Νεότερα Μεθοδολογικά Εργαλεία στην Πρωτοβάθμια Φροντίδα Υγείας: Μετα-Επιδημιολογία και Μετα-Μετα-Επιδημιολογία

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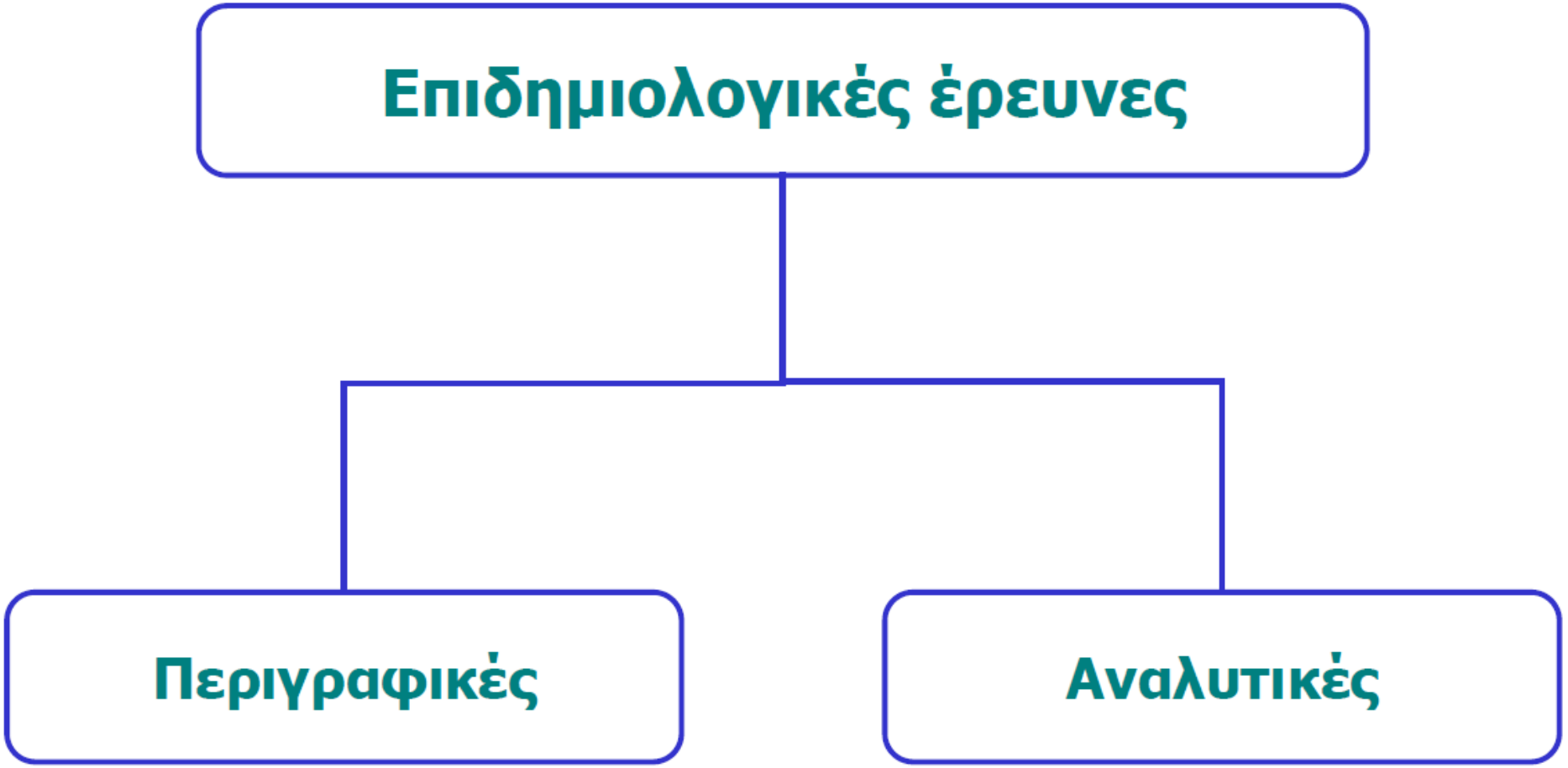
Ιατρική Σχολή ΕΚΠΑ

Καθηγητής-Σύμβουλος, Διοίκηση Μονάδων Υγείας, Ελληνικό Ανοικτό Πανεπιστήμιο

Δήλωση Σύγκρουσης Συμφέροντος (Conflict of Interest)

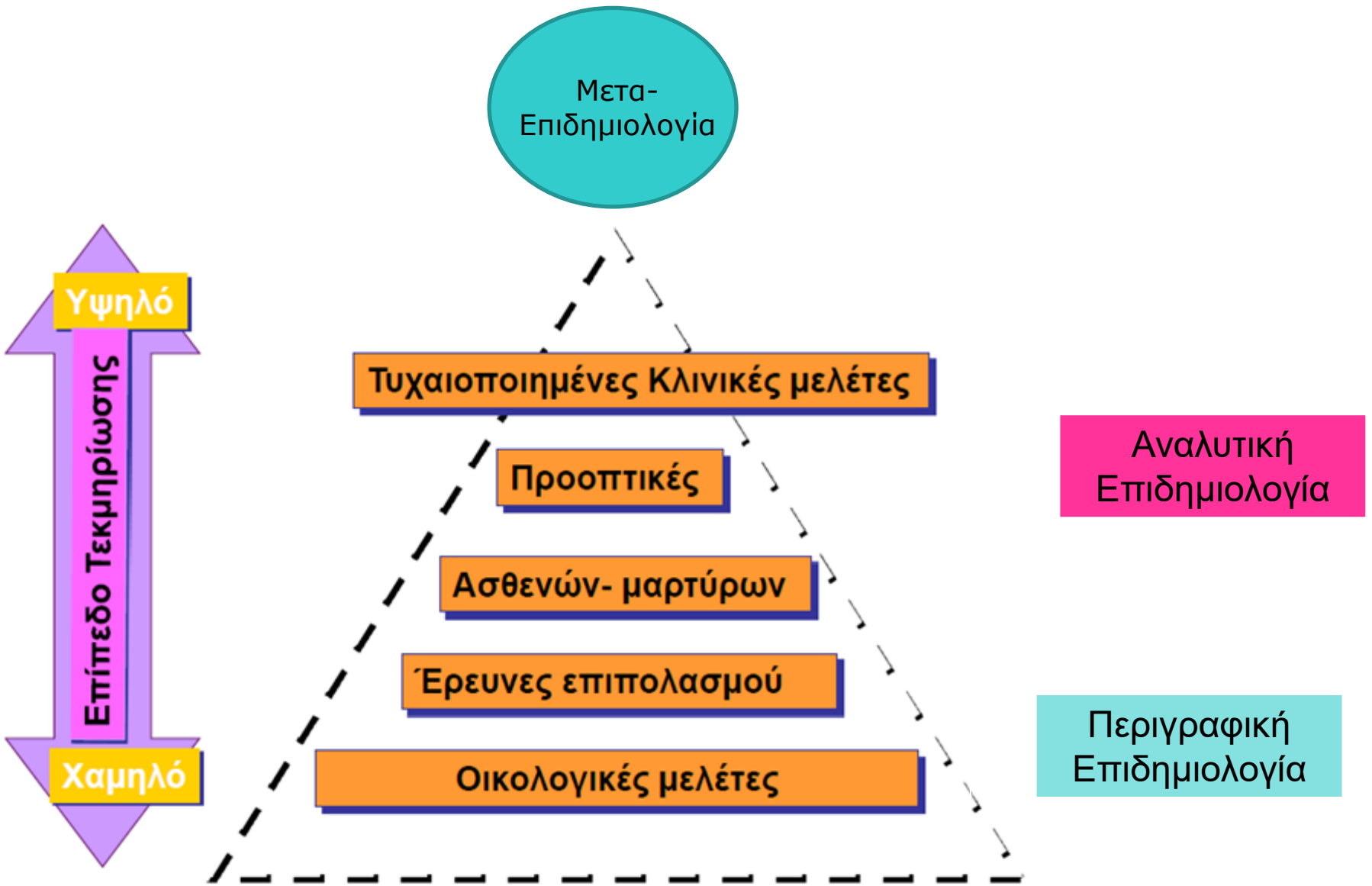
- Δεν έχω καμία σύγκρουση συμφέροντος


Επιδημιολογικές έρευνες
Περιγραφικές
Αναλυτικές

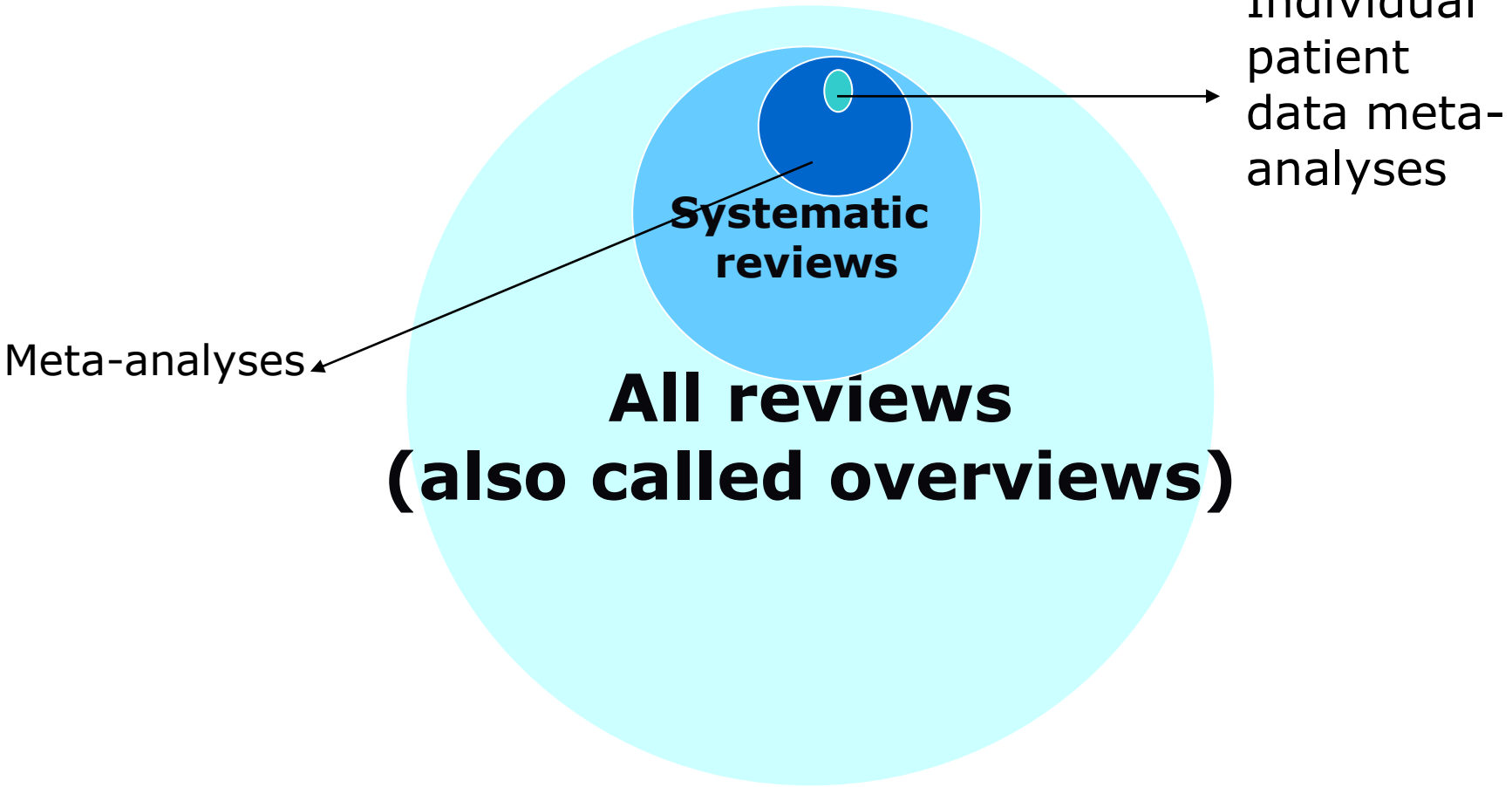

Επιδημιολογικές έρευνες
Περιγραφικές
Αναλυτικές
Συγχρονικές /μελέτες επιπολασμού
Οικολογικές μελέτες
Κλινικές περιπτώσεις
Προοπτικές
Ασθενών-Μαρτύρων
Κλινικές δοκιμές

Τύποι επιδημιολογικών ερευνών ανάλογα με τη δυνατότητα τεκμηρίωσης μιας αιτιολογικής συσχέτισης

Τύποι επιδημιολογικών ερευνών ανάλογα με τη δυνατότητα τεκμηρίωσης μιας αιτιολογικής συσχέτισης



Μετα-Επιδημιολογία



Συστηματική ανασκόπηση (systematic review): ορισμός

- Ανασκόπηση η οποία επιχειρεί να συνθέσει όλα τα εμπειρικά στοιχεία (empirical evidence) βάσει **προκαθορισμένων κριτηρίων επιλογής** (pre-specified eligibility criteria), ώστε να απαντήσει σε συγκεκριμένο ερευνητικό ερώτημα.

