Revue de la littérature et méta-analyse

UE MRCE

Pourquoi faire une revue de la littérature ?

Une étude **ne suffit pas** à tirer une conclusion forte :

- Problème de **réplication** des résultats
- **Manque de puissance**
- Sujet **complexe**

Besoin de collecter, comparer, combiner les résultats disponibles.

Exemple : THS et risque cardiovasculaire

POSTMENOPAUSAL ESTROGEN THERAPY AND CARDIOVASCULAR DISEASE

Ten-Year Follow-up from the Nurses' Health Study

Meir J. Stampfer, M.D., Graham A. Colditz, M.B., B.S., Walter C. Willett, M.D., JoAnn E. Manson, M.D., Bernard Rosner, Ph.D., Frank E. Speizer, M.D., and Charles H. Hennekens, M.D.

Abstract *Background.* The effect of postmenopausal estrogen therapy on the risk of cardiovascular disease remains controversial. Our 1985 report in the *Journal*, based on four years of follow-up, suggested that estrogen therapy reduced the risk of coronary heart disease, but a report published simultaneously from the Framingham Study suggested that the risk was increased. In addition, studies of the effect of estrogens on stroke have yielded conflicting results.

Methods. We followed 48,470 postmenopausal women, 30 to 63 years old, who were participants in the Nurses' Health Study and who did not have a history of cancer or cardiovascular disease at base line. During up to 10 years of follow-up (337,854 person-years), we documented 224 strokes, 405 cases of major coronary disease (nonfatal myocardial infarctions or deaths from coronary causes), and 1263 deaths from all causes.

Results. After adjustment for age and other risk factors, the overall relative risk of major coronary disease in women currently taking estrogen was 0.56 (95 percent confidence interval, 0.40 to 0.80); the risk was significantly reduced among women with either natural or surgical menopause. We observed no effect of the duration of estrogen use independent of age. The findings were similar in analyses limited to women who had recently visited their physicians (relative risk, 0.45; 95 percent confidence interval, 0.31 to 0.66) and in a low-risk group that excluded women reporting current cigarette smoking, diabetes, hypertension, hypercholesterolemia, or a Quetelet index above the 90th percentile (relative risk, 0.53; 95 percent confidence interval, 0.31 to 0.91). The relative risk for current and former users of estrogen as compared with those who had never used it was 0.89 (95 percent confidence interval, 0.78 to 1.00) for total mortality and 0.72 (95 percent confidence interval, 0.55 to 0.95) for mortality from cardiovascular disease. The relative risk of stroke when current users were compared with those who had never used estrogen was 0.97 (95 percent confidence interval, 0.65 to 1.45), with no marked differences according to type of stroke.

Conclusions. Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke. (N Engl J Med 1991; 325:756-62.)

A Prospective, Observational Study of Postmenopausal Hormone Therapy and Primary Prevention of Cardiovascular Disease

Francine Grodstein, ScD; JoAnn E. Manson, MD; Graham A. Colditz, MD; Walter C. Willett, MD; Frank E. Speizer, MD; and Meir J. Stampfer, MD

Background: Most primary prevention studies have found that long-term users of postmenopausal hormone therapy are at lower risk for coronary events, but numerous questions remain. An adverse influence of hormone therapy on cardiovascular risk has been suggested during the initial year of use; however, few data are available on short-term hormone therapy. In addition, the cardiovascular effects of daily doses of oral conjugated estrogen lower than 0.625 mg are unknown, and few studies have examined estrogen plus progestin in this regard.

Objective: To investigate duration, dose, and type of postmenopausal hormone therapy and primary prevention of cardiovascular disease.

Design: Prospective, observational cohort study.

Setting: Nurses' Health Study, with follow-up from 1976 to 1996.

Patients: 70 533 postmenopausal women, in whom 1258 major coronary events (nonfatal myocardial infarction or fatal coronary disease) and 767 strokes were identified.

Measurements: Details of postmenopausal hormone use were ascertained by using biennial questionnaires. Cardiovascular disease was established by using a questionnaire and was confirmed by medical record review. Logistic regression models were used to calculate relative risks and 95% CIs, adjusted for confounders.

Results: When all cardiovascular risk factors were considered, the risk for major coronary events was lower among current users of hormone therapy, including short-term users, compared with never-users (relative risk, 0.61 [95% CI, 0.52 to 0.71]). Among women taking oral conjugated estrogen, the risk for coronary events was similarly reduced in those currently taking 0.625 mg daily (relative risk, 0.54 [CI, 0.44 to 0.67]) and those taking 0.3 mg daily (relative risk, 0.58 [CI, 0.37 to 0.92]) compared with never-users. However, the risk for stroke was statistically significantly increased among women taking 0.625 mg or more of oral conjugated estrogen daily (relative risk, 1.35 [CI, 1.08 to 1.68] for 0.625 mg/d and 1.63 [CI, 1.18 to 2.26] for ≥ 1.25 mg/d) and those taking estrogen plus progestin (relative risk, 1.45 [CI, 1.10 to 1.92]). Overall, little relation was observed between combination hormone therapy and risk for cardiovascular disease (major coronary heart disease plus stroke) (relative risk, 0.91 [CI, 0.75 to 1.11]).

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16 608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

Interventions Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

Main Outcomes Measures The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Results On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10000 person-years.

Conclusions Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

JAMA. 2002;288:321-333 www.jama.com

Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women

Stephen Hulley, MD; Deborah Grady, MD; Trudy Bush, PhD; Curt Furberg, MD, PhD; David Herrington, MD; Betty Riggs, MD; Eric Vittinghoff, PhD; for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group

Context.—Observational studies have found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials.

Objective.—To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease.

Design.—Randomized, blinded, placebo-controlled secondary prevention trial.

Setting.—Outpatient and community settings at 20 US clinical centers.

Participants.—A total of 2763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years.

Intervention.—Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n = 1380) or a placebo of identical appearance (n = 1383). Follow-up averaged 4.1 years; 82% of those assigned to hormone treatment were taking it at the end of 1 year, and 75% at the end of 3 years.

Main Outcome Measures.—The primary outcome was the occurrence of nonfatal myocardial infarction (MI) or CHD death. Secondary cardiovascular outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered.

