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GRADE Summary of Findings Tabellen und Evidenzprofile richtig verstehen

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Interessenskonflikte

M. Csenar, C. Hirsch und C. Wagner: keine Interessenskonflikte

I. Töws und M. Goldkuhle: Mitglieder der GRADE Working Group

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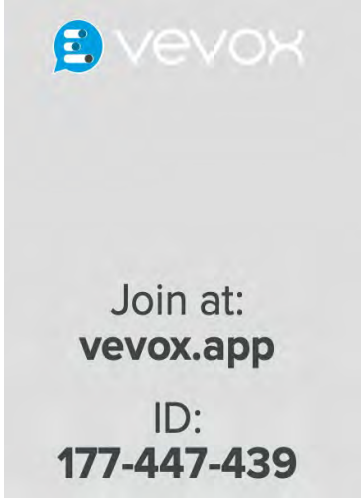
2. Elemente einer Summary of Findings Tabelle
3. Alternative Formate
4. Praktischer Teil
5. Diskussion und offene Fragen



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Inhalt

1. Hintergrund

Ziel:

„Summary of Findings“ Tabellen zur Vermittlung entscheidungsrelevanter Evidenz

…etwas näherbringen,
… wichtige Hintergründe erläutern und
… ein sicheres Verständnis der eingeschlossenen Informationen erreichen.

5. Diskussion und offene Fragen

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Einheitliches System zur:

- Bewertung der Vertrauenswürdigkeit der Evidenz
- Bewertung der Stärke von evidenzbasierten Empfehlungen
- Ableitung von evidenzbasierten Empfehlungen

→ Bisher Fragen zu alternativen Behandlungsstrategien unter Interventionen wie Therapie, Diagnose, Screening, Prävention und prognostische Fragestellungen

Was ist GRADE?

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Der GRADE Ansatz

Transparenter und strukturierter Prozess zur Entwicklung und Präsentation von Empfehlungen:

1. Formulierung von Fragestellungen

2. Auswahl und Priorisierung relevanter Endpunkte

3. Evaluation verfügbarer Evidenz

4. Zusammenfassung und Präsentation von Ergebnissen
   - **Summary of Findings Tabellen**
   - **Evidenzprofile**

5. Ableitung von Empfehlungen unter Berücksichtigung der gesamten, verfügbaren Evidenz

Wo finden sich Summary of Findings Tabellen und Evidenzprofile?

- Überall dort, wo systematische Reviews verwendet werden!

D.h.:

  - Mehrere Datenbanken durchsucht
  - Vorab bestimmte Ein-/Ausschlusskriterien
  - Gedoppelte und unabhängige Durchführung der Arbeitsschritte
  - Biasbewertung

→ In systematischen Reviews selber (z.B. Cochrane Reviews)

→ In Leitlinien

→ In Health Technology Assessment (HTA) Berichten

Warum Summary of Findings Tabellen und Evidenzprofile?

→ Übersichtliche und einheitliche Darstellung von Evidenzgrundlagen

- Transparente Darstellung von Entscheidungsfindungsprozessen

→ Kern- und entscheidungsrelevante Informationen schnell erkennbar

→ Ohne Verlust wichtiger Elemente

→ Evidenzbasierte Darstellungsweise!

- Schnellere und nachhaltigere Vermittlung von Schlüsselinformationen

Elemente einer Summary of Findings Tabelle

Vorstellung des Beispielreviews

Bitte lesen Sie den Abstract!

4. Adapted from: Guo et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database of Systematic Reviews 2019, Issue 4. Art. No.: CD004827. DOI: 10.1002/14651858.CD004827.pub5.

Vorstellung des Beispielreviews

Aktuelles Cochrane Review, publiziert 2019 (4)

Ziel: Untersuchung der Wirksamkeit und Sicherheit von Probiotika zur Prävention von Antibiotika-assoziierter Diarrhöe bei Kindern

Durchgeführt nach Cochrane Standards, z.B.:

- Suche in Medline, EMBASE, CINAHL, Web of Science, Studienregistern, Konferenzabstracts und Referenzen
- Gedoppelte und unabhängige Studienselektion, Datenextraktion und Biasbewertung

Einschluss von insgesamt 33 Studien mit 6352 teilnehmenden Kindern

Probiotika (alleine oder in Kombination): *Bacillus spp., Bifidobacterium spp., Clostridium butyricum, Lactobacilli spp., Lactococcus spp., Leuconostoc cremoris, Saccharomyces spp., oder Streptococcus spp.*

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Comparison: Control (placebo or non-active control)

Outcomes	Anticipated absolute effects * (95% CI)			Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Baseline risk	Corresponding risk					
	Risk in Control	Risk with Probiotics	Risk Difference				
Incidence of AAD Follow-up: 5 days to 12 weeks	**190 per 1000**[1]	**86 per 1000** (68 to 106)	**104 fewer AAD cases per 1000** (84 fewer to 122 fewer)	**RR 0.45** (0.36 to 0.56)	6352 (33 studies)	⊕⊕⊕◯ **Moderate**[2,3,4]	
Duration of diarrhea (days) Follow-up: 10 days to 12 weeks		**MD 0.91 fewer** (1.38 fewer to 0.44 fewer)			1263 (8 studies)	⊕⊕◯◯ **Low**[12,13]	

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Inhalt: PIC(O)

- Möglichst präzise entsprechend der Forschungsfrage formulieren!

Hier:

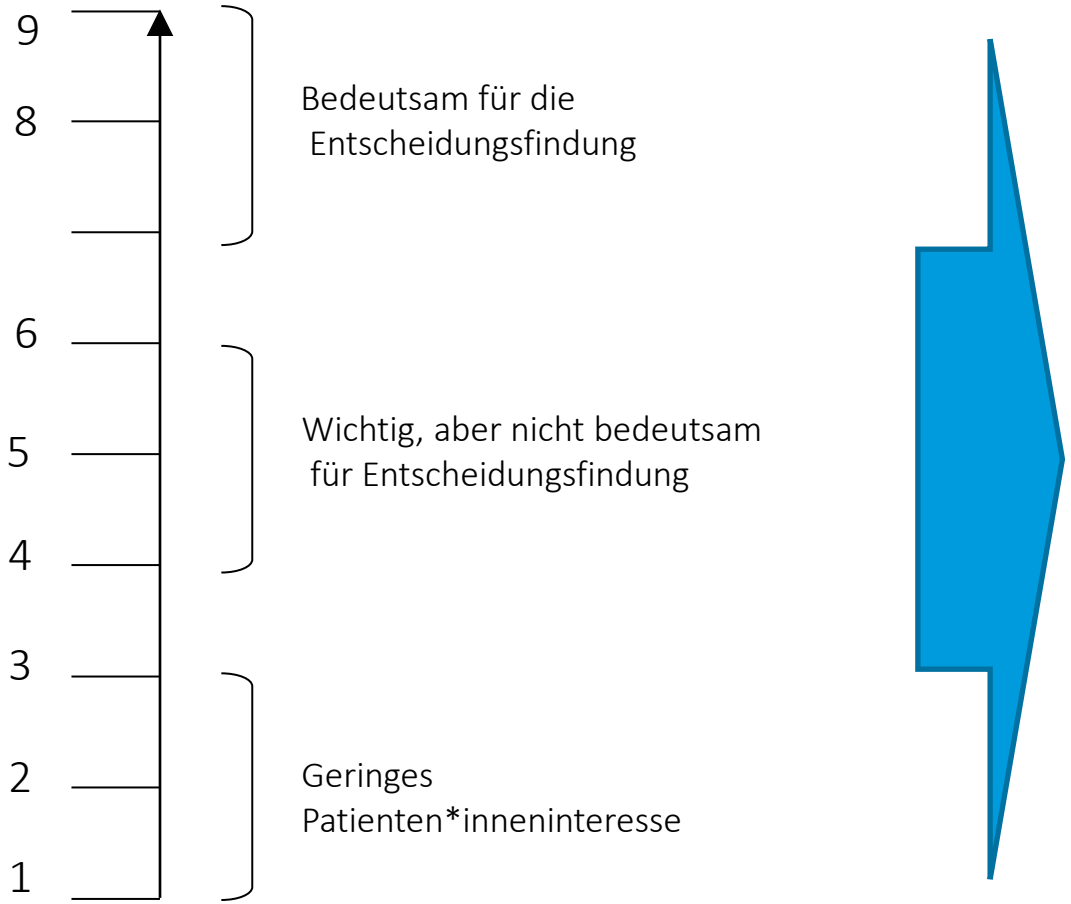
P	(Ziel-)**Population**	→	Kinder die Antibiotika erhalten
S	Setting	→	Ambulante und stationäre Versorgung
I	(Experimentelle) **Intervention**	→	Probiotika
C	Vergleichsintervention/**Kontrolle**	→	Placebo oder keine Probiotika
O	Endpunkt/**Outcome**	→	…

Inhalt: O(utcomes)

- Besondere Stellung → Darstellung und Bewertung der Evidenz nach Endpunkten
  - Unterschiede in der Bewertung zwischen den einzelnen Endpunkten denkbar!