- Ο συστηματικός χαρακτήρας αποσκοπεί στην ελαχιστοποίηση των συστηματικών σφαλμάτων (bias) και την ενίσχυση της αξιοπιστίας των ευρημάτων.

Συστηματική ανασκόπηση (systematic review): χαρακτηριστικά

α) σαφώς καθορισμένος στόχος με δηλωμένη, αναπαραγώγιμη μεθοδολογία - συγκεκριμένα κριτήρια επιλεξιμότητας

β) προσπάθεια εντοπισμού όλων των μελετων που πληρούν τα κριτήρια επιλεξιμότητας

γ) αξιολόγηση της εγκυρότητας των μελετών - αξιολόγηση συστηματικών σφαλμάτων

δ) συστηματική παρουσίαση των χαρακτηριστικών και των πορισμάτων των συμπεριλαμβανόμενων μελετών

Μετα-ανάλυση (meta-analysis): ορισμός

- Μια συστηματική ανασκόπηση με **ποσοτική, στατιστική σύνθεση** των επιμέρους αποτελεσμάτων

Meningiomas in children and adolescents: a meta-analysis of individual patient data

Rishi S Kotecha, Elaine M Pascoe, Elisabeth J Rushing, Lucy B Rorke-Adams, Ted Zwerdling, Xing Gao, Xin Li, Stephanie Greene, Abbas Amirjamshidi, Seung-Ki Kim, Marco A Lima, Po-Cheng Hung, Fayçal Lakhdar, Nirav Mehta, Yuguang Liu, B Indira Devi, B Jayanand Sudhir, Morten Lund-Johansen, Flemming Gjerris, Catherine H Cole, Nicholas G Gottardo

Summary

Background The epidemiological, prognostic, and therapeutic features of child and adolescent meningioma are poorly defined. Clinical knowledge has been drawn from small case series and extrapolation from adult studies. This study was done to pool and analyse the clinical evidence on child and adolescent meningioma.

Methods Searches of PubMed, Medline, and Embase identified 35 case series of child and adolescent meningioma completed over the past 21 years. Individual patient data were obtained from 30 studies via direct communication with investigators. Primary outcomes were relapse-free survival (RFS) and overall survival. Prognostic variables were extent of initial surgery, use of upfront radiotherapy, age, sex, presence of neurofibromatosis, tumour location, and tumour grade. RFS and overall survival were analysed using Kaplan-Meier survival curves and multivariable Cox regression models.

Findings From a total of 677 children and adolescents with meningioma, 518 were eligible for RFS analysis and 547 for overall survival analysis. Multivariable analysis showed that patients who underwent initial gross-total resection had better RFS (hazard ratio 0·16, 95% CI 0·10–0·25; p<0·0001) and overall survival (p<0·0001) than those who had subtotal resection. No significant benefit was seen for upfront radioth RFS (0·59, 0·30–1·16; p=0·128) or overall survival (1·10, 0·53–2·28; p=0·791). Patients with neurofib (NF2) had worse RFS than those without neurofibromatosis (2·36, 1·23–4·51; p=0·010). There v change in overall survival with time between patients with NF2 compared with those without ne (1·45, 1·09–1·92; p=0·011); although overall survival was initially better for patients with NF2 than f neurofibromatosis, overall survival at 10 years was worse for patients with NF2. Patients with WHO g had worse RFS than those with WHO grade I (3·90, 2·10–7·26; p<0·0001) and grade II tumours (p=0·027).

Lancet Oncol 2011; 12: 1229–3
Published Online
November 16, 2011
DOI:10.1016/S1470-2045(11)70275-3

See Comment page 1180

Department of Haematology and Oncology (R S Kotecha MB ChB, Prof C H Cole MBBS, N G Gottardo MB ChB), **and Department of Clinical Research and Education** (E M Pascoe M Biostat), **Princess**

DOI: 10.3310/hta13320 *Health Technology Assessment* 2009; Vol. 13: No. 32

Abstract

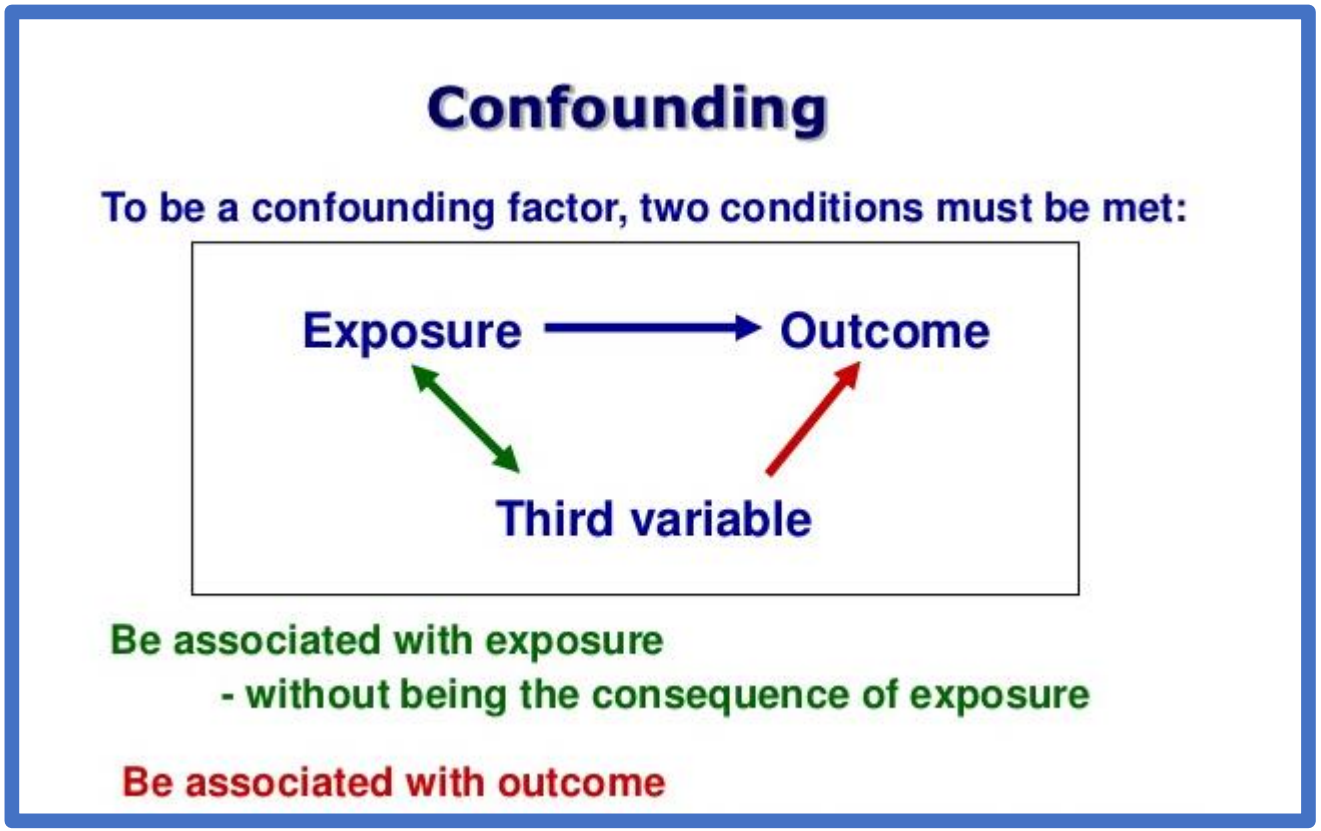
Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care

J Mant,[1*] J Doust,[2] A Roalfe,[1] P Barton,[3] MR Cowie,[4] P Glasziou,[5] D Mant,[5] RJ McManus,[1] R Holder,[1] J Deeks,[6] K Fletcher,[1] M Qume,[1] S Sohanpal,[1] S Sanders[2] and FDR Hobbs[1]

[1]Primary Care Clinical Sciences, University of Birmingham, UK
[2]Faculty of Health Sciences and Medicine, Bond University, Australia
[3]Health Economics Facility, University of Birmingham, UK
[4]National Heart and Lung Institute, Imperial College, London, UK
[5]Department of Primary Health Care, University of Oxford, UK
[6]Public Health and Epidemiology, University of Birmingham, UK