Results.—Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had MI or CHD death (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22). The lack of an overall effect occurred despite a net 11% lower low-density lipoprotein cholesterol level and 10% higher high-density lipoprotein cholesterol level in the hormone group compared with the placebo group (each $P < .001$). Within the overall null effect, there was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 vs 12; RH, 2.89; 95% CI, 1.50-5.58) and gallbladder disease (84 vs 62; RH, 1.38; 95% CI, 1.00-1.92). There were no significant differences in several other end points for which power was limited, including fracture, cancer, and total mortality (131 vs 123 deaths; RH, 1.08; 95% CI, 0.84-1.38).

Conclusions.—During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gallbladder disease. Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this treatment for the purpose of secondary prevention of CHD. However, given the favorable pattern of CHD events after several years of therapy, it could be appropriate for women already receiving this treatment to continue.

Exemple : THS et risque cardiovasculaire

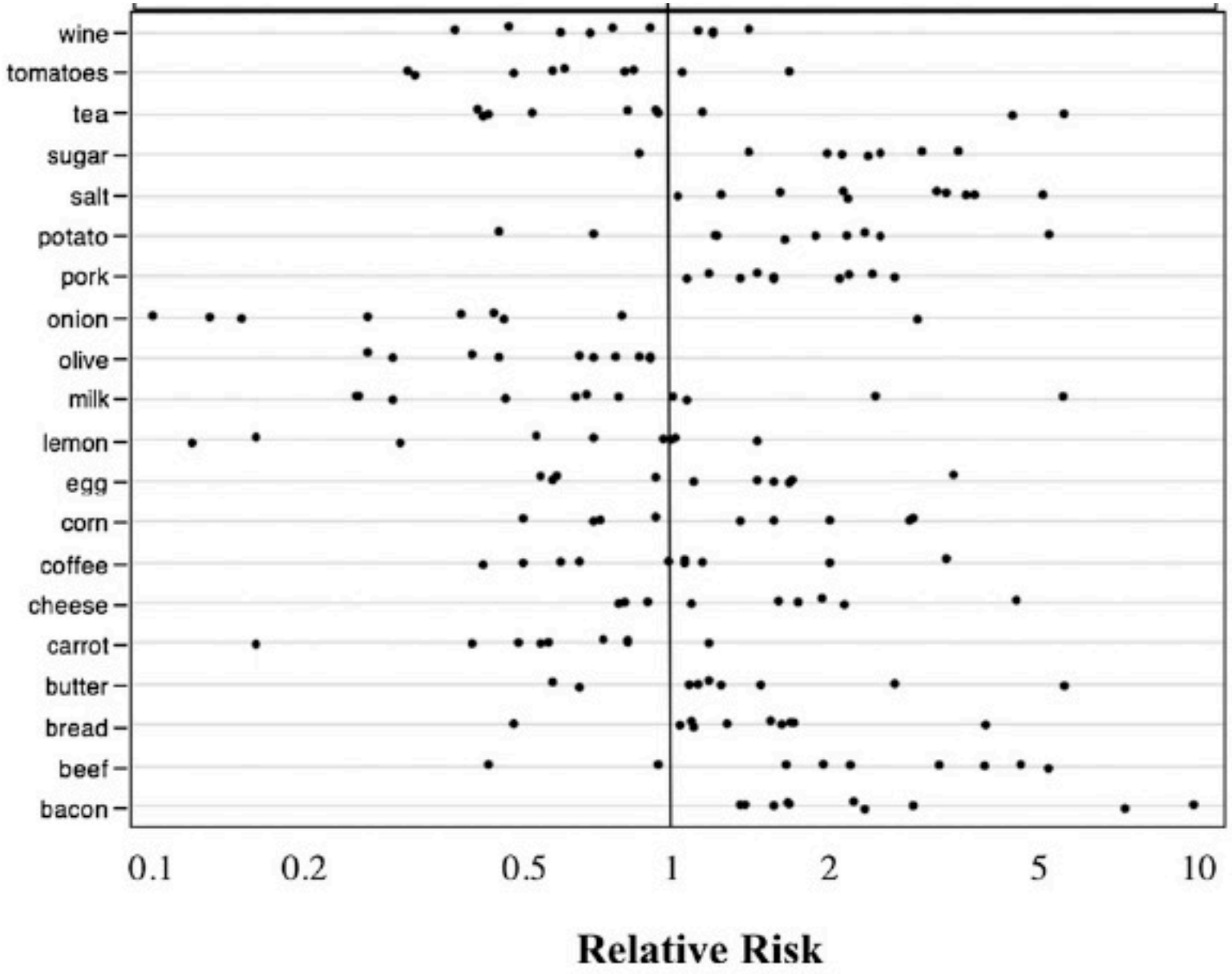
Plusieurs études de cohorte montre une diminution du risque cardiovasculaire chez les femmes sous THS

Les essais randomisés montrent au mieux une absence d'effet, au pire une augmentation du risque cardio-vasculaire liée aux THS

Le dernier essai a été arrêté prématurément à cause d'une augmentation du risque de cancer

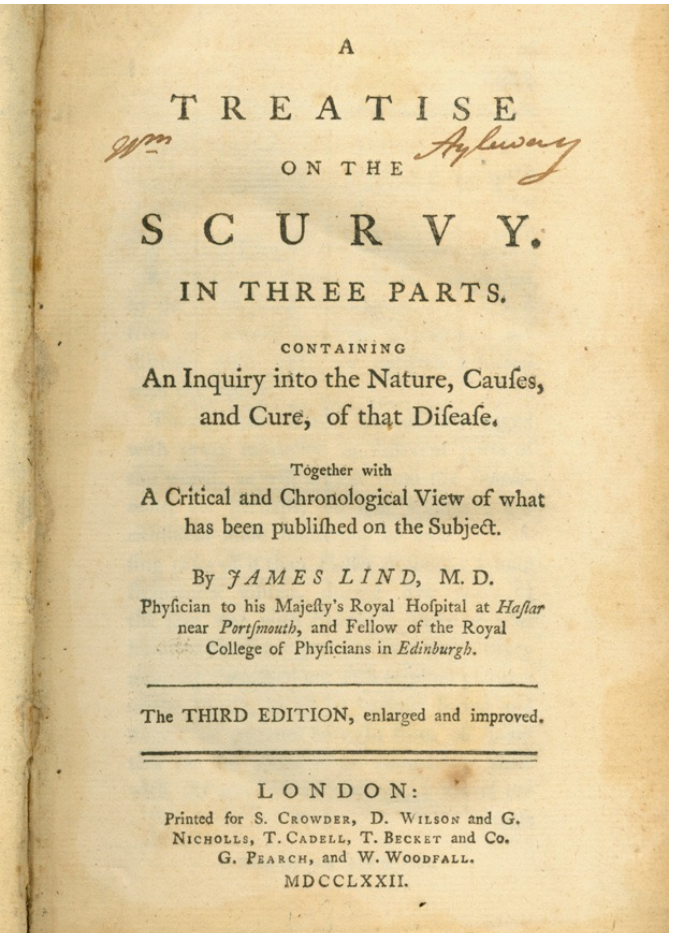
Est-ce que tout ce que nous mangeons est cancérigène ?