- Darstellung der wichtigsten Endpunkte
  - Wünschenswerte und unerwünschte Endpunkte
  - Patientenrelevanz (Gesamtüberleben, Lebensqualität, unerwünschte Ereignisse, …)
  - Auch wenn keine Evidenz verfügbar sein sollte!
  - Priorisiert nach dem von GRADE vorgesehenen Schema

Wichtigkeit des Endpunktes



Endpunkt	**„Critical“** unbedingt wichtig für die Entscheidungsfindung			**„Important“** wichtig für die Entscheidungsfindung			**„Not important“** geringe Bedeutung für Patient*innen		
	9	**8**	**7**	**6**	**5**	**4**	**3**	**2**	**1**

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Inhalt: O(utcomes)

- Definition in entsprechendem Feld hilfreich und oft erforderlich:
  - Komponenten kombinierter Endpunkte
  - Surrogatparameter
  - Zeitpunkte (z.B. Follow-Up)
  - Skalen

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Inhalt: Relative Effekte

- Zentral in der Bewertung → GRADE-Bewertung des relativen Effekts!

- Bevorzugtes Berichten von relativen Risiken
  - Konstant über Risikogruppen
  - Einfache Interpretierbarkeit
  - Abhängig von den Effektmaßen in den Studien der Meta-Analyse

- Konfidenzintervalle als Maß für die statistische Unsicherheit
- Keine p-Werte

- Vorsicht bei der Richtung von relativen Risiken („Wofür steht <1?“)

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Inhalt: Durchschnittswerte (kontinuierliche Outcomes)

- Durchschnittswert über alle Studien hinweg
- Zur Kombination und zum Vergleich von kontinuierlichen Werten der gleichen Skala
  - z.B. Gewicht, Blutdruck, Schmerzen, …
- Bei abweichenden Skalen: Standardisierung erforderlich → Standardisierter Mittelwert (SMD)
  - Differenz der mittleren Effekte in den Gruppen geteilt durch die kombinierte Standardabweichung (standardisierte Einheit und nicht mehr die Originaleinheit)
- Vorsicht bei der Richtung von Skalen („kleiner/ größer besser?“)

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Inhalt: Absolute Risiken und Effekte

- Notwendig für jeden Endpunkt:
  - Maß der üblichen Belastung/ Krankheitslast in der Zielpopulation („Basisrisiko“)
  - Grundlage der Risikokommunikation und Entscheidungsfindung (Kontextualisierung!)
  - Als natürliche Häufigkeiten

- Herkunft des Basisrisikos:
  - Qualitativ hochwertige Beobachtungsstudien oder systematischen Reviews (idealerweise)
  - Kontrollgruppen in den eingeschlossenen Studien: Median oder repräsentative Einzelstudie

- Bei Subgruppen mit unterschiedlichen Basisrisiken: Präsentation mehrerer Basisrisiken sinnvoll, z.B.:
  - Hoch-, (Moderat-) und Niedrigrisikopopulationen

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[1] Baseline/control group risk estimates come from pooled estimates of control group among 33 included studies.

[2] 20 of 33 studies were rated as high risk of bias to due to issues with lack of blinding, or lack of concealment of allocation, or loss to follow-up (LTFU) or industry sponsorship. Loss to follow-up was substantial (>20%) in 6 studies. In particular, LTFU was 46.4% (King 2010) and 36.6% in two small studies (Tankanow 1990), respectively; and 29% in two additional studies (Arvola 1999; Erdeve 2004), one of which was the largest eligible trial included in our review (n=653) (Erdeve 2004). However, a test for interaction between low risk of bias trials and high or unclear risk of bias trials was not statistically significant (P = 0.30). Further, we conducted a sensitivity analysis wherein we made assumptions about the outcomes for patients that went missing and found similar clinically important results (RR 0.61; 95% CI 0.49 to 0.77).

[3] I^2 is 57% with a P value less than 0.0001 suggesting substantial heterogeneity. We explored the heterogeneity based on nine a priori subgroups, with probiotic dose (high versus low) demonstrating a significant subgroup to help explain the moderate heterogeneity observed. We tested the credibility of this subgroup using published criteria and determined that the subgroup demonstrating increased efficacy of high probiotic dose (≥5 billion CFUs/day) is credible, thus we present the results for this subgroup analysis as separate row in the table.

[4] Regarding inconsistency (I^2 is 57%), given the variability in probiotic species and/or strains used, a priori we planned a subgroup analysis to explore if there were important differences in treatment effect between products with specific species and/or strains. Our subgroup analysis demonstrated no statistically significant difference between products based on our test of interaction (P = 0.94), demonstrating that variability in products used was a minor issue and we therefore did not rate down. However for AAD, given the minor issues with both risk of bias and inconsistency, we rated down once from high to moderate quality evidence.

[12] 8 of 33 trials reported duration of diarrhea, suggesting a selective reporting bias and we rated down.

[13] We further rated down for inconsistency given the large statistical heterogeneity (I^2 = 84%), very low P value [P<0.00001]), and given that point estimates and confidence intervals vary considerably.

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Incidence of AAD Follow-up: 5 days to 12 weeks	**190 per 1000**[1]	**86 per 1000** (68 to 106)	**104 fewer AAD cases per 1000** (84 fewer to 122 fewer)	**RR 0.45** (0.36 to 0.56)	6352 (33 studies)	⊕⊕⊕◯ **Moderate**[2,3,4]	
Duration of diarrhea (days) Follow-up: 10 days to 12 weeks		**MD 0.91 fewer** (1.38 fewer to 0.44 fewer)			1263 (8 studies)	⊕⊕◯◯ **Low**[12,13]	

*The basis for the **baseline risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD**: Mean difference; **RD**: Risk difference; **RR**: Risk Ratio
AAD: antibiotic-associated diarrhea;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Baseline/control group risk estimates come from pooled estimates of control group among 33 included studies.

[2] 20 of 33 studies were rated as high risk of bias to due to issues with lack of blinding, or lack of concealment of allocation, or loss to follow-up (LTFU) or industry sponsorship. Loss to follow-up was substantial (>20%) in 6 studies. In particular, LTFU was 46.4% (King 2010) and 36.6% in two small studies (Tankanow 1990), respectively; and 29% in two additional studies (Arvola 1999; Erdeve 2004), one of which was the largest eligible trial included in our review (n=653) (Erdeve 2004). However, a test for interaction between low risk of bias trials and high or unclear risk of bias trials was not statistically significant (P = 0.30). Further, we conducted a sensitivity analysis wherein we made assumptions about the outcomes for patients that went missing and found similar clinically important results (RR 0.61; 95% CI 0.49 to 0.77).

[3] I^2 is 57% with a P value less than 0.0001 suggesting substantial heterogeneity. We explored the heterogeneity based on nine a priori subgroups, with probiotic dose (high versus low) demonstrating a significant subgroup to help explain the moderate heterogeneity observed. We tested the credibility of this subgroup using published criteria and determined that the subgroup demonstrating increased efficacy of high probiotic dose (≥5 billion CFUs/day) is credible, thus we present the results for this subgroup analysis as separate row in the table.