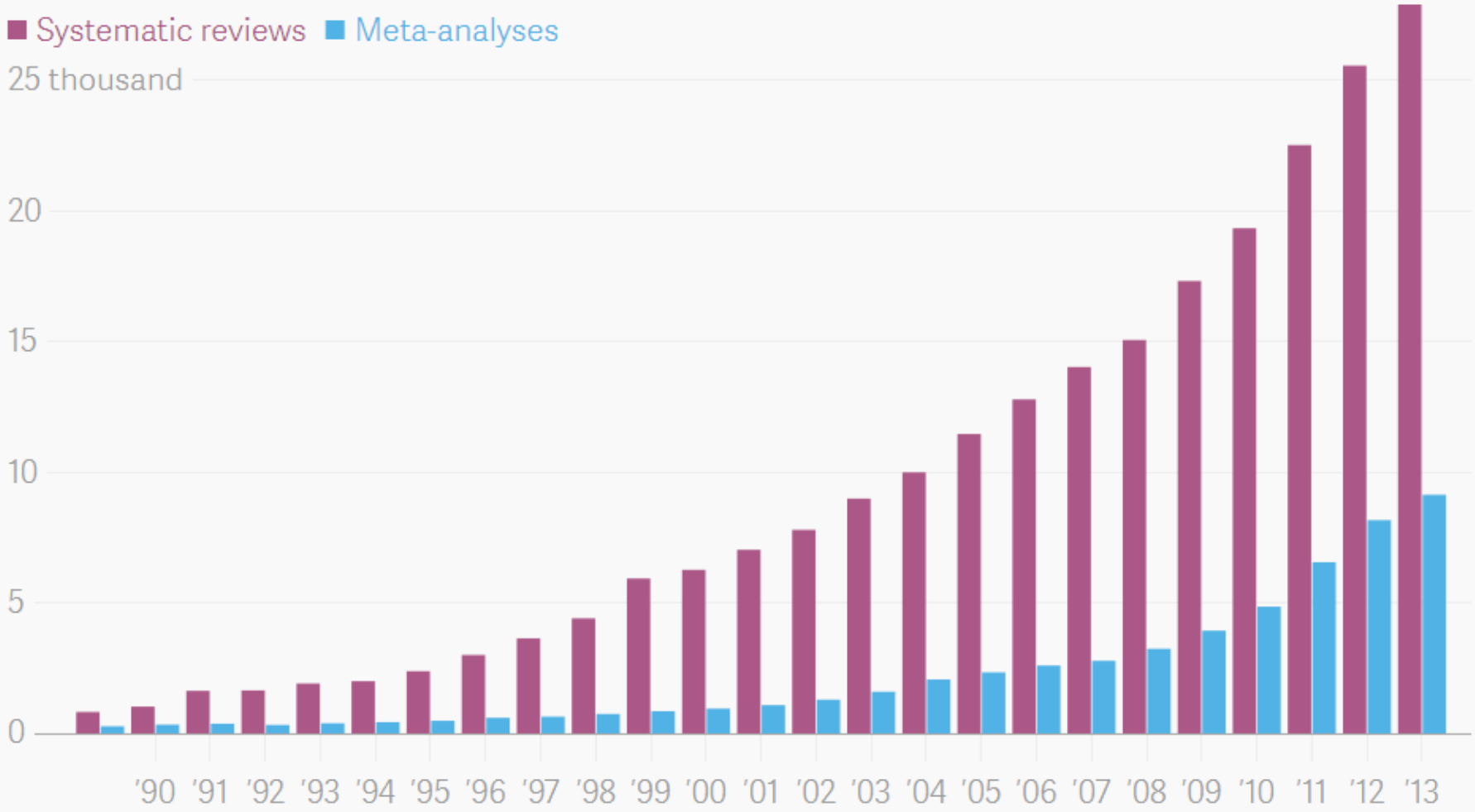
- IPD meta-analysis: οι ερευνητές δεν περιορίζονται στα δημοσιευμένα άρθρα, αλλά λαμβάνουν **το πλήρες set δεδομένων** από τις επιμέρους έρευνες και προχωρούν σε περαιτέρω αναλύσεις

Συγχυτικοί παράγοντες στην Επιδημιολογία: συγκεκριμένο παράδειγμα



Συγχυτικός παράγοντας: συσχέτιση με την έκθεση και με το αποτέλεσμα
(χωρίς να βρίσκεται στο αιτιολογικό μονοπάτι έκθεσης → αποτελέσματος)

Number of systematic reviews & meta-analyses published each year



Data: Ioannidis/Milbank Quarterly

Η έννοια του “effect size”

- Μετα-ανάλυση: **ποσοτική, στατιστική σύνθεση**

Συνεπώς

- Αναγκαία η ταυτοποίηση ενός κοινού **«μεγέθους αποτελέσματος» (effect size)**

Παραδείγματα effect size

- Odds ratio: εκτίμηση του OR μέσω λογαριθμιστικής παλινδρόμησης (logistic regression) σε μελέτες ασθενών-μαρτύρων (case-control), σε ελεγχόμενες έρευνες θεραπευτικής παρέμβασης (RCT) κοκ.
- Relative risk
- Hazard ratio

- Θεωρώντας τη νόσο σπάνια, το OR τείνει στο σχετικό κίνδυνο RR (relative risk)

Ο «πυρήνας» της μετα-ανάλυσης: Διάγραμμα δάσους (forest plot)

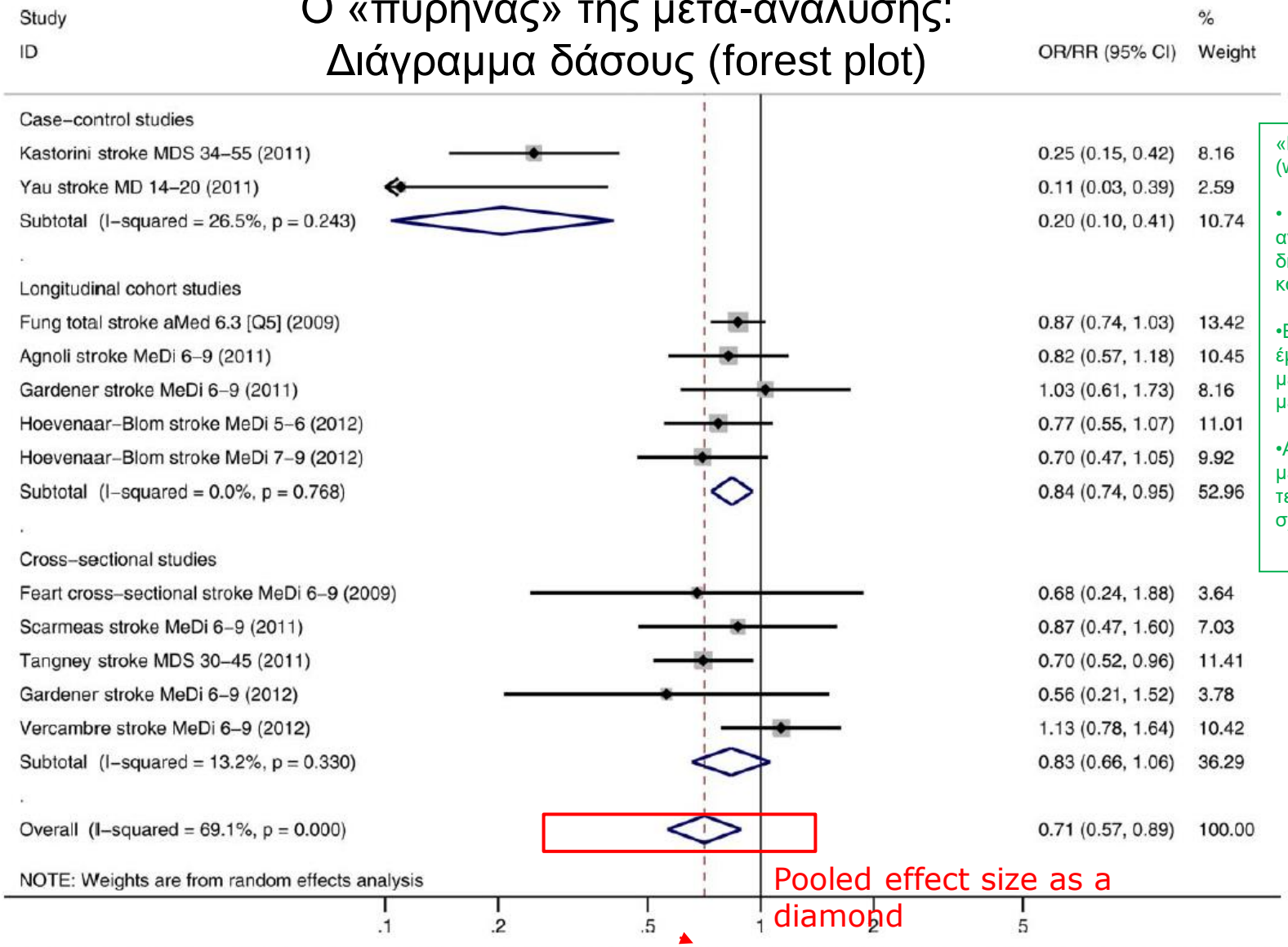


FIGURE 1: Forest plot describing the association between high adherence to Mediterranean diet and risk for stroke. Apart from the overall analysis, the subanalyses on case–control (upper rows), longitudinal cohort (middle rows), and cross-sectional studies (lower rows) are presented.

«Βάρη» (weights):

- Σχετίζονται αντίστροφα με τη διακύμανση της κάθε μελέτης.
- Εκφράζουν έμμεσα το μέγεθος της μελέτης.
- Αντιστοιχούν στο μέγεθος των τετραγώνων του σχήματος.

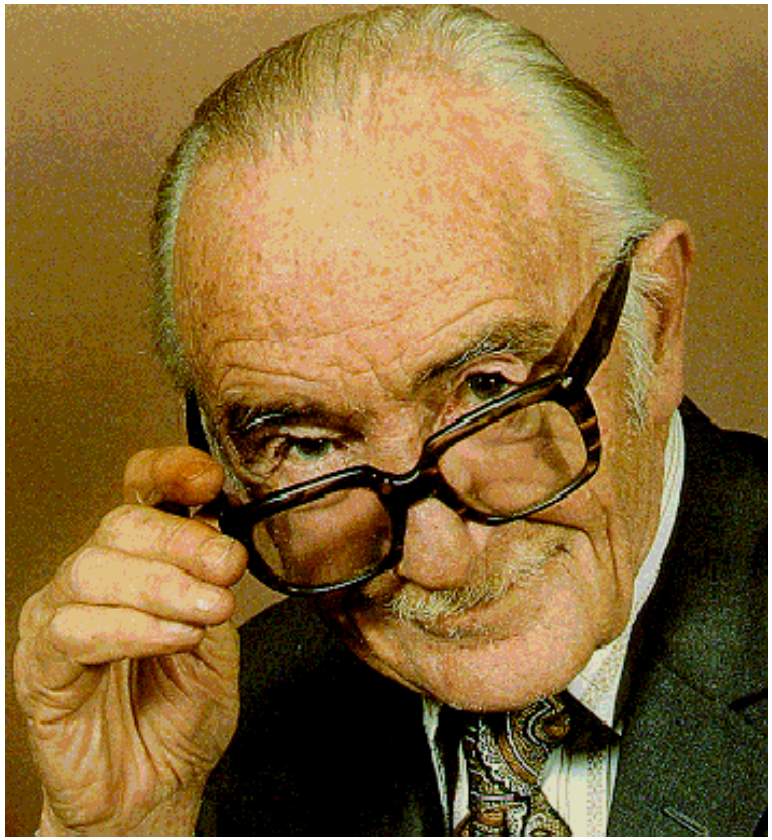
Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. Ann Neurol 2013;74(4):580-91.

Στάδια κατά τη διεξαγωγή μιας συστηματικής ανασκόπησης και μετα-ανάλυσης

http://handbook-5-1.cochrane.org/

Prof Archibald Cochrane, CBE (1909 - 1988)

- Cochrane Collaboration: από τον Archie Cochrane, Βρετανό ερευνητή



- Το 1979 έγραψε, *"It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials"*

Source: http://www.cochrane.org/cochrane/archieco.htm

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Our contributors work together to produce systematic assessments of healthcare interventions, known as Cochrane Reviews, which are published online in *The Cochrane Library*. Cochrane Reviews are intended to help providers, practitioners and patients make informed decisions about health care, and are the most comprehensive, reliable and relevant source of evidence on which to base these decisions.

"The Cochrane Collaboration is an enterprise that rivals the Human Genome Project in its potential implications for modern medicine."
- The Lancet

Cochrane in the News

Examiner.com (US) spotlights a new Cochrane review in an article on how smoking bans in public places reduce exposure to secondhand smoke and associated health impacts.