- Étude de JD Schoenfeld et JPA Ioannidis en 2013
- 50 ingrédients issus de recettes tirées au hasard dans un livre de cuisine
- Recherche d'études associant ces ingrédients au cancer



Schoenfeld and Ioannidis. Am J Clin Nutr 2013. PMID : 23193004

Un peu d'histoire



A

TREATISE

Wm Aylward

ON THE

SCURVY.

IN THREE PARTS.

CONTAINING

An Inquiry into the Nature, Cauſes, and Cure, of that Diſeaſe.

Together with

A Critical and Chronological View of what has been publiſhed on the Subject.

By *JAMES LIND*, M. D.

Phyſician to his Majeſty's Royal Hoſpital at *Haſlar* near *Portſmouth*, and Fellow of the Royal College of Phyſicians in *Edinburgh*.

The THIRD EDITION, enlarged and improved.

LONDON:

Printed for S. Crowder, D. Wilson and G. Nicholls, T. Cadell, T. Becket and Co. G. Pearch, and W. Woodfall.

MDCCLXXII.

- 1753 James Lind, traité sur le scorbut

Un peu d'histoire

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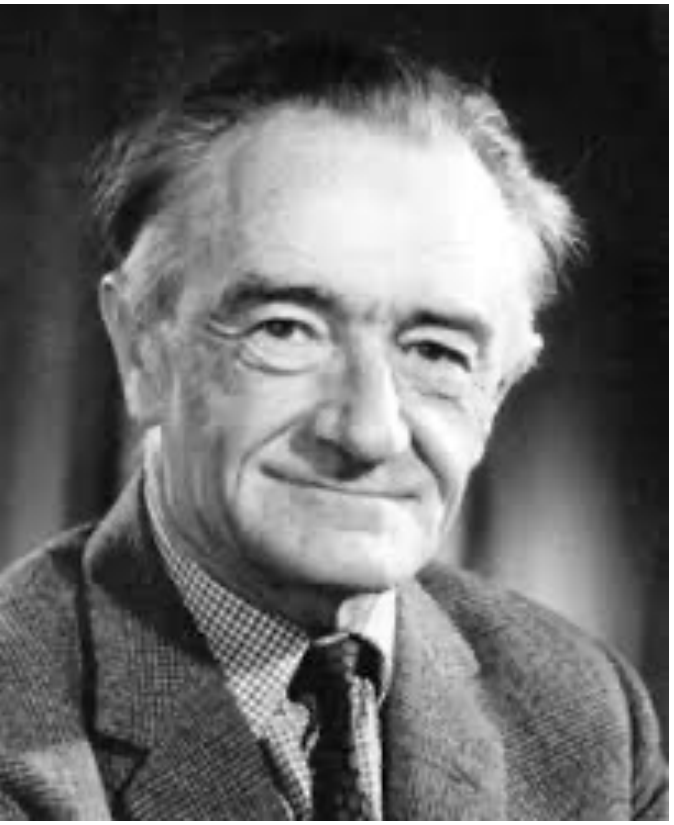
- 1904 Karl Pearson, méta-analyse sur la vaccination anti-typhoïde

Un peu d'histoire



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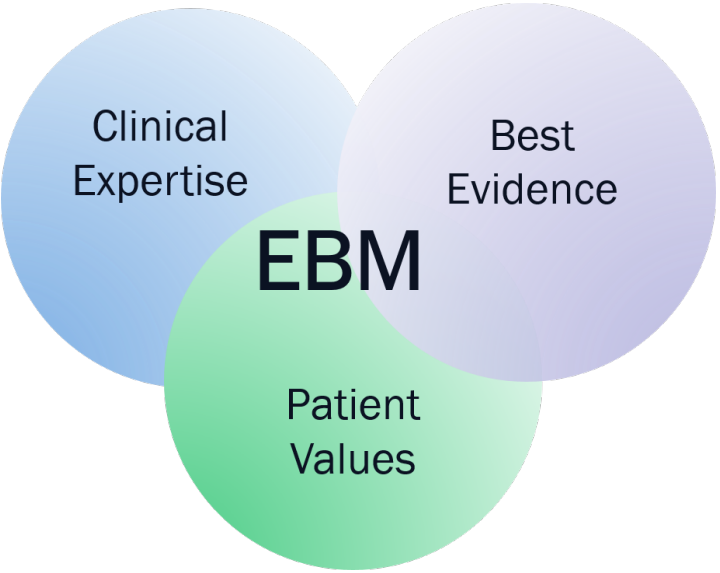
Un peu d'histoire