[4] Regarding inconsistency (I^2 is 57%), given the variability in probiotic species and/or strains used, a priori we planned a subgroup analysis to explore if there were important differences in treatment effect between products with specific species and/or strains. Our subgroup analysis demonstrated no statistically significant difference between products based on our test of interaction (P = 0.94), demonstrating that variability in products used was a minor issue and we therefore did not rate down. However for AAD, given the minor issues with both risk of bias and inconsistency, we rated down once from high to moderate quality evidence.

[12] 8 of 33 trials reported duration of diarrhea, suggesting a selective reporting bias and we rated down.

[13] We further rated down for inconsistency given the large statistical heterogeneity (I^2 = 84%), very low P value [P<0.00001]), and given that point estimates and confidence intervals vary considerably.

Vertrauensbewertung

Hohe Vertrauenswürdigkeit ⨁⨁⨁⨁

Moderate Vertrauenswürdigkeit ⨁⨁⨁◯

Niedrige Vertrauenswürdigkeit ⨁⨁◯◯

Sehr niedrige Vertrauenswürdigkeit ⨁◯◯◯

Balshem et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64(4): 401-406.

Vertrauensbewertung (systematisches Review)

⊕⊕⊕⊕ *„high“*	Hohes Vertrauen	Wir sind uns sehr sicher, dass der wahre Effekt nahe dem Effektschätzer liegt
⊕⊕⊕◯ *„moderate“*	Moderates Vertrauen	**Wir sind einigermaßen sicher in Hinblick auf den Effektschätzer:** Der wahre Effekt liegt wahrscheinlich nahe bei dem Effektschätzer, allerdings besteht die Möglichkeit, dass er substantiell unterschiedlich ist
⊕⊕◯◯ *„low“*	Niedriges Vertrauen:	**Unser Vertrauen in den Effektschätzer ist begrenzt:** Der wahre Effekt ist vermutlich substantiell verschieden vom Effektschätzer
⊕◯◯◯ *„very low“*	Sehr niedriges Vertrauen	**Wir haben nur sehr geringes Vertrauen in den Effektschätzer** Der wahre Effekt ist wahrscheinlich substantiell unterschiedlich vom Effektschätzer

Balshem et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64(4): 401-406.

Vertrauensbewertung

Vertrauenswürdigkeit		*Studiendesign*
Hoch	⨁⨁⨁⨁	Randomisierte Studie/ Beobachtungsstudie (nur wenn mit ROBINS-I bewertet)
Moderat	⨁⨁⨁◯	
Niedrig	⨁⨁◯◯	Beobachtungsstudie
Sehr niedrig	⨁◯◯◯	

Balshem et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64(4): 401-406.

Vertrauen herabstufen

- 5 Kriterien

    1. Mängel in Studienmethodik - Study limitations („Risk of Bias“)
    2. Inkonsistenz
    3. Indirekte Evidenz – Indirectness
    4. Unzureichende Präzision
    5. Publikationsbias

- Jedes zu bewertende Kriterium kann bis zu 2 Punkte herabgestuft werden („serious“/“very serious“)
- Transparente Dokumentation erforderlich!

Inhalt: Vertrauenswürdigkeit der Evidenz nach GRADE

1. Mängel in Studienmethodik - Study limitations („Risk of Bias“)

- Keine adäquate Randomisierung
- Inadäquate Verblindung
- Keine Intention-to-treat Analyse
- Viele Patient*innen in der Nachbeobachtungszeit „verloren“ (lost to follow-up)
- Selektiver Ergebnisbericht
- …..

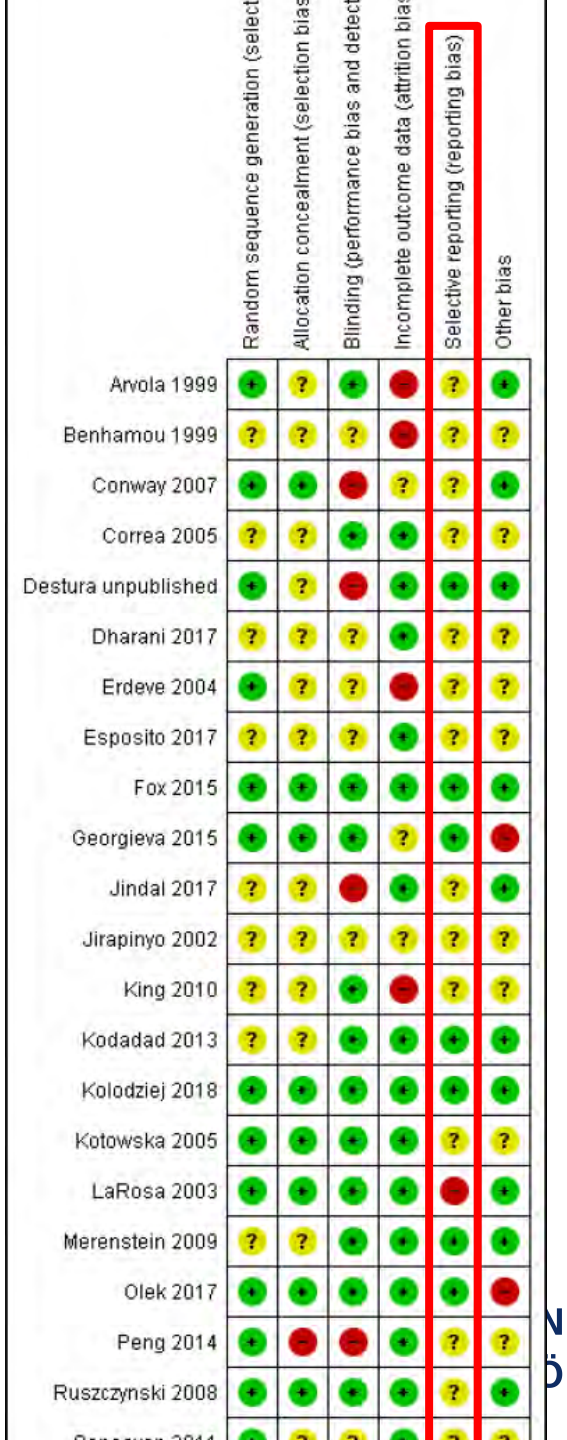
→ Endpunktspezifische Bewertung!

Guyatt et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol 2011;64(4): 407-415.

In unserem Beispiel -

Duration of diarrhea (days) Follow-up: 10 days to 12 weeks	**MD 0.91 fewer** (1.38 fewer to 0.44 fewer)	1263 (8 studies)	⨁⨁◯◯ **Low**[12,13]	

8 von 33 Studien berichten diesen Endpunkt (niedriges Biasrisiko)



VEVOX Umfrage

vevox.app
ID: 177-447-439

Ist das **Risiko einer Verzerrung**…

- **Nicht schwerwiegend** → ⊕⊕⊕⊕ (Hohes Vertrauen)
- **Schwerwiegend** → ⊕⊕⊕◯ (Moderates Vertrauen)
- **Sehr schwerwiegend** → ⊕⊕◯◯ (Niedriges Vertrauen)

…sodass das Vertrauen in das Ergebnis beeinträchtigt wird?

Beginn bei: ⊕⊕⊕⊕

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In unserem Beispiel -

Duration of diarrhea (days) Follow-up: 10 days to 12 weeks	**MD 0.91 fewer** (1.38 fewer to 0.44 fewer)	1263 (8 studies)	⨁⨁◯◯ **Low**[12,13]	

Herabwerten der Vertrauenswürdigkeit für **selektive Berichterstattung** bei **Dauer der Diarrhoe**:

Nur 8 von 33 Studien berichteten die Dauer der Diarrhoe

Inhalt: Vertrauenswürdigkeit der Evidenz nach GRADE

2. Inkonsistenz

- Klinisch
  - Subgruppenanalysen
- Methodisch
- Statistisch
  - Keine überlappenden Konfidenzintervalle
  - Hohes I^2 (> 60%)
  - Variation in der Richtung des Effekts
- Sonderfall: 1 Studie → Keine Heterogenität

Guyatt et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. J Clin Epidemiol 2011; 64(12): 1294-1302.