1 of 91 ››

All news

Cochrane Multimedia


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5th Workshop of the Cochrane Collaboration
"Writing a protocol for a Cochrane systematic review"
AKISA "Attikon" University Hospital
Athens, 28th & 29th September 2018


4th Workshop
Cochrane Collaboration - Gynaecology and Fertility Group
"Assessing risk of bias"
18-20/5
"Σουκάκειο" Ορθοπεδικό
Κέντρο Έρευνας & Εκπαίδευσης
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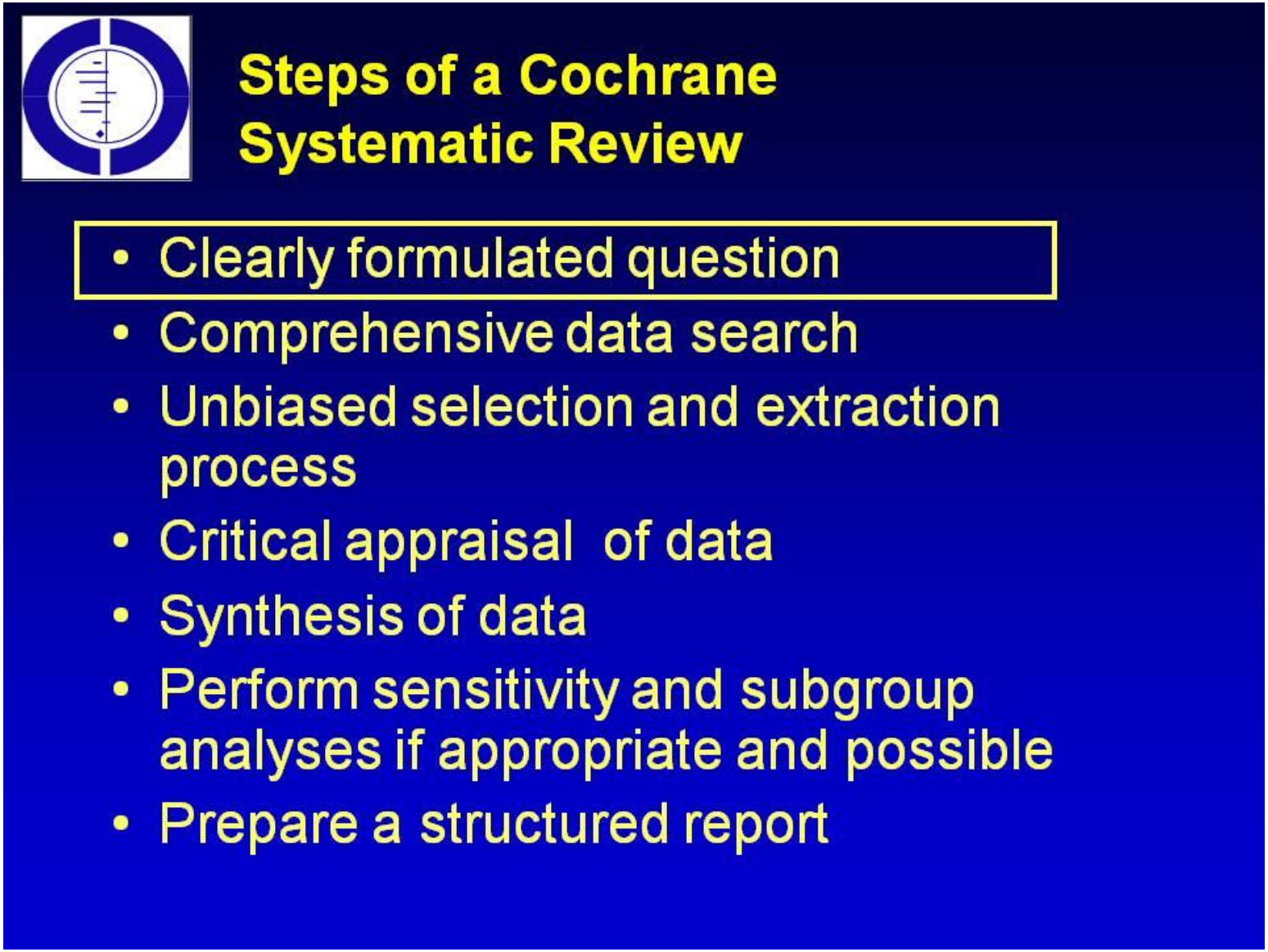
- https://training.cochrane.org/how-conduct-cochrane-systematic-review-athens-greece

- Contact: evivogiatzi@gmail.com

Τα επτά στάδια της μετα-ανάλυσης



Στάδιο 1: η υπόθεση

ΠΑΡΕΛΘΟΝ

Επιβεβαίωση (validation) των αποτελεσμάτων των επιμέρους μελετών

ΜΕΛΛΟΝ

Διαμόρφωση νέων υποθέσεων (meta-analysis as a hypothesis-generating tool)

Μετα-ανάλυση: ο Ιανός της Επιδημιολογίας;

Παραδείγματα για τη διαμόρφωση νέων υποθέσεων

Breast Cancer Res Treat (2010) 120:211–216
DOI 10.1007/s10549-009-0467-1

EPIDEMIOLOGY

Differential effects of MDM2 SNP309 polymorphism on breast cancer risk along with race: a meta-analysis

Konstantinos P. Economopoulos ·
Theodoros N. Sergentanis

Παραδείγματα για τη διαμόρφωση νέων υποθέσεων

NCBI Resources How To

PubMed.gov
U.S. National Library of Medicine
National Institutes of Health

Search: PubMed RSS Save search Limits

Cancer [so] Sergentanis latitude

Display Settings: Abstract

Cancer. 2010 Jul 15;116(14):3523.

Latitude may modify the effect of TP53 codon 72 polymorphism on cancer risk.

Sergentanis TN, Economopoulos KP.

PMID: 20564066 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources

Παραδείγματα για τη διαμόρφωση νέων υποθέσεων

Table 2. Results of the Meta-Analysis

Variable	Odds Ratio (95% CI)	Test for Heterogeneity	Alternative Odds Ratio (95% CI) vs. Patients not Receiving Any α_1-Blocker	Test for Heterogeneity
Current tamsulosin use	**393.1 (159.5–968.6)***	$P < 0.001$	**672.0 (216.4–2086.7)***	$P < 0.001$
Current alfuzosin use	**9.7 (2.0–48.7)***	$P=0.044$	**40.7 (3.2–514.8)***	$P=0.001$
Current terazosin use	**5.5 (1.3–23.0)†**	$P=0.206$	**15.1 (2.8–81.1)†**	$P=0.093$
Current doxazosin use	6.4 (0.9–44.1)*	$P < 0.001$	**24.2 (1.7–351.7)***	$P < 0.001$
Hypertension	**2.2 (1.2–4.2)†**	$P=0.697$	N/A	N/A
Diabetes mellitus	1.3 (0.7–2.2)†	$P=0.736$	N/A	N/A

CI = confidence interval; N/A= not applicable.
*Odds ratio derived from random-effects analysis.
†Odds ratio derived from fixed-effects analysis.
The third and forth columns present the results of the alternative approach versus patients not receiving any α_1-blocker. Statistically significant associations are highlighted in bold.

Chatziralli IP & Sergentanis TN. Risk Factors for Intraoperative Floppy Iris Syndrome: A Meta-Analysis.
Ophthalmology 2011 Apr;118(4):730-5.

BMJ Open

Overtesting and undertesting in primary care: a systematic review and meta-analysis

Jack W O'Sullivan,[1] Ali Albasri,[1] Brian D Nicholson,[1] Rafael Perera,[1] Jeffrey K Aronson,[1] Nia Roberts,[2] Carl Heneghan[1]

To cite: O'Sullivan JW, Albasri A, Nicholson BD, *et al*. Overtesting and undertesting in primary care: a systematic review and meta-analysis. *BMJ Open* 2018;**8**:e018557. doi:10.1136/bmjopen-2017-018557

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-018557).

Received 6 July 2017
Revised 12 December 2017
Accepted 13 December 2017

ABSTRACT

Background Health systems are currently subject to unprecedented financial strains. Inappropriate test use wastes finite health resources (overuse) and delays diagnoses and treatment (underuse). As most patient care is provided in primary care, it represents an ideal setting to mitigate waste.

Objective To identify overuse and underuse of diagnostic tests in primary care.

Design Systematic review and meta-analysis.

Data sources and eligibility criteria We searched MEDLINE and Embase from January 1999 to October 2017 for studies that measured the inappropriateness of any diagnostic test (measured against a national or international guideline) ordered for adult patients in primary care.

Results We included 357 171 patients from 63 studies in 15 countries. We extracted 103 measures of inappropriateness (41 underuse and 62 overuse) from

Strengths and limitations of this study

- Generates rate of undertesting and overtesting for specific diagnostic tests against national or international guidelines.
- Only includes data from real clinical encounters rather than surveys or hypothetical clinical vignettes.
- Quantified inappropriate ordering of all types of diagnostic tests rather than just laboratory.
- Systematic reviews are restricted to published literature; thus, rates of inappropriate ordering are not available for all tests available to primary care physicians.
- Included studies measure appropriateness of testing in a particular healthcare setting against a particular guideline, thus reflect test ordering in a specific healthcare setting.

Στάδιο 2: η αναζήτηση των δεδομένων

- Αναζήτηση των βιβλιογραφικών βάσεων δεδομένων (π.χ. Pubmed, Cochrane, EMBASE)

- Αναζήτηση full-text των δημοσιεύσεων και των σχετικών αναφορών (“**snow-balling” technique**)

Στάδιο 2: η αναζήτηση των δεδομένων

- Να αναφέρονται ακριβώς οι **λέξεις-κλειδιά** και οι συνδυασμοί τους (αναπαραγωγιμότητα)

- Να αναφέρεται η **καταληκτική ημερομηνία αναζήτησης**

Eligible articles were identified by a search of MEDLINE bibliographical database for the period up to May 31, 2012. The search strategy included the following keywords: (breast AND (neoplasms OR neoplasm OR cancer OR cancers OR carcinoma OR carcinomas)) AND ((mTOR AND inhibitor) OR BEZ235 OR NVP-BEZ235 OR everolimus OR RAD001 OR rapamycin OR sirolimus OR PI-103 OR temsirolimus OR torisel OR AZD8055 OR Ku-0063794 OR PF-04691502 OR CH5132799 OR GDC-0980 OR RG7422 OR WAY-600 OR WYE-125132 OR WYE-687 OR GSK2126458 OR PKI-587 OR PP-121 OR OSI-027 OR "palomid 529" OR P529 OR PP242 OR XL765 OR GSK1059615 OR WYE-354 OR deforolimus OR ridaforolimus).

Zagouri F, Sergentanis TN, Chrysikos D, Filipits M, Bartsch R. mTOR inhibitors in breast cancer: a systematic review. Gynecol Oncol. 2012 Dec;127(3):662-72.

BMJ Open

Overtesting and undertesting in primary care: a systematic review and meta-analysis

supplementary file 1: search Strategy). Our search strategy can be summarised as: 'Ambulatory Care AND adherence AND guideline AND diagnostic tests AND inappropriate'. Conference abstracts published after 2015 were also searched for in these databases to capture data not yet published. We also searched the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), ClinicalTrials.gov, and the reference lists of included studies.