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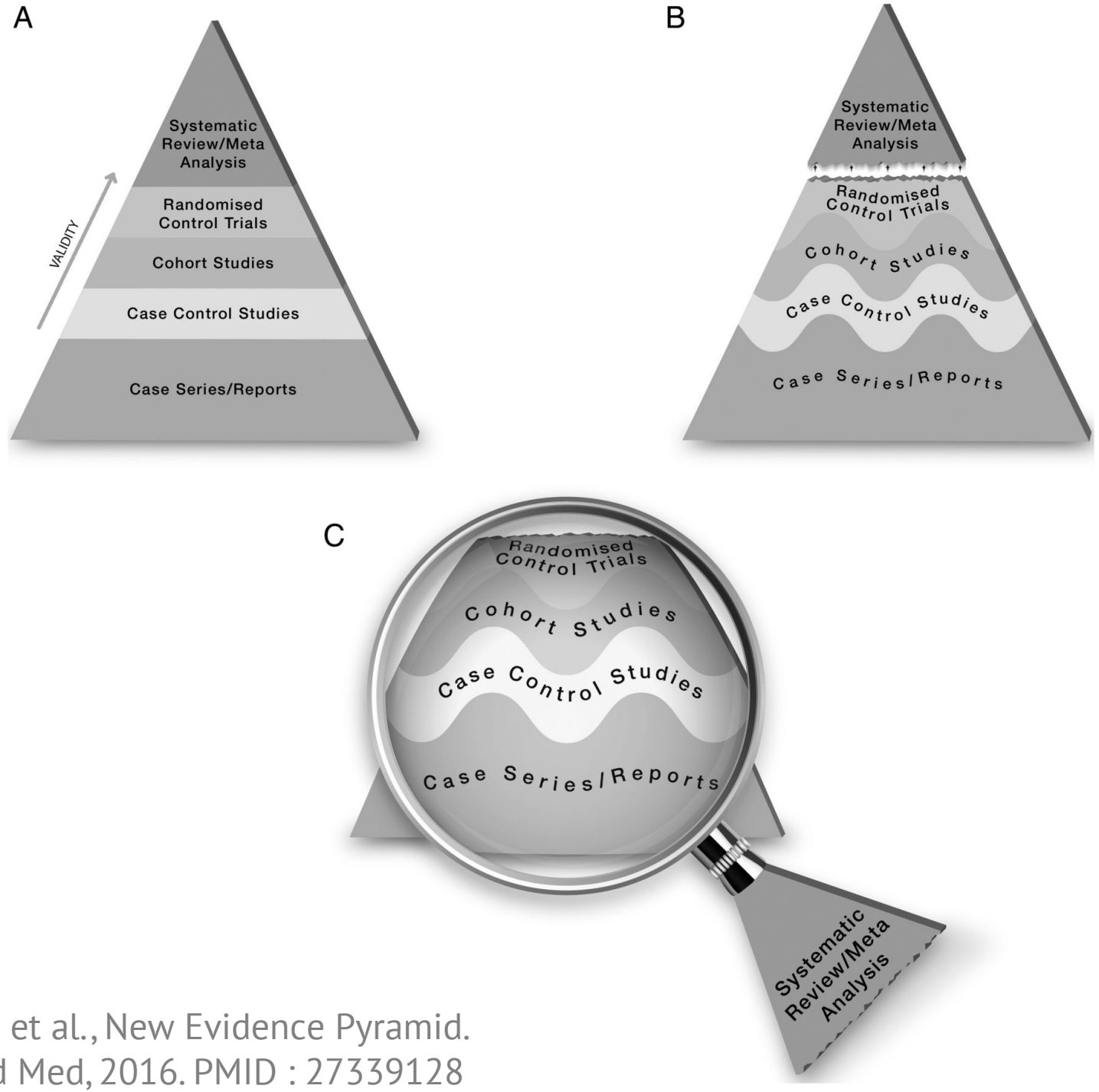
- 1990-2000 Evidence-based medicine

Niveau de preuve

NIVEAU DE PREUVE SCIENTIFIQUE FOURNI PAR LA LITTERATURE	GRADE DES RECOMMANDATIONS
Niveau 1 - Essais comparatifs randomisés de forte puissance – Méta analyse d'essais comparatifs randomisés - Analyse de décision basée sur des études bien menées	**A** Preuve scientifique établie
Niveau 2 - Essais comparatifs randomisés de faible puissance - Études comparatives non randomisées bien menées - Études de cohorte	**B** Présomption scientifique
Niveau 3 - Études cas témoin C **Niveau 4** - Études comparatives comportant des biais importants - Études rétrospectives - Séries de cas - Études épidémiologiques descriptives (transversale, longitudinale)	**C** Faible niveau de preuve scientifique

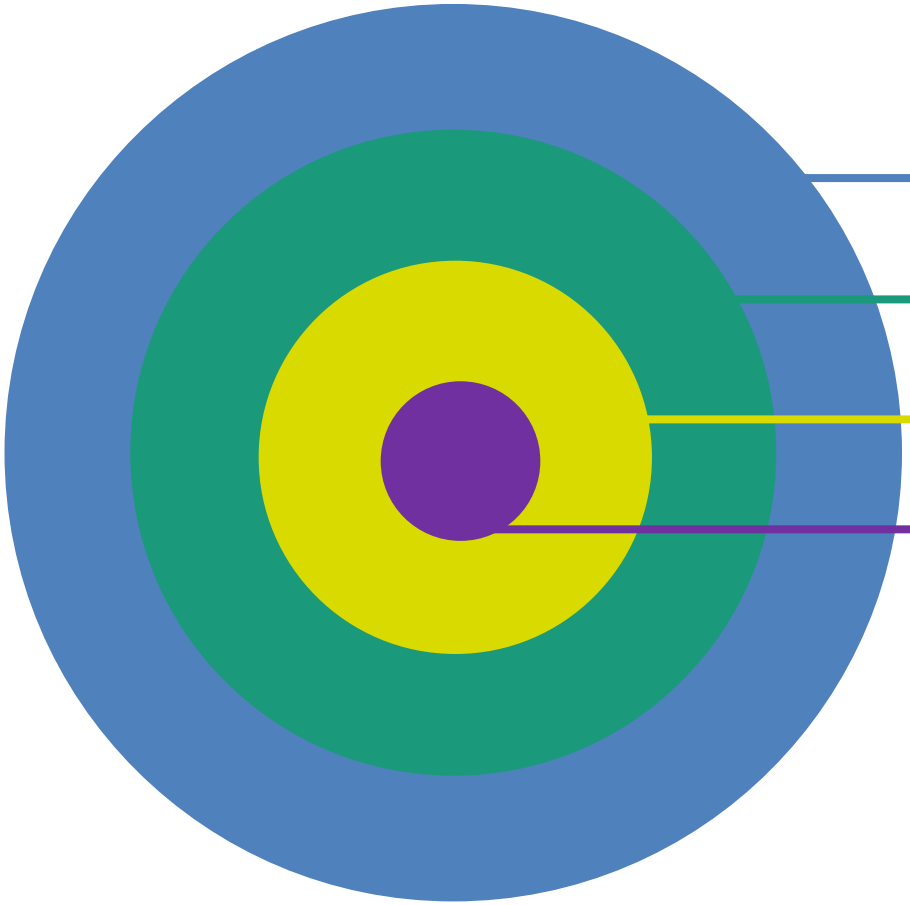
Niveau de preuve selon la HAS

« Pyramide des preuves »