In unserem Beispiel – Dauer der Diarrhoe

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Arvola 1999	60	4 (1.5)	59	4 (1.5)		12.93%	0[-0.54,0.54]
Correa 2005	80	3.9 (2.5)	77	5 (2.8)		10.51%	-1.08[-1.91,-0.25]
Destura unpublished	162	4 (3.5)	161	3.9 (2.3)		12.12%	0.14[-0.5,0.78]
Esposito 2017	30	1.5 (1.5)	30	2.8 (1.6)		10.86%	-1.3[-2.08,-0.52]
LaRosa 2003	56	0.7 (1.4)	54	1.6 (2)		12.03%	-0.9[-1.55,-0.25]
Peng 2014	56	3.2 (1.2)	56	5.3 (1.6)		13.06%	-2.1[-2.62,-1.58]
Vanderhoof 1999	93	4.7 (1.5)	95	5.9 (1.6)		13.69%	-1.18[-1.62,-0.74]
Zhang 2015	102	3.2 (1.1)	92	4 (0.9)		14.8%	-0.85[-1.12,-0.58]
Total ***	**639**		**624**			**100%**	**-0.91[-1.38,-0.44]**
Heterogeneity: Tau^2=0.37; Chi^2=43.93, df=7(P<0.0001); I^2=84.07%							
Test for overall effect: Z=3.79(P=0)							

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VEVOX Umfrage

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ID: 177-447-439

Ist die **Inkonsistenz**…

- **Nicht schwerwiegend** → ⊕⊕⊕⊕ (Hohes Vertrauen)
- **Schwerwiegend** → ⊕⊕⊕◯ (Moderates Vertrauen)
- **Sehr schwerwiegend** → ⊕⊕◯◯ (Niedriges Vertrauen)

…sodass das Vertrauen in das Ergebnis beeinträchtigt wird?

Beginn bei: ⊕⊕⊕⊕

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In unserem Beispiel – Dauer der Diarrhoe

Duration of diarrhea (days) Follow-up: 10 days to 12 weeks		**MD 0.91 fewer** (1.38 fewer to 0.44 fewer)	1263 (8 studies)	⊕⊕◯◯ **Low**[12,13]

Herabwerten der Vertrauenswürdigkeit für **Inkonsistenz** bei **Dauer der Diarrhoe**

Inhalt: Vertrauenswürdigkeit der Evidenz nach GRADE

3. Indirekte Evidenz - Indirectness

- Patient*innen
  - Kinder vs. Erwachsene
- Interventionen
  - Dosierung
  - Gleiche Wirkstoffklasse
- Endpunkte
  - Patient*innenrelevant vs. Surrogatparameter

Guyatt et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. J Clin Epidemiol 2011; 64(12): 1303-1310.

VEVOX Umfrage

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ID: 177-447-439

Ist die **Indirectness**…

- **Nicht schwerwiegend** → ⊕⊕⊕⊕ (Hohes Vertrauen)
- **Schwerwiegend** → ⊕⊕⊕◯ (Moderates Vertrauen)
- **Sehr schwerwiegend** → ⊕⊕◯◯ (Niedriges Vertrauen)

…sodass das Vertrauen in das Ergebnis beeinträchtigt wird?

Beginn bei: ⊕⊕⊕⊕

UNIKLINIK KÖLN

Inhalt: Vertrauenswürdigkeit der Evidenz nach GRADE

3. Indirekte Evidenz - Indirectness

- Patient*innenen
  - Kinder vs. Erwachsene
- Interventionen
  - Dosierung
  - Gleiche Wirkstoffklasse
- Endpunkte
  - Patient*innenenrelevant vs. Surrogatparameter

Keine Probleme der Direktheit in unserem Beispiel

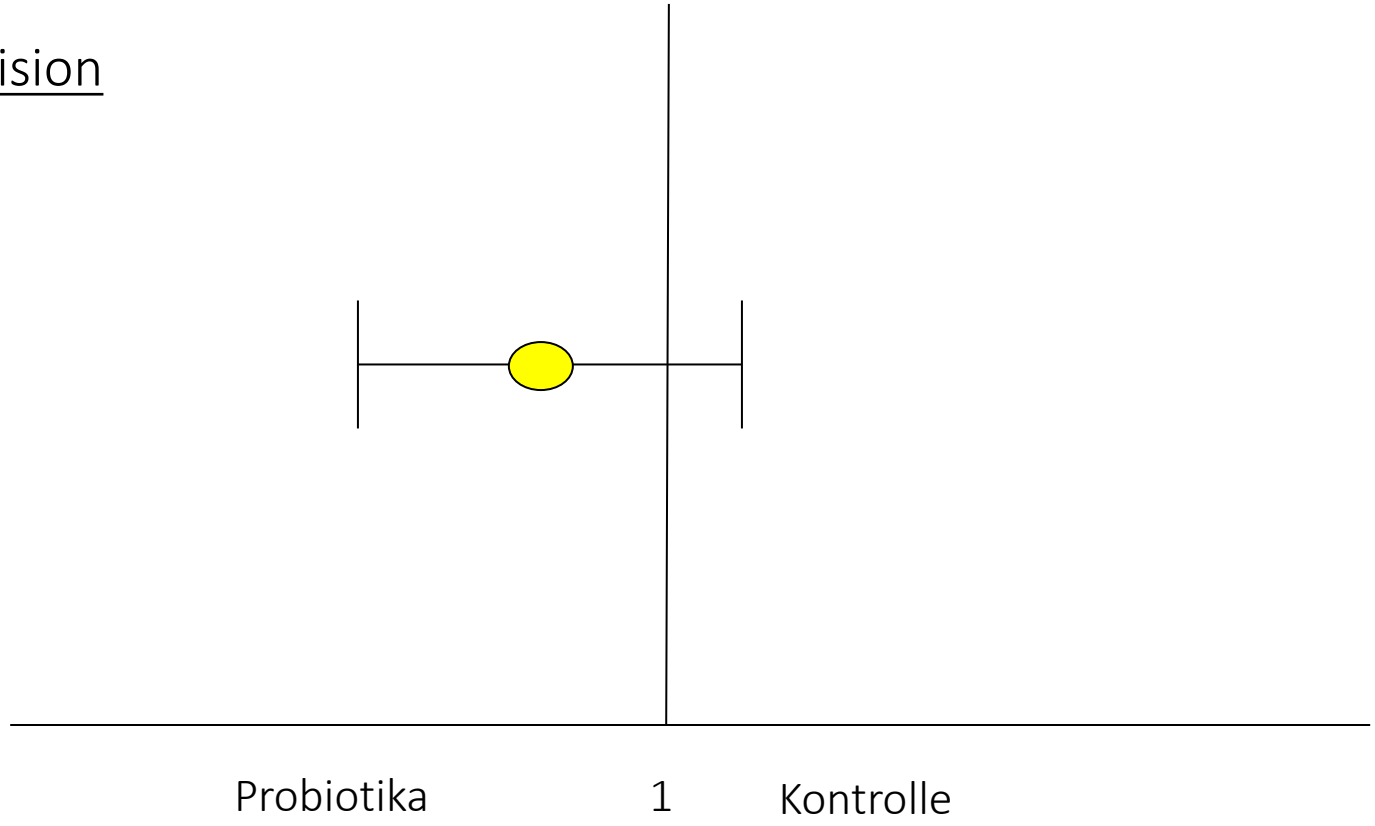
Guyatt et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. J Clin Epidemiol 2011; 64(12): 1303-1310.