«Παγίδες» κατά την αναζήτηση των δεδομένων

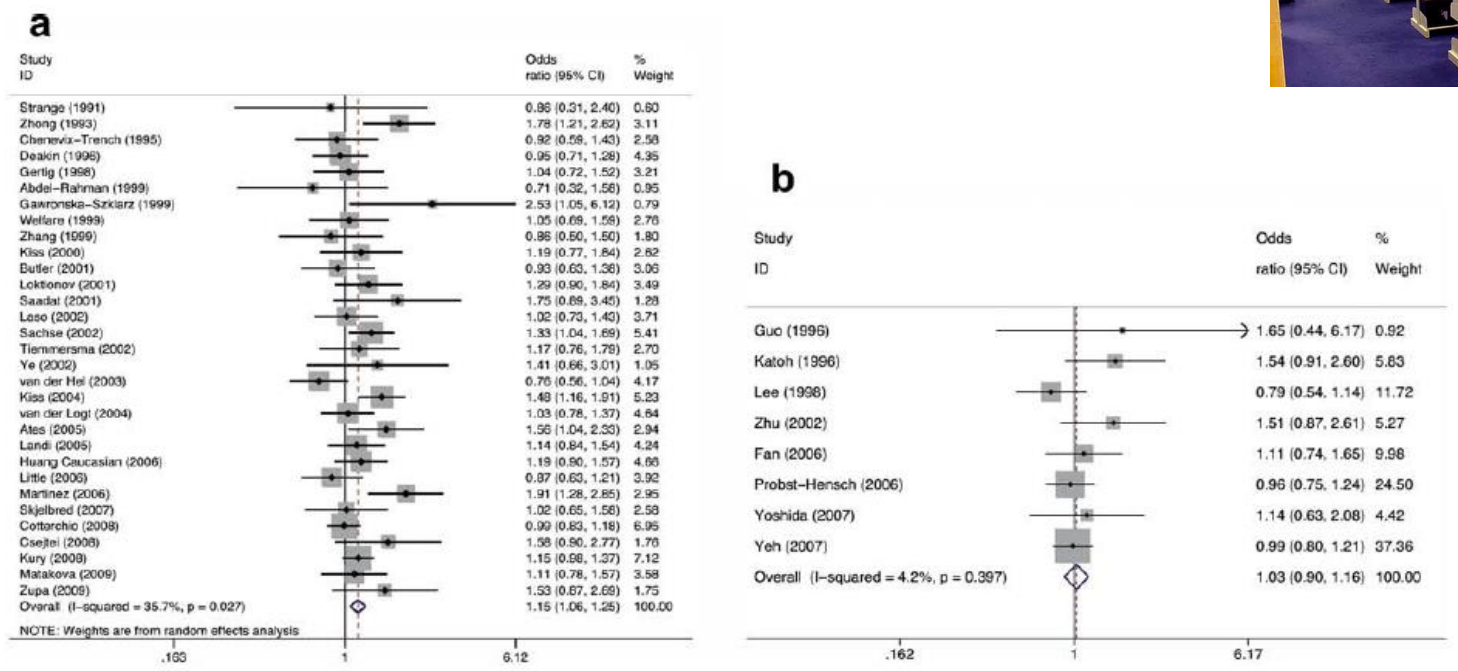


Fig. 2 – Forest plot for the overall association between null GSTM1 genotype and colorectal cancer risk for (a) Caucasian and (b) Chinese subjects. Each study is shown by the point estimate of the Odds Ratio (OR) (the size of the square is proportional to the weight of each study) and 95% confidence interval for the OR (extending lines); the pooled OR and 95% confidence interval have been appropriately derived from: (a) random and (b) fixed-effects models.

- Η σημασία των **γλωσσικών περιορισμών** (language restrictions)

Economopoulos KP & Sergentanis TN, GSTM1, GSTT1, GSTP1, GSTA1 and colorectal cancer risk: a comprehensive meta-analysis. Eur J Cancer. 2010;46(9):1617-31.

Acknowledgement

The authors would like to thank Dr. Luo Tong for the translation of the articles in Chinese that have been included in this meta-analysis.

Cochrane Library

Cochrane Database of Systematic Reviews

Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility (Review)

Skalkidou A, Sergentanis TN, Gialamas SP, Georgakis MK, Psaltopoulou T, Trivella M, Siristatidis CS, Evangelou E, Petridou E

Search methods for identification of studies

Electronic searches

We searched CENTRAL (Issue 7, 2016), MEDLINE via Ovid (1960 to July week 3 2016) and Embase via Ovid (1980 to week 31 2016). We searched the CENTRAL database for reasons of completeness because, although this review was based on non-randomised studies (NRSs), CENTRAL contains controlled clinical trials (CCTs), interrupted time series and controlled before and after series, in addition to randomised controlled trials (RCTs). The search terms included a combination of thesaurus-based and free-text terms. CENTRAL, MEDLINE and Embase search strategies are presented in Appendix 1, Appendix 2 and Appendix 3, respectively.

Searching other resources

Reference lists of included studies and any relevant systematic reviews identified were also searched to identify eligible studies for inclusion. The review authors tried to identify the relevant grey literature by looking at the following:

- OpenGrey, a system for grey literature produced in Europe, such as research reports, doctoral dissertations and conference papers (http://www.opengrey.eu/);
- ProQuest dissertation and thesis databases (http://www.proquest.com/en-US/catalogs/databases/detail/pqdt.shtml);
- Published or ongoing trials in the trial registers for ongoing and registered trials: 'ClinicalTrials.gov', a service of the US National Institutes of Health (http://clinicaltrials.gov/ct2/home) and http://www.controlled-trials.com, as well as the World Health Organization International Trials Registry Platform search portal (http://www.who.int/trialsearch/Default.aspx), and Physicians Data Query (http://www.nci.nih.gov);
- Conference proceedings and abstracts through ZETOC (http://zetoc.mimas.ac.uk) and WorldCat Dissertations;
- Reports of conferences in the following: *Gynecologic Oncology* (Annual Meeting of the American Society of Gynecologic Oncologists), *International Journal of Gynecological Cancer* (Annual Meeting of the International Gynecologic Cancer Society), *British Journal of Cancer* (British Cancer Research Meeting, Annual Meeting of the European Society of Medical Oncology (ESMO) and Annual Meeting of the American Society of Clinical Oncology (ASCO);
- Personal communication with experts in the field who had been conducting/had led research in the field and on the specific hypothesis of this review.

Στάδιο 3: η επιλογή των μελετών και η εξαγωγή των δεδομένων

➢*Κριτήρια για εισδοχή της μελέτης στη μετα-ανάλυση (inclusion criteria):*

•Σχεδιασμός μελέτης

•Πληθυσμός

•Παρεμβάσεις (interventions)

•Αυστηρός ορισμός του «αποτελέσματος» (outcome)

Το διάγραμμα ροής (flow chart) της συστηματικής ανασκόπησης

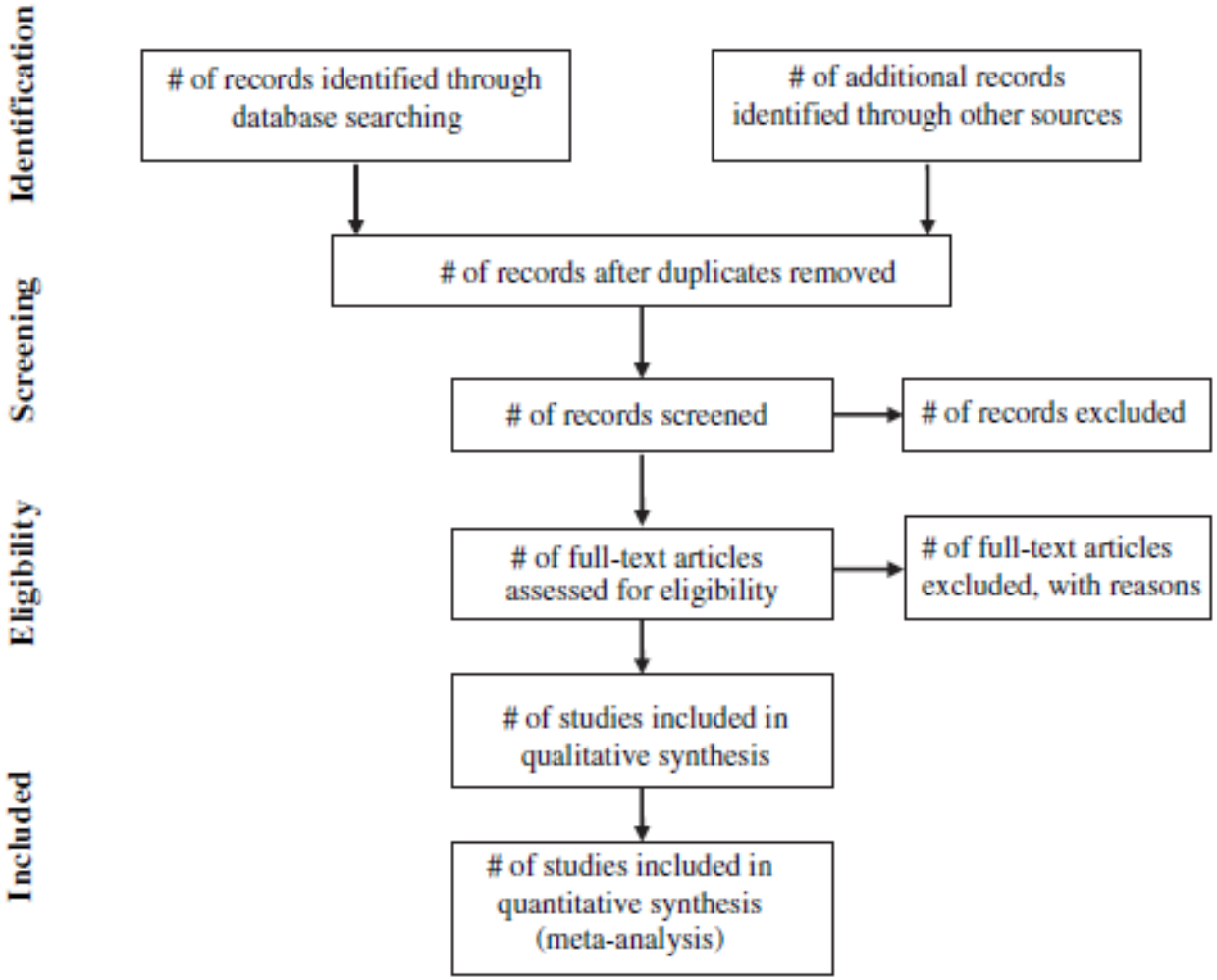


Fig. 1. Flow of information through the different phases of a systematic review.

Liberati et al. *J Clin Epidemiol* 2009;62 :e1-34

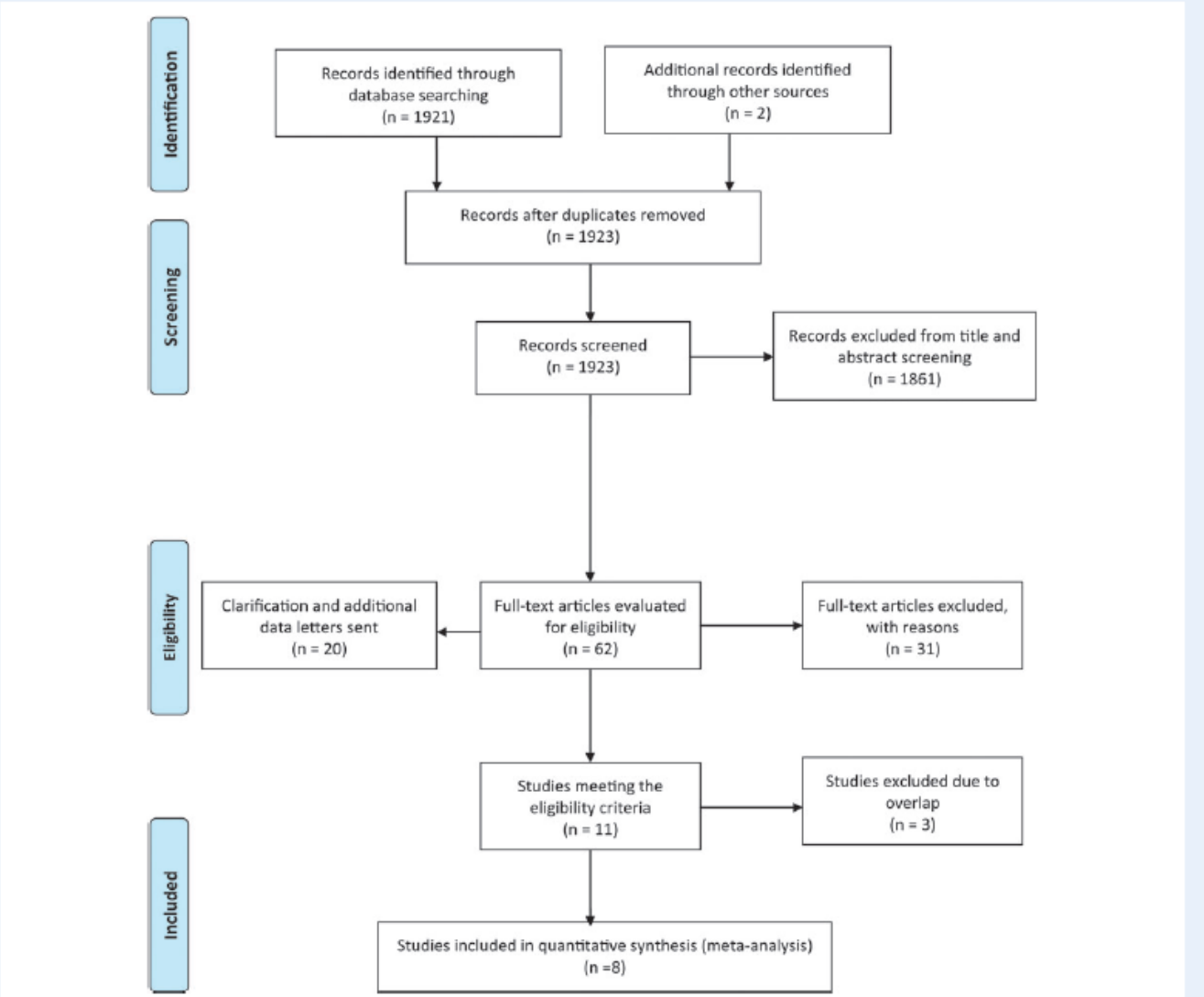


Figure 1 PRISMA flow chart for systematic review of IVF and breast cancer.