Murad HM et al., New Evidence Pyramid.
Evid Based Med, 2016. PMID : 27339128

Quelques notions



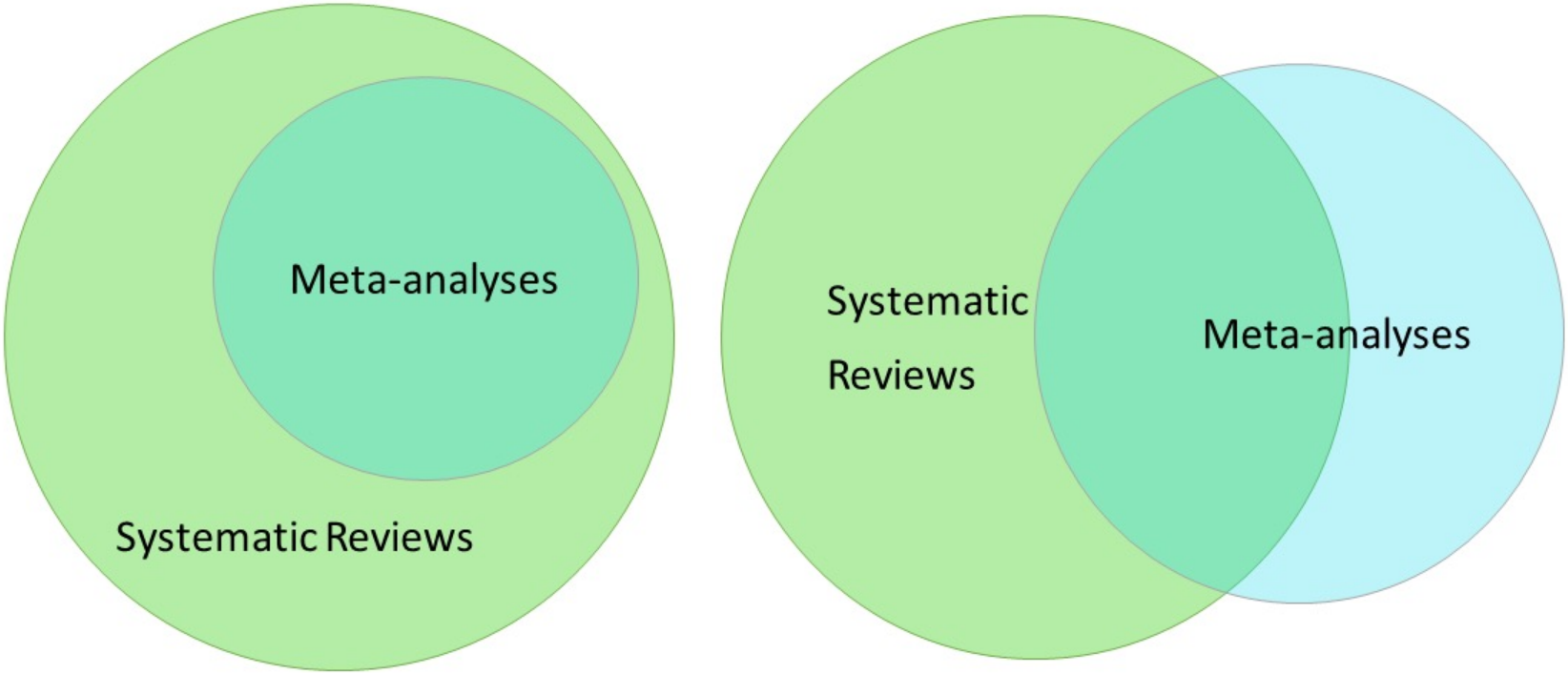
Revues
(narratives et systématiques)

Revues systématiques

Méta-analyses

Méta-analyses sur données individuelles

Expectations versus reality



D'après Jennifer Hanratty, meta-evidence blog

Comment réaliser une revue systématique ?

1. Poser la question de recherche
2. Construire l'équation de recherche
3. Interroger les bases
4. Inclure les études
5. Extraire les données
6. Analyser les résultats

1. Poser la question de recherche

Population

Intervention

Comparaison

Outcome

Exemple : Chez les amputés de sexe masculin souffrant du syndrome du membre phantôme, la gabapentine, comparée au placebo, permet-elle de réduire la symptomatologie douloureuse ?

2. Construire l'équation de recherche

- Trouver les **synonymes** et termes associés
- Trouver les **graphies alternatives**
- Joindre par les **connecteurs logiques**

Dépend beaucoup des bases de données utilisées, **l'aide d'un documentaliste peut être grandement appréciée !**

Exemple : recherche pour la notion de maladie d'Alzheimer dans PubMed

("Alzheimer Disease"[mh] OR "alzheimer's"[tiab] OR "alzheimer"[tiab] OR ad[tiab] OR "alzheimers"[tiab] OR "alzhiemer"[tiab] OR "alzhiemers"[tiab] OR "alzhiemer's"[tiab] OR "cognition disorders"[mh] OR cognitive[tiab] OR cognition[tiab] OR "dementia"[mh:noexp] OR dementia[tiab])

Adapté de https://guides.lib.umich.edu/c.php?g=283340&p=2126706

3. Interroger les bases de données bibliographiques

Principales bases de données à tester*

- Medline (Ovid ou Pubmed)
- Embase
- Web of Science
- Google Scholar (200 plus pertinents)

Autres bases :