Inhalt: Vertrauenswürdigkeit der Evidenz nach GRADE

4. Unzureichende Präzision

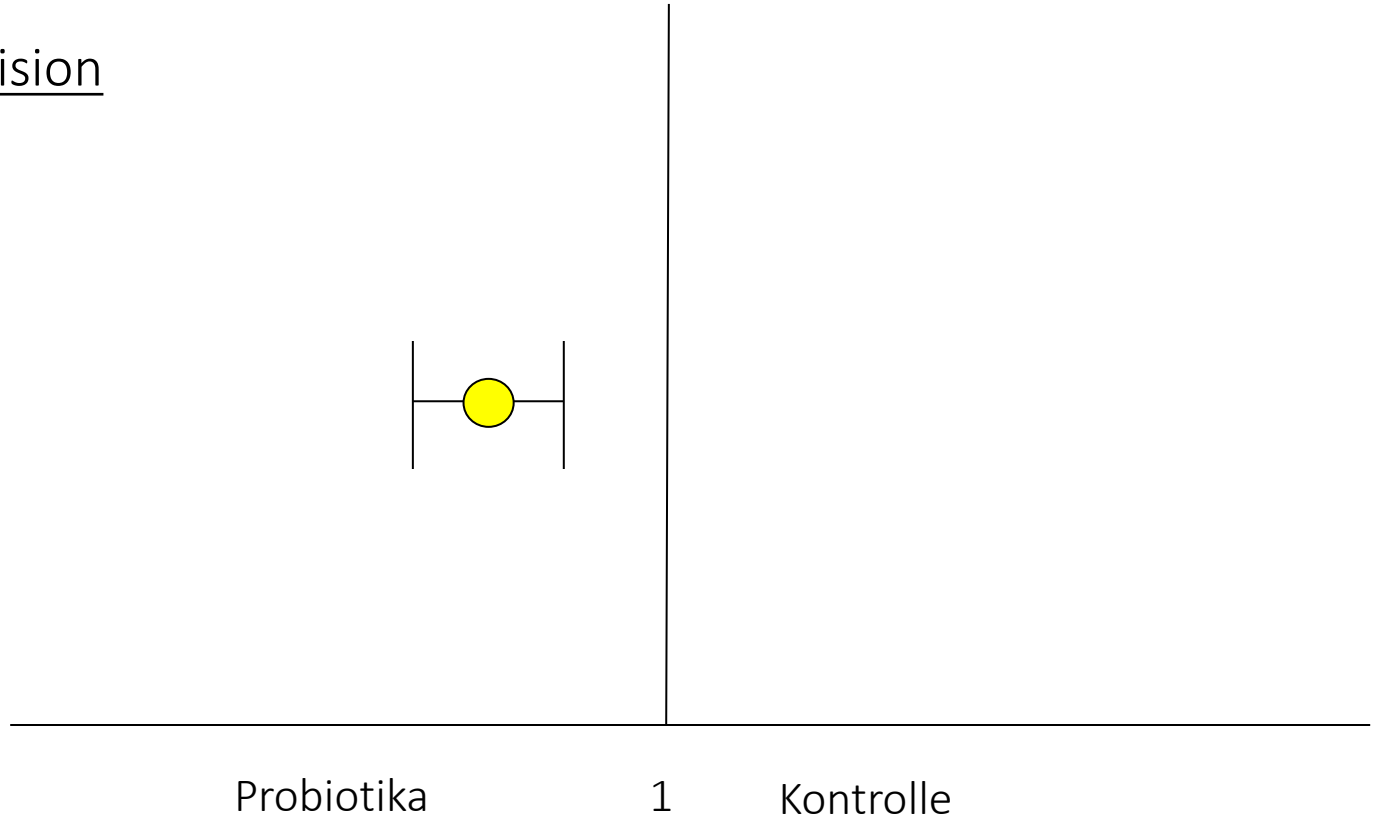
- Wenige Ereignisse
- Betrachtung der Konfidenzintervalle …

4. Unzureichende Präzision



Guyatt et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. J Clin Epidemiol 2011; 64(12): 1283-1293.

4. Unzureichende Präzision



Guyatt et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. J Clin Epidemiol 2011; 64(12): 1283-1293.

4. Unzureichende Präzision

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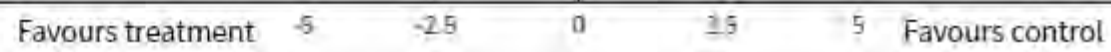

Guyatt et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. J Clin Epidemiol 2011; 64(12): 1283-1293.

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VEVOX Umfrage

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Ist die **unzureichende Präzision**…

- **Nicht schwerwiegend** → ⊕⊕⊕⊕ (Hohes Vertrauen)
- **Schwerwiegend** → ⊕⊕⊕◯ (Moderates Vertrauen)
- **Sehr schwerwiegend** → ⊕⊕◯◯ (Niedriges Vertrauen)

…sodass das Vertrauen in das Ergebnis beeinträchtigt wird?

Beginn bei: ⊕⊕⊕⊕

UNIKLINIK KÖLN

4. Unzureichende Präzision

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
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Total ***	**639**		**624**			**100%**	**-0.91[-1.38,-0.44]**

Heterogeneity: Tau^2=0.37; Chi^2=43.93, df=7(P<0.0001); I^2=84.07%

Test for overall effect: Z=3.79(P=0)

Keine Probleme der Präzision in unserem Beispiel

Guyatt et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. J Clin Epidemiol 2011; 64(12): 1283-1293.

Inhalt: Vertrauenswürdigkeit der Evidenz nach GRADE

5. Publikationsbias

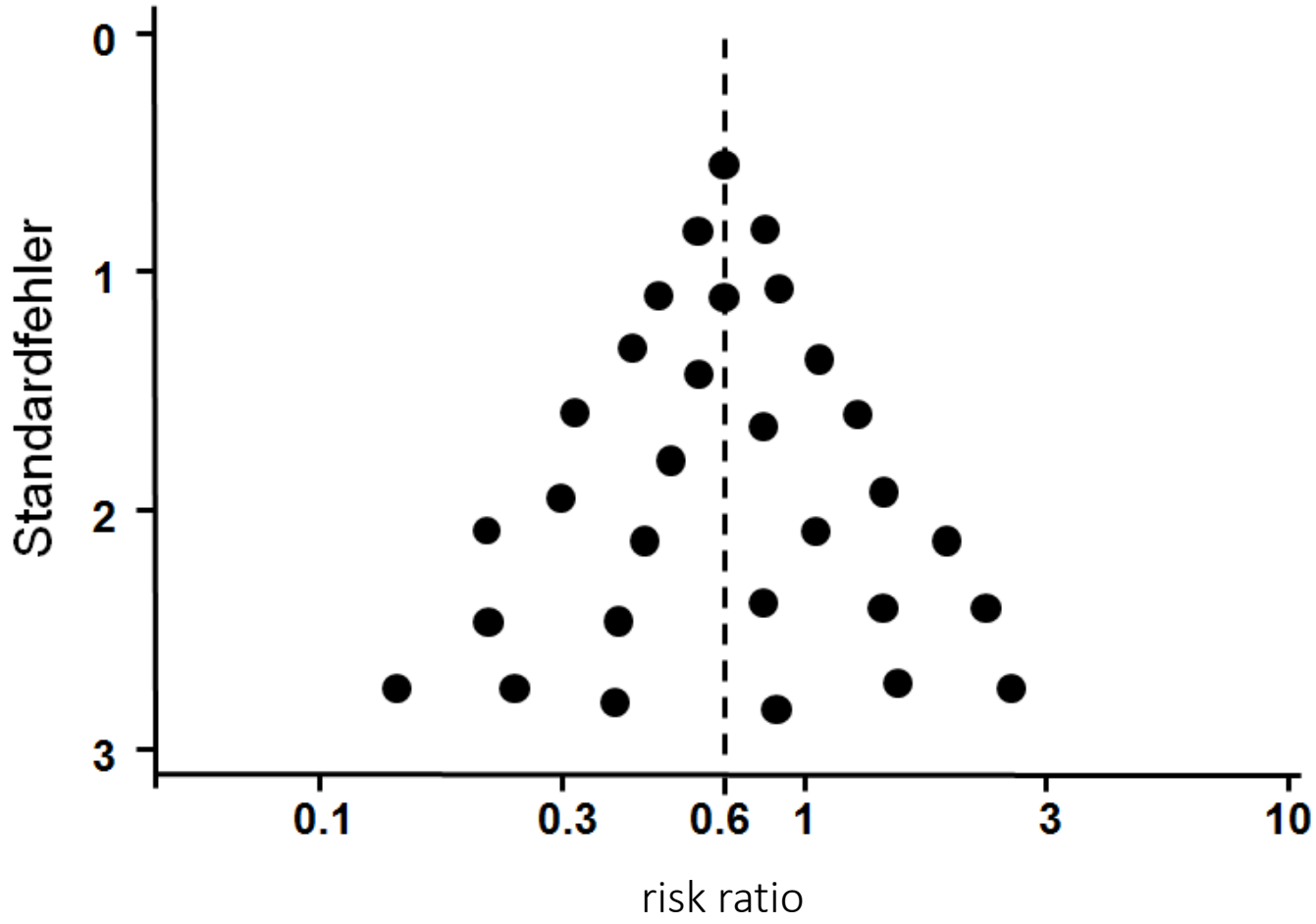
- Studien mit negativem/nicht-signifikantem Ergebnis werden …
  - seltener publiziert
  - langsamer publiziert

- Verdachtsmoment: Ausschließlich industrie-gesponserte Studien verfügbar

- Grafische und statistische Tests können zur Urteilsfindung beitragen
- Voraussetzung adäquate Literatursuche (Registersuche!)