Sergentanis TN, Diamantaras AA, Perlepe C, Kanavidis P, Skalkidou A, Petridou ET.
IVF and breast cancer: a systematic review and meta-analysis.
Hum Reprod Update. 2014 Jan-Feb;20(1):106-23.

Επικοινωνία με τους συγγραφείς για τα δεδομένα

ELSEVIER

Journal of Clinical Epidemiology ■ (2008) ■

Journal of Clinical Epidemiology

REVIEW ARTICLE

Systematic reviewers commonly contact study authors but do so with limited rigor

Rebecca J. Mullan[a], David N. Flynn[a,b], Bo Carlberg[c], Imad M. Tleyjeh[d,e], Celia C. Kamath[f], Matthew L. LaBella[a,g], Patricia J. Erwin[a,h], Gordon H. Guyatt[i], Victor M. Montori[a,j,*]

BMJ Global Health

Primary health care financing interventions: a systematic review and stakeholder-driven research agenda for the Asia-Pacific region

Blake Angell,[1] Rebecca Dodd,[1] Anna Palagyi,[1,2] Thomas Gadsden,[1] Seye Abimbola,[1,2] Shankar Prinja,[3] Stephen Jan,[1] David Peiris[1]

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ABSTRACT

Introduction Interventions targeting the financing of primary health care (PHC) systems could accelerate progress towards universal health coverage; however, there is limited evidence to guide best-practice implementation of these interventions. This study aimed to generate a stakeholder-led research agenda in the area of PHC financing interventions in the Asia-Pacific region.

Methods We adopted a two-stage process: (1) a systematic review of financing interventions targeting PHC service delivery in the Asia-Pacific region was conducted to develop an evidence gap map and (2) an electronic-Delphi (e-Delphi) exercise with key national PHC stakeholders was undertaken to prioritise these evidence needs.

Results Thirty-one peer-reviewed articles (including 10 systematic reviews) and 10 grey literature reports were included in the review. There was limited consistency in results across studies but there was evidence that some interventions (removal of user fees, ownership models of providers and contracting arrangements) could impact PHC service access, efficiency and out-of-pocket cost outcomes. The e-Delphi exercise highlighted the importance of contextual factors and prioritised research in the areas of: (1) interventions to limit out-of-pocket costs; (2) financing models to enhance health system performance and maintain PHC budgets; (3) the design of incentives to promote optimal care without unintended

Key questions

What is already known?

- Effective and sustainable primary health care systems are essential if the low-income and middle-income nations of the Asia-Pacific region are to achieve universal health coverage.
- Financing interventions have been used across the world to incentivise the demand for and delivery of quality healthcare.
- The role that research plays in informing policy decisions is often limited by insufficient attention to context, policymakers' priorities and the broader system-wide impacts of interventions.

What are the new findings?

- While national primary health care stakeholders see an important role for financing interventions in the push to achieve universal health coverage in the Asia-Pacific region, there are key gaps in the evidence needed to inform policy decisions.
- Evidence priorities for primary health care financing include the role of interventions at the: (1) community level, to improve access to services and financial protection of individuals; (2) provider level, to incentivise appropriate care and ensure appropriate management decisions and (3) system level, to improve

Στάδιο 3: η επιλογή των μελετών και η εξαγωγή των δεδομένων

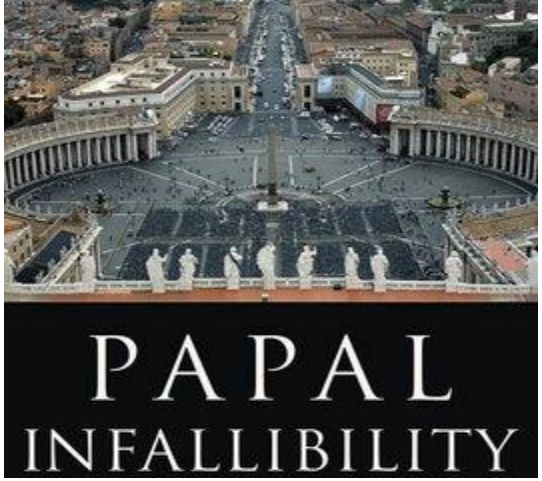
➢*Η εξαγωγή των δεδομένων (data extraction):*

- 2 ανεξάρτητοι ερευνητές
- Προκατασκευασμένες ηλεκτρονικές φόρμες (χαρακτηριστικά των ασθενών, σχεδιασμός της μελέτης, αποτελέσματα κ.ο.κ).

- Οι διαφορές λύνονται με συμφωνία (consensus) με τρίτο κριτή ή το σύνολο της ομάδας

Αναλυτικός πίνακας
– ποικίλλει ανά συστηματική ανασκόπηση

- Μέγεθος της μελέτης
- Τόπος διεξαγωγής
- Χαρακτηριστικά των συμμετεχόντων
- Αναλυτική περιγραφή των παρεμβάσεων
- Λεπτομέρειες για τα outcomes
- Μεθοδολογικά χαρακτηριστικά των μελετών



Η επιλογή των μελετών και η εξαγωγή των δεδομένων: υπάρχει αλάθητο;

Results: 5

Re: Jiang et al.: Meta-analysis of association between TP53 Arg72Pro polymorphism and bladder cancer risk (Urology 2010;76:765).

1. Sergentanis TN, Economopoulos KP.
Urology. 2011 Jan;77(1):259-60. No abstract available.
PMID: 21195855 [PubMed - indexed for MEDLINE]
Related citations

Methodological remarks concerning the recent meta-analysis on p53 codon 72 polymorphism and colorectal cancer risk.

2. Economopoulos KP, Sergentanis TN.
Eur J Surg Oncol. 2010 Dec;36(12):1225-6; author reply 1227-8. No abstract available.
PMID: 20937554 [PubMed - indexed for MEDLINE]
Related citations

Does race modify the association between CYP1B1 Val432Leu polymorphism and breast cancer risk? A critical appraisal of a recent meta-analysis.

3. Economopoulos KP, Sergentanis TN.
Breast Cancer Res Treat. 2010 Nov;124(1):293-4. Epub 2010 Aug 5. No abstract available.
PMID: 20686834 [PubMed - indexed for MEDLINE]
Related citations

Eligible and not eligible studies in the recent meta-analysis about p53 polymorphism and breast cancer risk.

4. Sergentanis TN, Economopoulos KP.
Breast Cancer Res Treat. 2010 Feb;120(1):261-2. Epub 2009 Sep 17. No abstract available.
PMID: 19760041 [PubMed - indexed for MEDLINE]
Related citations

Need for clarification of data in the recent meta-analysis about p53 polymorphism and gastric cancer risk.

5. Economopoulos KP, Sergentanis TN.
Int J Cancer. 2010 May 15;126(10):2509. No abstract available.
PMID: 19739120 [PubMed - indexed for MEDLINE]
Related citations

Στάδιο 4: κριτική αξιολόγηση των επιμέρους μελετών

Supplemental Table 3. Evaluation of quality based on the Newcastle-Ottawa scale for the included cohort studies.

	Selection				Comparability		Outcome			Total
Study	Representativeness	Selection of non-exposed	Ascertainment of exposure	Outcome not present at start	On age	On other risk factors	Assessment of outcome	Long enough follow-up (median ≥5 years)	Adequacy (completeness) of follow-up	
Blair (2005)	1	1	0	1	0	1	1	1	1	7
Ganstur (2012)	1	1	0	1	1	1	1	1	1	8
Heinen (2013)	1	1	0	1	1	1	1	1	1	8
Kanda (2010)	1	1	0	0	0	0	1	1	1	5
Klatsky (2009)	0	1	0	1	1	1	1	1	1	7
Kroll (2012)	1	1	0	1	0	1	1	1	1	7
Neasham (2011)	1	1	0	0	0	0	1	1	1	5
Ozasa (2007)	1	1	0	0	1	1	1	1	1	7
Troy (2010)	1	1	0	1	1	1	1	1	1	8
Wang -CTS (2013)	0	1	0	1	1	1	1	1	1	7

CTS: California Teachers Study

Supplemental Table 4. Evaluation of quality based on the Newcastle-Ottawa scale for the included case-control studies.

	Selection				Comparability		Exposure			Total
Study	Case definition	Representativeness of the cases	Selection of controls	Definition of controls	On age	On other risk factors	Assessment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Andreotti (2013)	1	1	1	0	1	1	1	1	0	7
Benedetti (2009)	1	1	1	0	1	1	1	1	0	7
Boffetta (1989)	1	1	1	0	1	1	0	1	0	6
Brown (1992)	1	1	1	0	1	1	1	1	1	8
Brown (1997)	1	1	1	0	1	1	1	1	0	7
Deandrea (2007)	1	1	0	0	0	1	1	1	0	5
De Stefani (2013)	1	1	0	0	1	1	1	1	1	7
Ellison-Loschmann (2007)	1	1	0	0	1	1	1	1	0	6
Glass (2003)	1	1	1	0	1	0	1	1	0	6
Hosgood (2007)	1	1	1	0	1	1	1	1	1	8
Kokouva (2011)	1	1	0	1	1	1	1	1	0	7
Linet (1987)	1	1	0	1	1	1	1	1	0	7
Monnereau (2008)	1	1	0	1	1	1	1	1	0	7
Pasqualetti (1990)	1	1	0	1	1	1	1	1	0	7
Pekmezovic (2002)	1	1	0	0	0	0	1	1	0	4
Wang -LAMMCC (2013)	1	1	1	0	1	1	0	1	0	6