- Cochrane CENTRAL
- PsychINFO
- …

Autres sources :

- Experts
- Littérature « grise »
- Congrès

* Selon Bramer et al. Syst Rev, 2017, PMID : 29208034

4. Inclure les études / 5. Extraire les données

1. Gestion des **doublons**
2. Screening sur les **titres et abstracts**
3. Screening sur les **textes entiers**
4. Extraction des **données** (date, population, résultats, qualité+++)

Selon la collaboration Cochrane : par **2 relecteurs**, avec analyse des désaccords

Outils utiles :

- Logiciel de gestion biblio (Zotero)
- Logiciel spécifique (AbstrackR)

Évaluation de la qualité des études

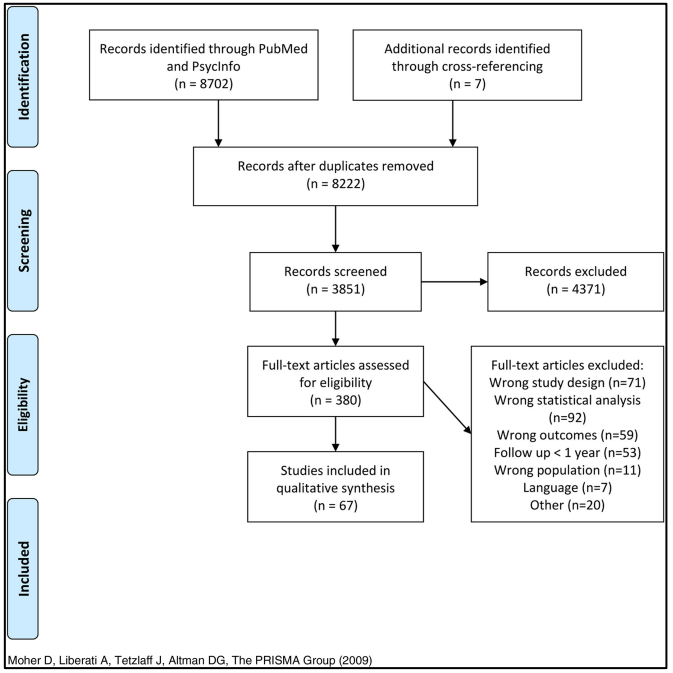
Utile pour exclusion ou ajustement !

Outils intéressants :

- Cochrane study quality guide
- Newcastle Ottawa scale (cohortes et cas-témoins)
- QUADAS2 (études diagnostiques)
- Jadad (RCT)
- ICROMS (plusieurs types d'études)

6. Analyser les résultats

- **Descriptive**
  - Tableaux, figures etc.
  - **Diagramme de flux** (*flow chart*) — *template disponible sur la Cochrane*
  - **Présentation tabulaires** des données



