result in a very small decrease in cancer mortality</td>
</tr>
<tr>
<td>Prostate cancer mortality b,c</td>
<td>1 (Up to: 14 years follow-up)</td>
<td>RR 1.56 (0.93 to 2.63)</td>
<td>6 per 1,000</td>
<td>3 more per 1,000 (0 fewer to 10 more)</td>
<td>VERY LOW d Due to observational design, imprecision</td>
<td>We are uncertain of the effects of unprocessed red meat on prostate cancer mortality</td>
</tr>
<tr>
<td>Overall cancer incidence</td>
<td>2 (Up to: 5 to 9 years follow-up, 71,858 participants)</td>
<td>RR 0.93 (0.83 to 1.04)</td>
<td>185 per 1,000</td>
<td>13 fewer per 1,000 (31 fewer to 7 more)</td>
<td>VERY LOW d Due to observational design, imprecision</td>
<td>We are uncertain of the effects of unprocessed red meat on all cancer incidence</td>
</tr>
<tr>
<td>Esophageal cancer incidence</td>
<td>1 (Mean: 11 years follow-up, 472,538 participants)</td>
<td>RR 1.00 (0.72 to 1.39)</td>
<td>7 per 1,000</td>
<td>0 fewer per 1,000 (2 fewer to 3 more)</td>
<td>VERY LOW e Due to observational design, risk of bias</td>
<td>We are uncertain of the effects of unprocessed red meat on esophageal cancer incidence</td>
</tr>
</tbody>
</table>

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**GRADE guidelines:** 1
## Domains that contribute to the strength of recommendation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance between desirable and undesirable outcomes</td>
<td>The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation is warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely a weak recommendation is warranted</td>
</tr>
<tr>
<td>Certainty of evidence</td>
<td>The higher the certainty of evidence, the more likely a strong recommendation is warranted</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely a weak recommendation is warranted</td>
</tr>
<tr>
<td>Resource use</td>
<td>The higher the costs of an intervention (the more resources consumed), the less likely a strong recommendation is warranted</td>
</tr>
</tbody>
</table>

GRADE guidelines: 15
Strength of recommendation

- **Strong recommendations:**
  1. Desirable consequences clearly outweigh undesirable consequences (or vice versa).
  2. All or almost all fully informed individuals in the target population would choose the recommended course of action.

- **Weak recommendations:**
  1. Low certainty in evidence and/or
  2. Close balance between desirable and undesirable consequences.
  3. The majority of fully informed individuals in the target population would choose the recommended course of action but a substantial minority would not.

GRADE guidelines:14
Conclusion

Explicit rules
- Transparent, informative

GRADE
Complex assessment
simple as possible, transparent, systematic
Increasing wide adoption
Captures all key elements of EBM approach

Clinicians, policy makers need summaries
- Certainty of evidence
- Strength of recommendations

Apply to various questions