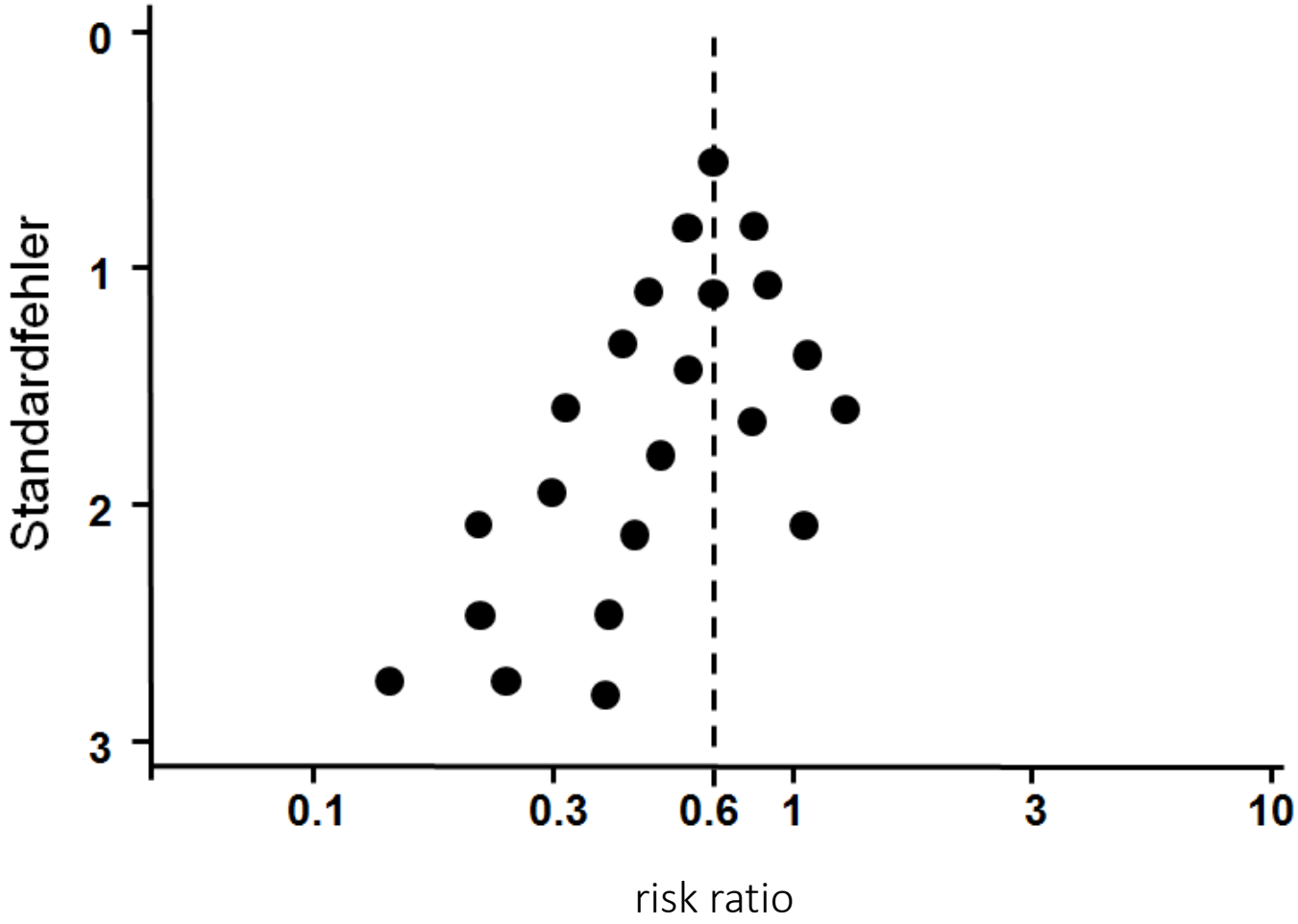
Guyatt et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol 2011;64(12): 1277-1282.

Funnel plot



UNIKLINIK KÖLN

Funnel plot



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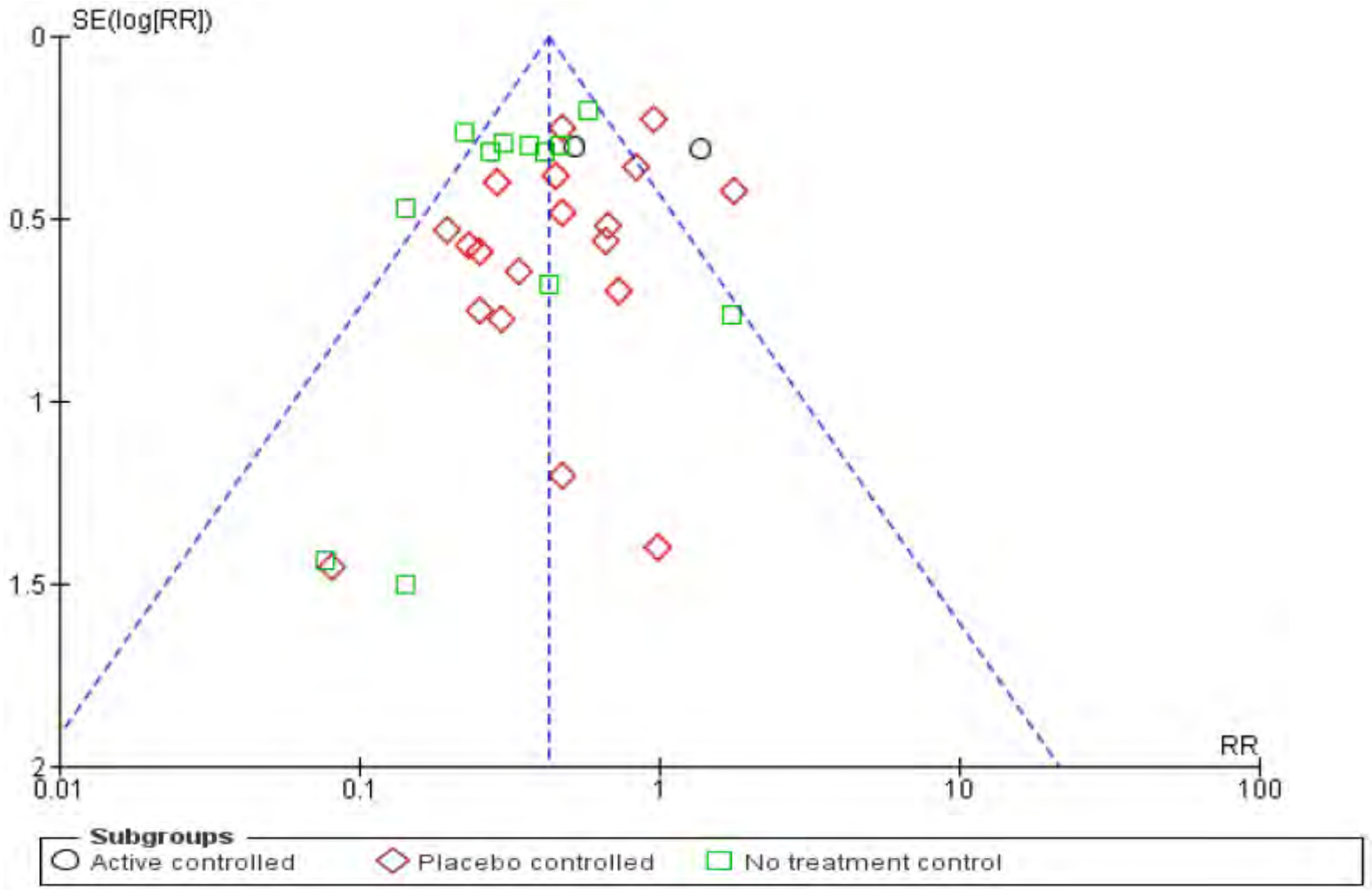
In unserem Beispiel – Auftreten einer Diarrhoe