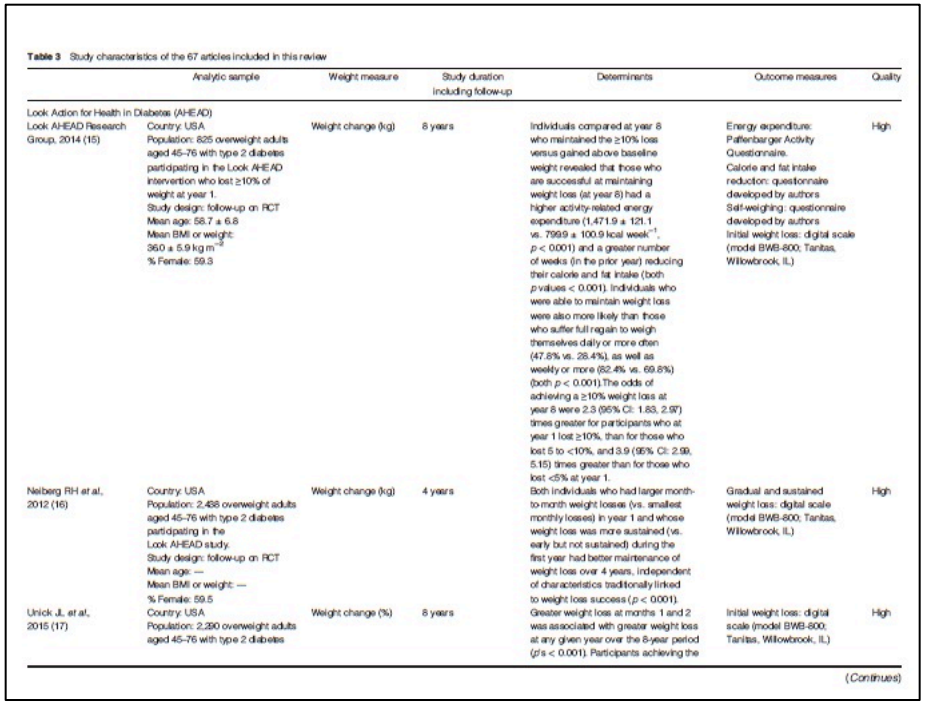


Table 3 Study characteristics of the 67 articles included in this review

	Analytic sample	Weight measure	Study duration including follow-up	Determinants	Outcome measures	Quality
Look Action for Health in Diabetes (AHEAD)						
Look AHEAD Research Group, 2014 (15)	Country: USA Population: 825 overweight adults aged 45–76 with type 2 diabetes participating in the Look AHEAD intervention who lost ≥10% of weight at year 1. Study design: follow-up on RCT Mean age: 58.7 ± 6.8 Mean BMI or weight: 36.0 ± 5.9 kg m^{-2} % Female: 59.3	Weight change (kg)	8 years	Individuals compared at year 8 who maintained the ≥10% loss versus gained above baseline weight revealed that those who are successful at maintaining weight loss (at year 8) had a higher activity-related energy expenditure (1,471.9 ± 121.1 vs. 799.9 ± 100.9 kcal week^{-1}, $p < 0.001$) and a greater number of weeks (in the prior year) reducing their calorie and fat intake (both p values < 0.001). Individuals who were able to maintain weight loss were also more likely than those who suffer full regain to weigh themselves daily or more often (47.8% vs. 28.4%), as well as weekly or more (82.4% vs. 69.8%) (both $p < 0.001$). The odds of achieving a ≥10% weight loss at year 8 were 2.3 (95% CI: 1.83, 2.97) times greater for participants who at year 1 lost ≥10%, than for those who lost 5 to <10%, and 3.9 (95% CI: 2.99, 5.15) times greater than for those who lost <5% at year 1.	Energy expenditure: Paffenbarger Activity Questionnaire. Calorie and fat intake reduction: questionnaire developed by authors Self-weighing: questionnaire developed by authors Initial weight loss: digital scale (model BWB-800; Tanitas, Willowbrook, IL)	High
Neiberg RH *et al.*, 2012 (16)	Country: USA Population: 2,438 overweight adults aged 45–76 with type 2 diabetes participating in the Look AHEAD study. Study design: follow-up on RCT Mean age: — Mean BMI or weight: — % Female: 59.5	Weight change (kg)	4 years	Both individuals who had larger month-to-month weight losses (vs. smallest monthly losses) in year 1 and whose weight loss was more sustained (vs. early but not sustained) during the first year had better maintenance of weight loss over 4 years, independent of characteristics traditionally linked to weight loss success ($p < 0.001$).	Gradual and sustained weight loss: digital scale (model BWB-800; Tanitas, Willowbrook, IL)	High
Unick JL *et al.*, 2015 (17)	Country: USA Population: 2,290 overweight adults aged 45–76 with type 2 diabetes	Weight change (%)	8 years	Greater weight loss at months 1 and 2 was associated with greater weight loss at any given year over the 8-year period (p's < 0.001). Participants achieving the	Initial weight loss: digital scale (model BWB-800; Tanitas, Willowbrook, IL)	High

(*Continues*)

D'après Varkevisser et al. Obes rev. 2019 PMID : 30324651

6. Analyser les résultats

- **Quantitative**
  - **Évaluation de l'hétérogénéité** entre les études :
    - Qualitativement (étude des populations, contextes, etc.)
    - Quantitativement (Test Q de Cochrane, indicateur I^2)

  - Si pas trop d'hétérogénéité : **Méta-analyse**
    - Calcul d'un effet « moyen » – *voir vidéo sur l'espace madoc*
    - Réalisation d'un diagramme en forêt (*forest plot*)

  - Prise en compte de l'hétérogénéité :
    - Analyse en sous-groupe
    - Analyse de sensibilité
    - Modélisation (méta-regression)

Forest plot

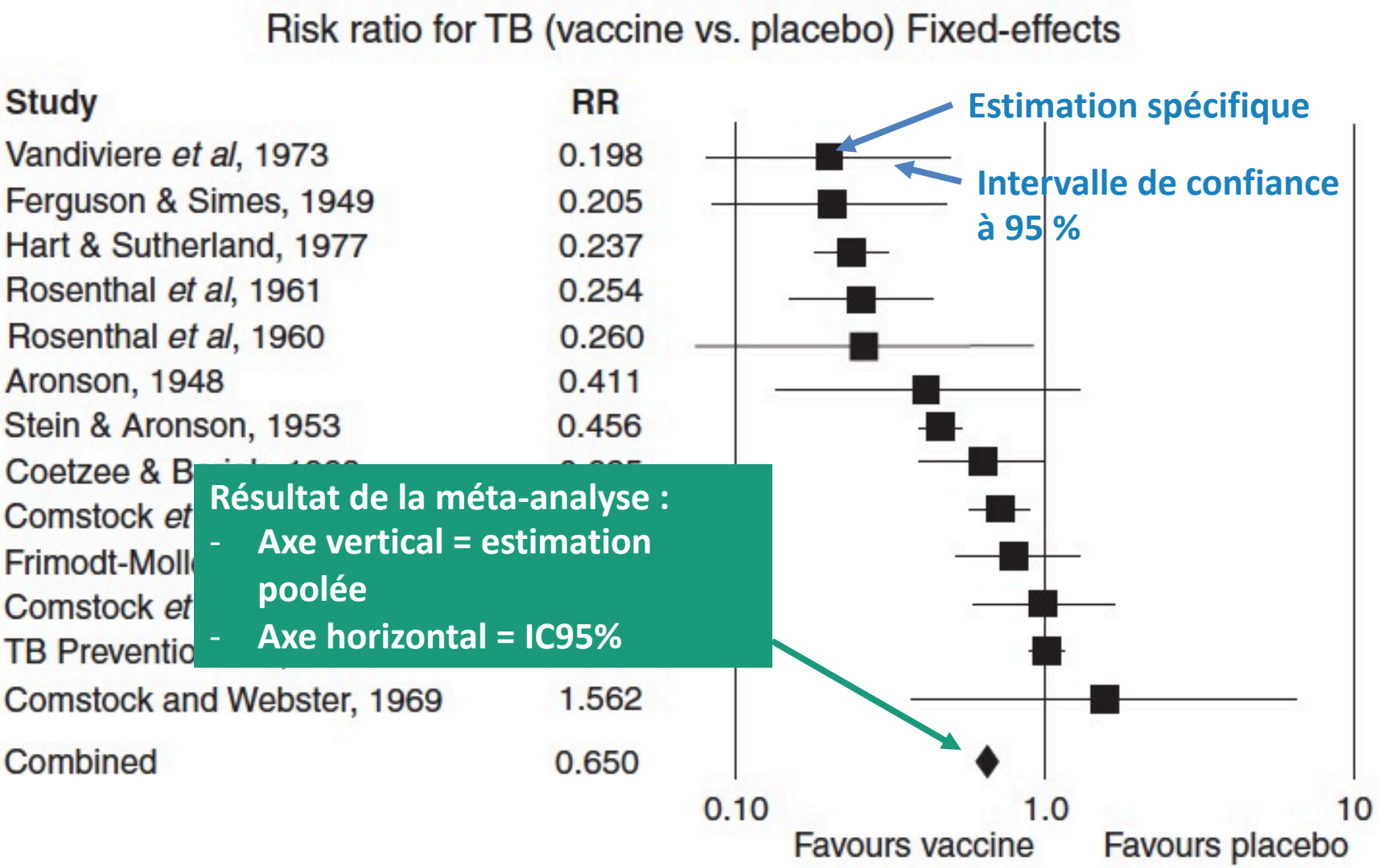


Figure 20.1 Fixed-effect model – forest plot for the BCG data.