LAMMCC: Los Angeles Multiple Myeloma Case-Control Study

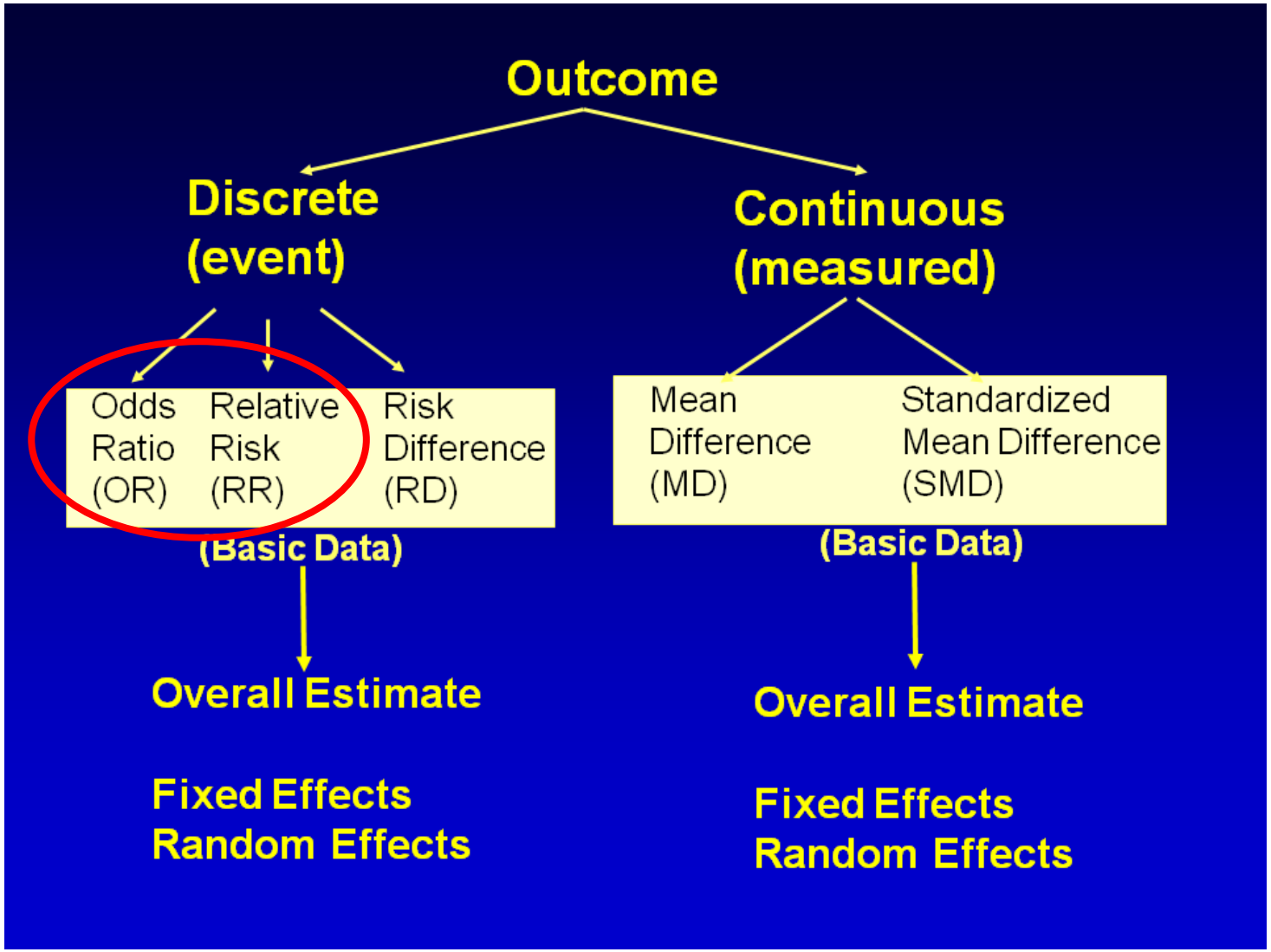
Αυθεντικότητα (accuracy)
Η τιμή που μετράται εκφράζει το πραγματικό αντικείμενο της με μικρό σφάλμα
(«η απόσταση από την πραγματικότητα»)

Ακρίβεια (precision)
Η έλλειψη τυχαίου σφάλματος

- Σφάλμα τύπου I
- Σφάλμα τύπου II

Εγκυρότητα (validity)
Η έλλειψη συστηματικού σφάλματος

Στάδιο 5: η στατιστική σύνθεση των επιμέρους αποτελεσμάτων



Αναγκαία η αναζήτηση της ετερογένειας

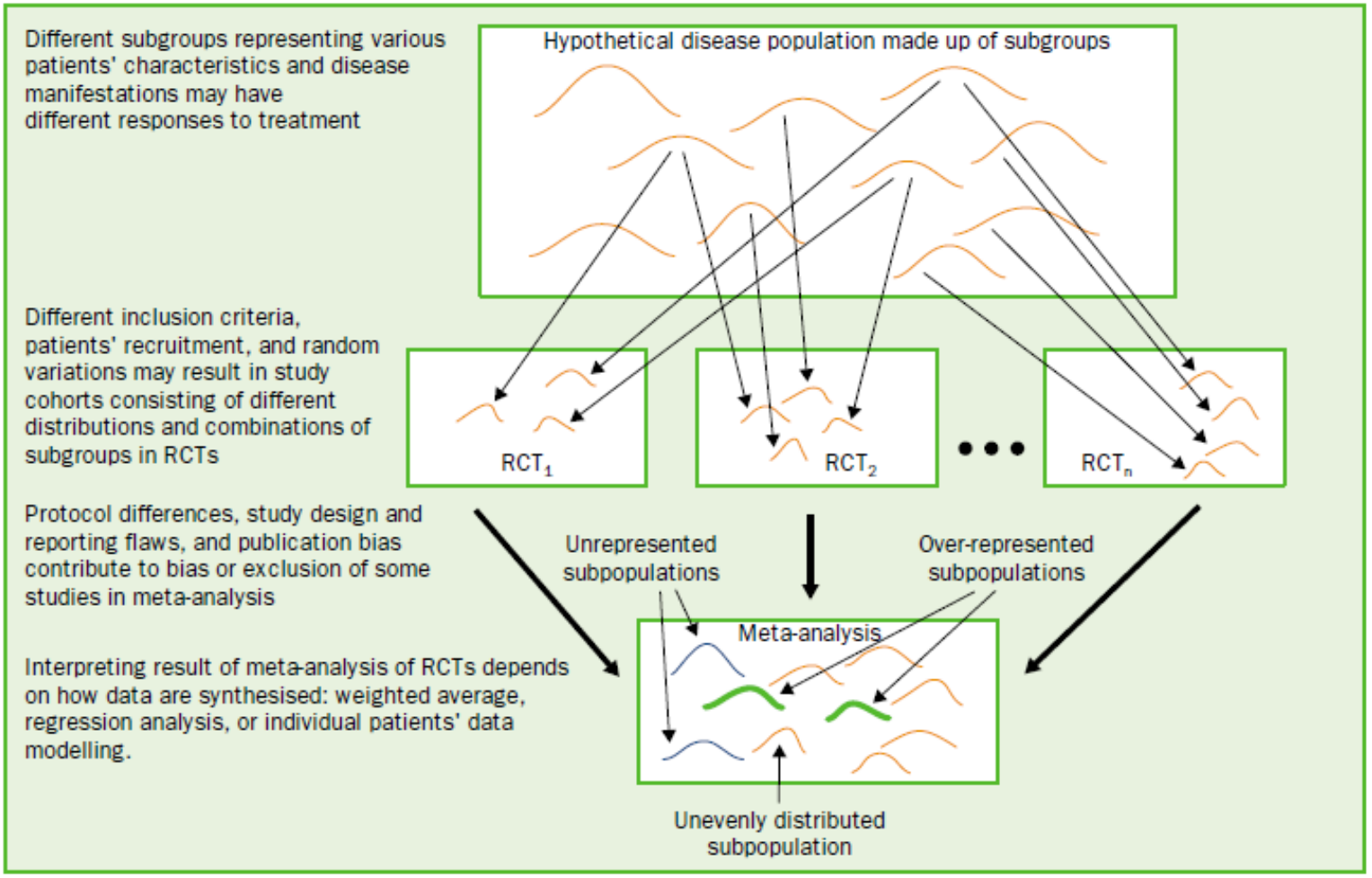


Figure 1: **Diversity in populations of patients in clinical trials and meta-analyses**

Lau J, Ioannidis JP, Schmid CH. *Lancet* 1998;351(9096):123-7.

Πηγές ετερογένειας

- Σχεδιασμός των μελετών (κριτήρια ένταξης των ασθενών, θεραπεία, διάρκεια θεραπείας)
- Ποιότητα των μελετών (τυχαιοποίηση, απλά ή διπλά τυφλές μελέτες)
- Επίπεδο ατόμου (προγνωστικοί παράγοντες, πληθυσμός όπου το άτομο ανήκει)
- Outcomes (αξιολόγησή τους)

Πιθανά μοντέλα μετα-αναλύσεων
Fixed-Effects Model

Θεωρεί ότι το *πραγματικό* μέγεθος αποτελέσματος είναι κοινό σε όλες τις μελέτες

Πιθανά μοντέλα μετα-αναλύσεων
Random-Effects Model

- Ευρύτερα χρησιμοποιούμενο
- Θεωρεί ότι το *πραγματικό* μέγεθος αποτελέσματος διαφέρει από μελέτη σε μελέτη
- Το μοντέλο επιλογής επί σημαντικής ετερογένειας

Random-Effects Model (DerSimonian-Laird approach)

- **Δύο πηγές μεταβλητότητας:**
  - within studies (between patients)
  - between studies (heterogeneity)

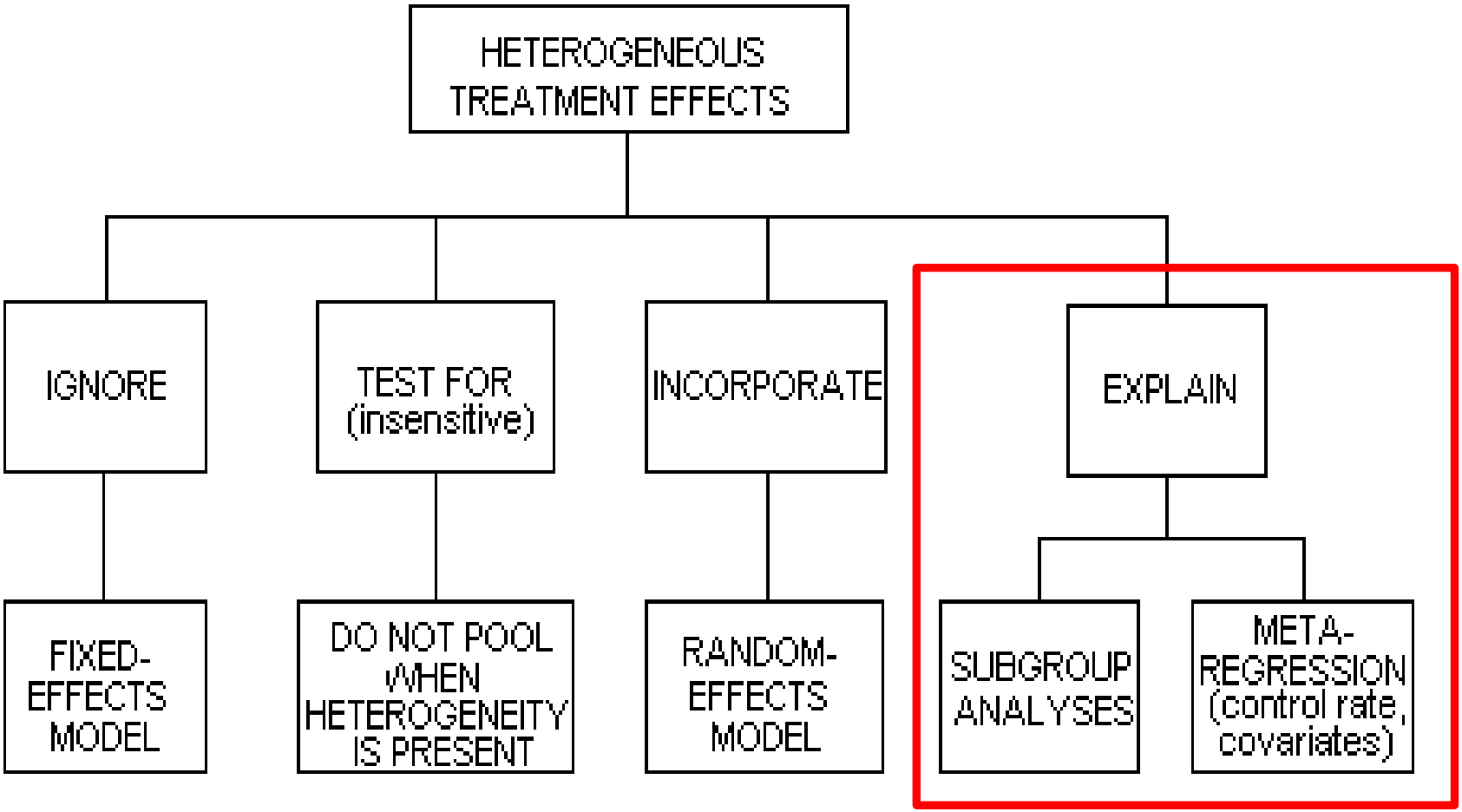
- **Λαμβάνουμε**
  - **διαφορετικό pooled estimate**
  - **ευρύτερα διαστήματα εμπιστοσύνης (CI)**
  - **μεγαλύτερο *p*-value**