UNIKLINIK KÖLN

VEVOX Umfrage

vevox.app
ID: 177-447-439

Ist der **Publikationsbias**…

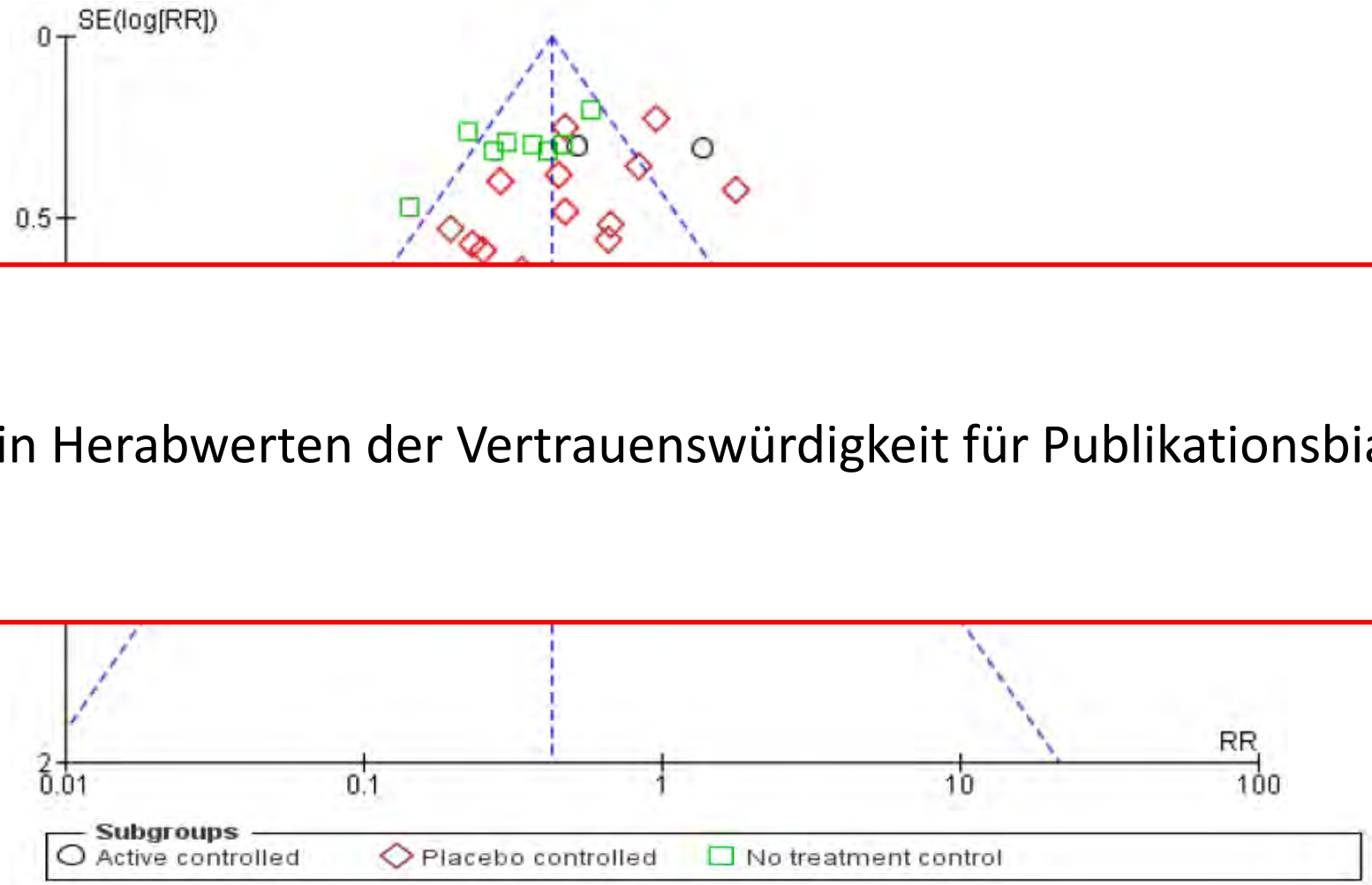
- **Nicht schwerwiegend** → ⊕⊕⊕⊕ (Hohes Vertrauen)
- **Schwerwiegend** → ⊕⊕⊕◯ (Moderates Vertrauen)
- **Sehr schwerwiegend** → ⊕⊕◯◯ (Niedriges Vertrauen)

…sodass das Vertrauen in das Ergebnis beeinträchtigt wird?

Beginn bei: ⊕⊕⊕⊕

UNIKLINIK KÖLN

In unserem Beispiel – Auftreten einer Diarrhoe



Kein Herabwerten der Vertrauenswürdigkeit für Publikationsbias

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Inhalt: Vertrauenswürdigkeit der Evidenz nach GRADE

Vertrauen heraufstufen

- Nur, wenn bisher nicht herabgestuft wurde
- Üblicherweise bei non-RCTs

Guyatt et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011; 64(12): 1311-1316

Inhalt: Vertrauenswürdigkeit der Evidenz nach GRADE

1. Dosis-Wirkungsbeziehung

2. Residual confounding in entgegengesetzte Richtung

3. Großer Effekt

Guyatt et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011; 64(12): 1311-1316

Arten von Summary of Findings Tabellen

Demonstration anhand eines Beispielreviews in GRADEpro GDT:

https://www.gradepro.org/

- Evidenzprofil
- Summary of Findings Tabelle v3
- Interaktive Summary of Findings Tabelle

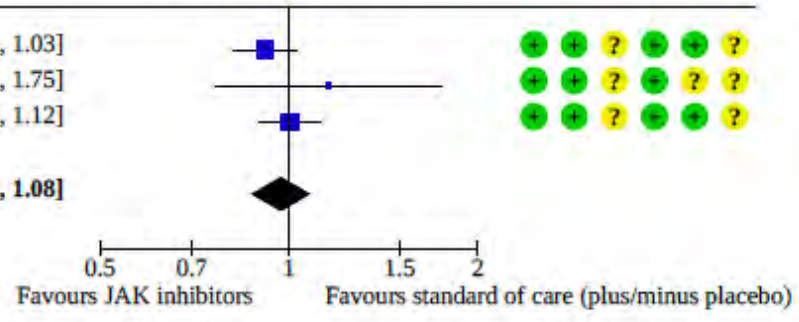
Beispiel: Janus kinase inhibitors for the treatment of COVID-19

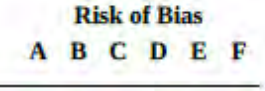
Fragestellung: JAK inhibitors plus standard of care compared to standard of care (plus/minus placebo) in individuals with moderate to severe COVID-19

Endpunkt: Adverse events, any grade

Study or Subgroup	JAK inhibitors Events	JAK inhibitors Total	Standard of care (plus/minus placebo) Events	Standard of care (plus/minus placebo) Total	Weight	Risk Ratio M-H, Random, 95% CI
Ely 2022	44	50	47	49	46.0%	0.92 [0.82 , 1.03]
Guimarães 2021	37	142	32	142	5.8%	1.16 [0.77 , 1.75]
Marconi 2021	334	750	334	752	48.2%	1.00 [0.90 , 1.12]
Total (95% CI)		**942**		**943**	**100.0%**	**0.97 [0.88 , 1.08]**
Total events:	415		413			

Heterogeneity: Tau² = 0.00; Chi² = 2.75, df = 2 (P = 0.25); I² = 27%
Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable





Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Kramer A, Prinz C, Fichtner F, Fischer AL, Thieme V, Grundeis F, et al. Janus kinase inhibitors for the treatment of COVID-19. Cochrane Database Syst Rev. 2022 Jun 13;6(6):CD015209. doi: 10.1002/14651858.CD015209.