Exemple de méta-régression

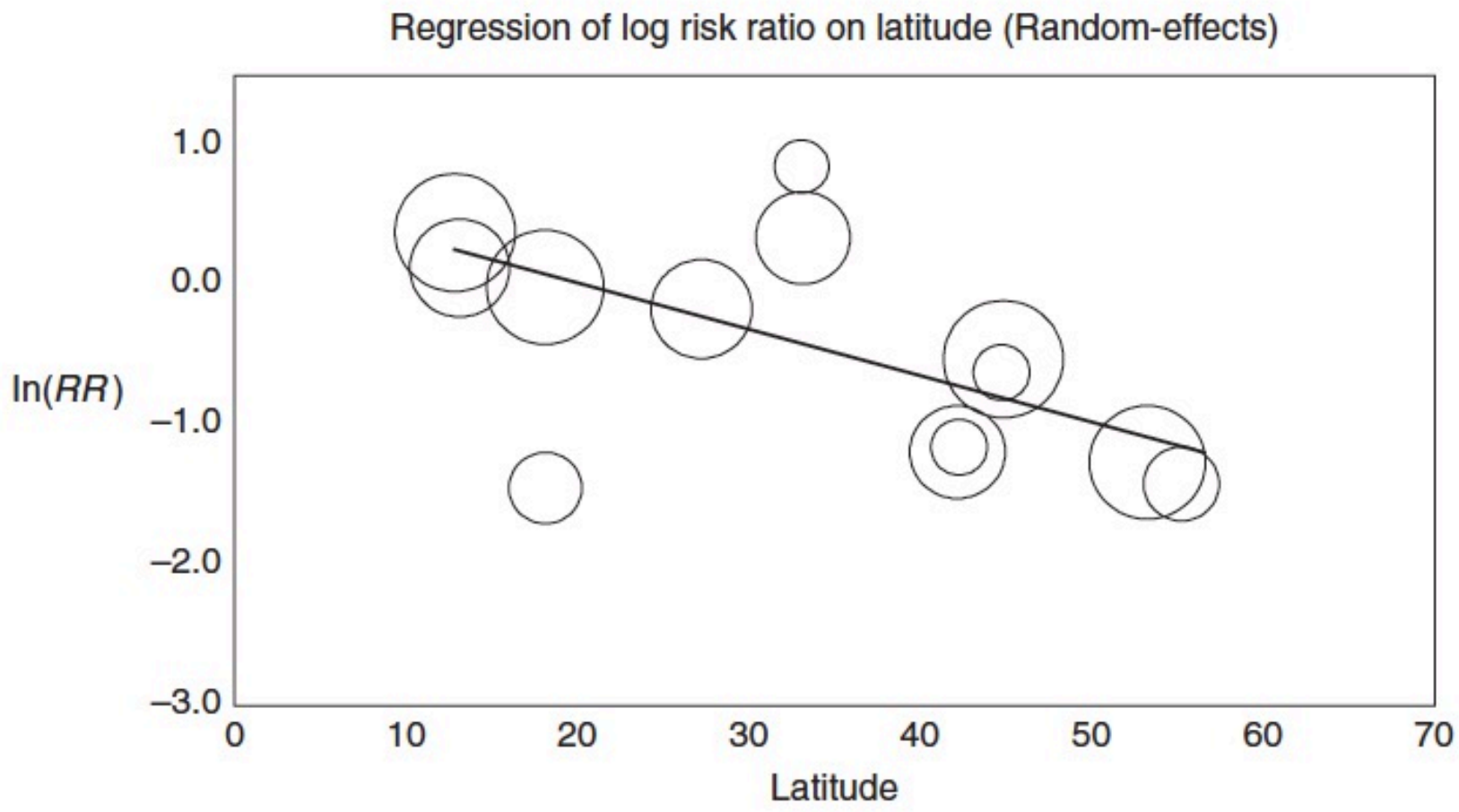


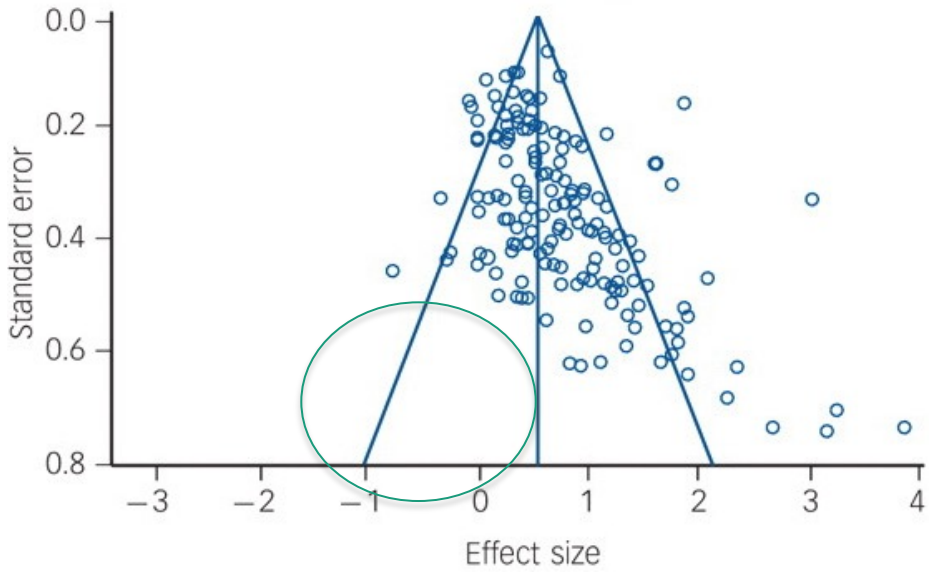
Figure 20.6 Random-effects model – regression of log risk ratio on latitude.

Un biais spécifique : le biais de publication

Les études **ont plus de chance d'être publiées** si elles sont :

- En anglais
- De **grande taille**
- **Positives**

Exploration du biais : **diagramme en entonnoir** (*funnel plot*)



Manque de publications négatives
De petites tailles