UNIKLINIK KÖLN

Beispiel: Janus kinase inhibitors for the treatment of COVID-19

Janus kinase inhibitors plus standard care compared to standard care (plus/minus placebo) in individuals with moderate to severe COVID-19

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty	What happens
	Risk with standard care (plus/minus placebo)	Risk with Janus kinase inhibitors plus standard care				
Adverse events (any grade)	438 per 1.000	**425 per 1.000** (385 to 473)	**RR 0.97** (0.88 to 1.08)	1885 (3 RCTs)	⨁⨁⨁◯ Moderate [a]	

Add outcome | Import outcome(s)

Beispiel: Janus kinase inhibitors for the treatment of COVID-19

Janus kinase inhibitors plus standard care compared to standard care (plus/minus placebo) in individuals with moderate to severe COVID-19

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty	What happens
	Risk with standard care (plus/minus placebo)	Risk with Janus kinase inhibitors plus standard care				
Adverse events (any grade)	438 per 1.000	**425 per 1.000** (385 to 473)	**RR 0.97** (0.88 to 1.08)	1885 (3 RCTs)	⨁⨁⨁◯ Moderate [a]	

Add outcome | Import outcome(s)

GRADE evidence profile

Summary of Findings table

GRADE profile (v2)

Summary of Findings table (v2)

Summary of Findings table (v3)

Interactive SoF

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Beispiel: Janus kinase inhibitors for the treatment of COVID-19

Janus kinase inhibitors plus standard care compared to standard care (plus/minus placebo) in individuals with moderate to severe COVID-19

Summary of Findings table

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty	What happens
	Risk with standard care (plus/minus placebo)	Risk with Janus kinase inhibitors plus standard care				
Adverse events (any grade)	438 per 1.000	**425 per 1.000** (385 to 473)	**RR 0.97** (0.88 to 1.08)	1885 (3 RCTs)	⨁⨁⨁◯ Moderate [a]	

Add outcome | Import outcome(s)

GRADE evidence profile

Certainty assessment							Summary of findings					
							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Janus kinase inhibitors	Standard of care (plus/minus placebo)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Adverse events (any grade)												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	415/942 (44.1%)	413/943 (43.8%)	**RR 0.97** (0.88 to 1.08)	**13 fewer per 1.000** (from 53 fewer to 35 more)	⨁⨁⨁◯ Moderate	

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Summary of Findings table

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty	What happens
	Risk with standard care (plus/minus placebo)	Risk with Janus kinase inhibitors plus standard care				
Adverse events (any grade)	438 per 1.000	**425 per 1.000** (385 to 473)	**RR 0.97** (0.88 to 1.08)	1885 (3 RCTs)	⨁⨁⨁◯ Moderate [a]	

Add outcome | Import outcome(s)

Summary of Findings table (v3)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Without Janus kinase inhibitors	With Janus kinase inhibitors	Difference		
Adverse events (any grade) № of participants: 1885 (3 RCTs)	**RR 0.97** (0.88 to 1.08)	43.8%	**42.5%** (38.5 to 47.3)	**1.3% fewer** (5,3 fewer to 3,5 more)	⨁⨁⨁◯ Moderate [a]	

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Beispiel: Janus kinase inhibitors for the treatment of COVID-19

Janus kinase inhibitors plus standard care compared to standard care (plus/minus placebo) in individuals with moderate to severe COVID-19

Summary of Findings table

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty	What happens
	Risk with standard care (plus/minus placebo)	Risk with Janus kinase inhibitors plus standard care				
Adverse events (any grade)	438 per 1.000	**425 per 1.000** (385 to 473)	**RR 0.97** (0.88 to 1.08)	1885 (3 RCTs)	⨁⨁⨁◯ Moderate [a]	

Add outcome | Import outcome(s)

Interactive SoF

Outcomes	Plain language statements	Absolute Effect: With standard of care (plus/minus placebo)	Absolute Effect: With Janus kinase inhibitors	Relative effect (95% CI)	Certainty of the evidence GRADE
Adverse events (any grade)	*Click here to add summary*	438 per 1000	425 per 1000	RR 0.97 (0.88 to 1.08)	⨁⨁⨁◯ MODERATE

Difference: 13 fewer per 1000 patients (95% CI: 53 fewer to 35 more per 1000 patients)
Based on data from 1885 patients in 3 studies

Due to serious risk of bias.

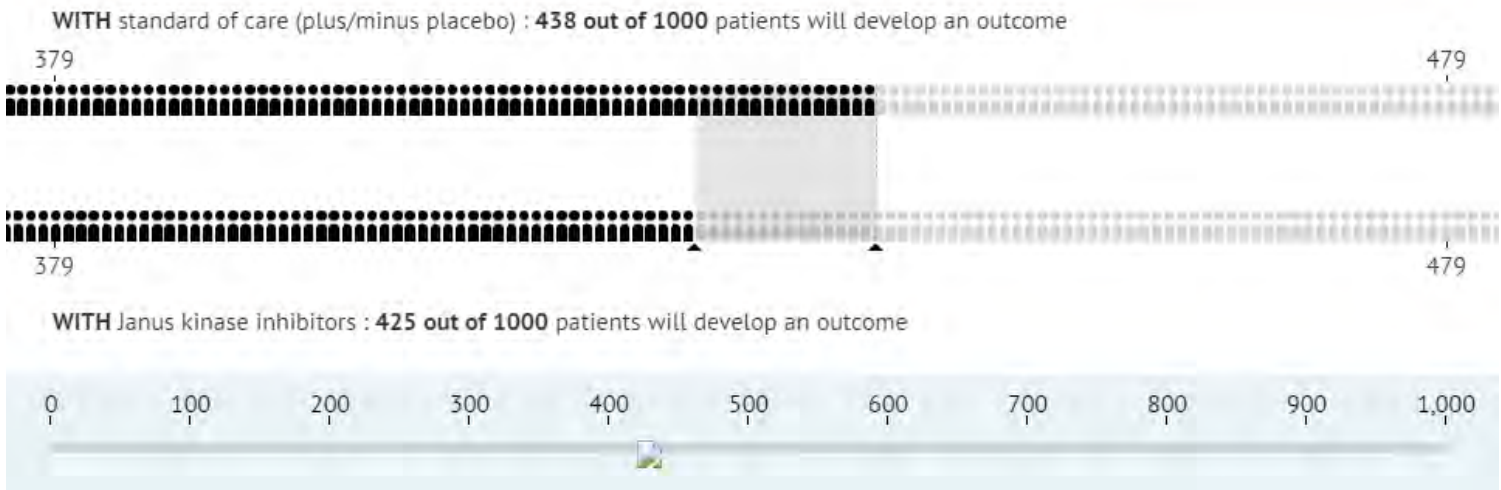
Beispiel: Janus kinase inhibitors for the treatment of COVID-19

Interactive SoF

Outcomes	Plain language statements	Absolute Effect: With standard of care (plus/minus placebo)	Absolute Effect: With Janus kinase inhibitors	Relative effect (95% CI)	Certainty of the evidence GRADE
Adverse events (any grade)	Click here to add sum				⨁⨁⨁◯ MODERATE Due to serious risk of bias.

Chance of: **Adverse events (any grade)**

Let's zoom in. **13 fewer** patients with Janus kinase inhibitors will develop an outcome compared to with standard of care (plus/minus placebo) . This is our best estimate of the difference.



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Vielen Dank für Ihre Aufmerksamkeit!

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