  - **Άρα «πιο συντηρητικά» αποτελέσματα**

Σε παρουσία σημαντικής ετερογένειας

- Υποαναλύσεις (subgroup analyses)
- Μετα-παλινδρόμηση

} ώστε να «εξηγηθεί» η ετερογένεια



Αναλύσεις υπο-ομάδων

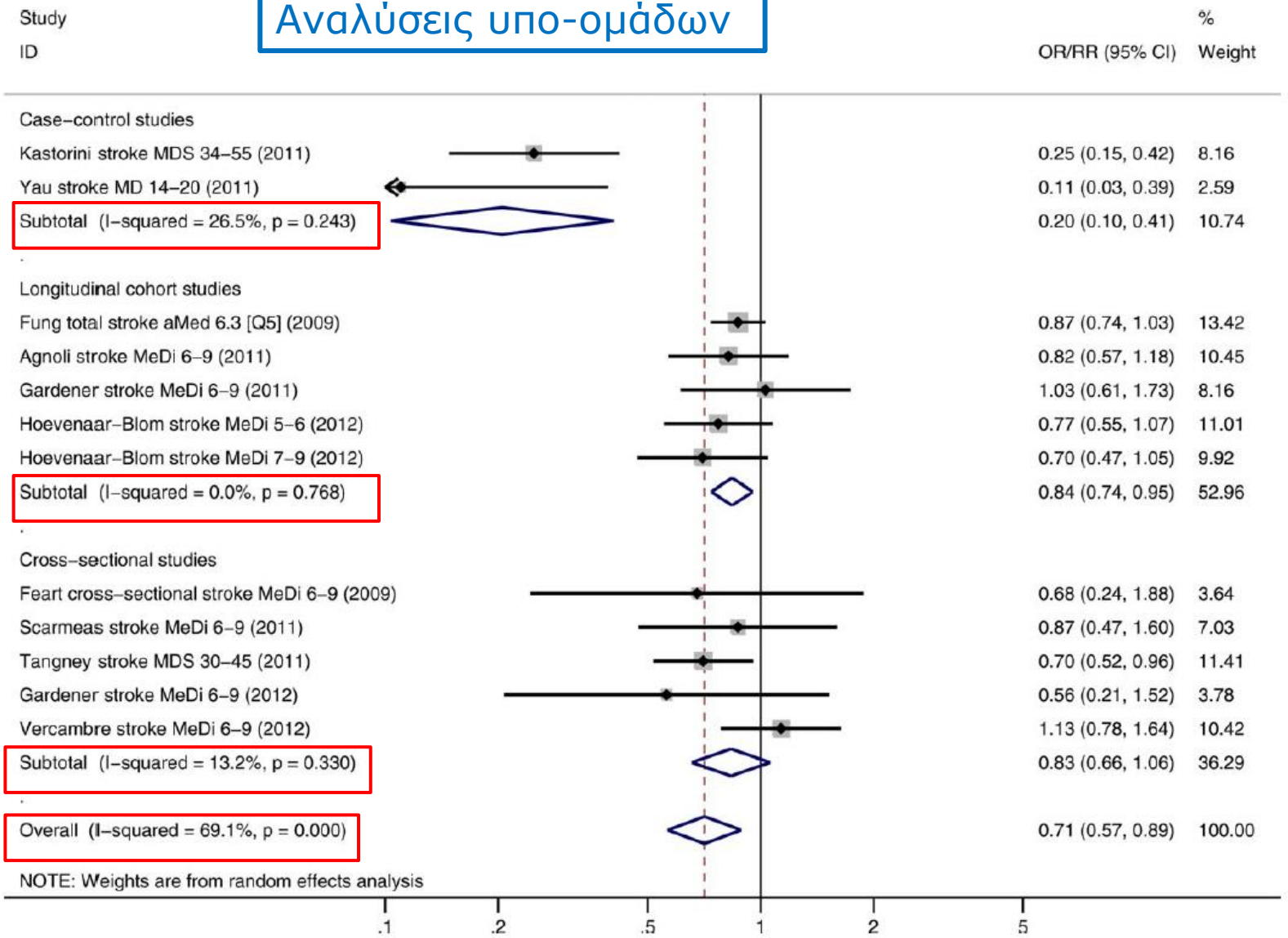
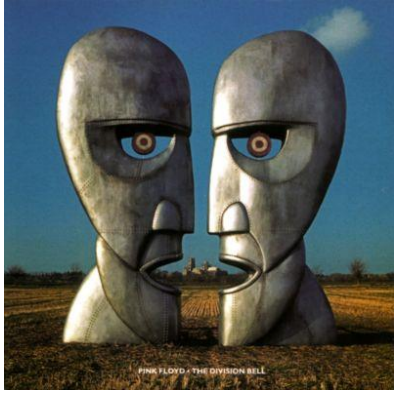


FIGURE 1: Forest plot describing the association between high adherence to Mediterranean diet and risk for stroke. Apart from the overall analysis, the subanalyses on case–control (upper rows), longitudinal cohort (middle rows), and cross-sectional studies (lower rows) are presented.

Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. Ann Neurol 2013;74(4):580-91.

Ανάλυση σε υποομάδες



Breast Cancer Res Treat
DOI 10.1007/s10549-009-0694-5

EPIDEMIOLOGY

Four polymorphisms in cytochrome P450 1A1 (CYP1A1) gene and breast cancer risk: a meta-analysis

Theodoros N. Sergentanis ·
Konstantinos P. Economopoulos

Table 4 Pooled ORs by race for heterozygous, homozygous carriers, dominant, and recessive models for the C2453A (Thr461Asp) polymorphism

Race	Heterozygous (AC vs. CC)		Homozygous (AA vs. CC)	
	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity
Overall (n = 11)	0.985 (0.868–1.117)	$P = 0.824$	1.546 (0.862–2.722)	$P = 0.923$
Premenopausal ($n = 5$)	1.020 (0.638–1.630)	$P = 0.263$	2.709 (0.560–13.107)	$P = 0.793$
Postmenopausal ($n = 6$)	0.931 (0.797–1.088)	$P = 0.305$	1.641 (0.781–3.450)	$P = 0.518$
Race	Dominant model (AA and AC vs. CC)		Recessive model (AA vs. CC and AC)	
	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity
Overall ($n = 11$)	0.992 (0.880–1.120)	$P = 0.822$	1.535 (0.856–2.751)	$P = 0.929$
Premenopausal ($n = 5$)	0.944 (0.633–1.410)	$P = 0.510$	2.796 (0.580–13.482)	$P = 0.793$
Postmenopausal ($n = 6$)	1.090 (0.769–1.544)^{R}	$P = 0.092$	1.633 (0.777–3.432)	$P = 0.541$

All pooled ORs were derived from fixed-effect models except for cells marked with (random^{R})

Table 4 Results of the meta-analyses examining the association between paternal age and risk of childhood leukemia

	"Oldest versus middle" comparison			"Youngest versus middle" comparison			Paternal age in increments		
	n[a]	RR (95 % CI)	Heterogeneity I^2, p	n[a]	RR (95 % CI)	Heterogeneity I^2, p	n[a]	RR (95 % CI)	Heterogeneity I^2, p
Analysis on ALL									
Overall analysis	25	**1.10 (1.02–1.19)**	45.2 %, 0.008	22	**1.09 (1.00–1.20)**	25.6 %, 0.134	10	**1.04 (1.00–1.08)**	70.9 %, <0.001
Subgroups by study design									
Case–control studies	22	**1.09 (1.01–1.18)**	47.1 %, 0.008	19	**1.11 (1.01–1.22)**	33.0 %, 0.082	8	**1.04 (1.00–1.08)**	73.2 %, <0.001
Cohort studies	3	1.29 (0.99–1.70)	11.8 %, 0.322	3	0.94 (0.70–1.26)	0.0 %, 0.778	2	1.07 (0.98–1.17)	30.3 %, 0.231
Subgroups by geographic region									
Europe	14	**1.13 (1.05–1.23)**	26.2 %, 0.173	14	1.10 (0.97–1.24)	25.1 %, 0.184	6	**1.05 (1.02–1.08)**	0.0 %, 0.580
USA/Canada	4	1.19 (0.94–1.52)	72.1 %, 0.013	2	0.93 (0.82–1.06)	0.0 %, 0.911	3	1.07 (0.97–1.18)	88.0 %, <0.001
Asia	2	0.79 (0.57–1.09)	0.0 %, 0.425	2	1.17 (0.80–1.71)	15.3 %, 0.277	0	No studies	
Australia-NZ	4	0.96 (0.75–1.24)	47.9 %, 0.124	4	**1.24 (1.07–1.43)**	0.0 %, 0.863	1	0.86 (0.74–1.00)	NC
Latin America	1	0.93 (0.46–1.89)	NC	0	No studies		0	No studies	
Subgroups by degree of adjustment									
No adjustment	18	**1.09 (1.00–1.20)**	47.4 %, 0.014	14	**1.14 (1.00–1.29)**	41.8 %, 0.050	3	**1.09 (1.00–1.19)**	57.5 %, 0.095
Adjustment—no mutual adjustment for maternal and paternal age	3	1.21 (0.78–1.85)	60.6 %, 0.079	5	0.97 (0.86–1.09)	0.0 %, 0.834	4	1.03 (0.97–1.08)	75.0 %, 0.007
Mutual adjustment for maternal and paternal age	4	1.06 (0.90–1.25)	20.7 %, 0.286	3	1.10 (0.81–1.51)	0.0 %, 0.957	3	1.03 (0.98–1.08)	0.0 %, 0.520
Subgroups by overall study quality									
Low (NOS 1–3)	0	No studies		0	No studies		0	No studies	
Intermediate (NOS 4–6)	9	1.08 (0.98–1.20)	38.1 %, 0.114	8	**1.16 (1.01–1.35)**	44.3 %, 0.083	0	No studies	
High (NOS 7–9)	16	**1.12 (1.00–1.25)**	50.6 %, 0.011	14	1.00 (0.91–1.10)	0.0 %, 0.578	10	**1.04 (1.00–1.08)**	70.9 %, <0.001

Sergentanis TN, Thomopoulos TP, Gialamas SP, Karalexi MA, Biniaris-Georgallis SI, Kontogeorgi E, Papathoma P, Tsilimidos G, Skalkidou A, Iliadou AN, Petridou ET. Risk for childhood leukemia associated with maternal and paternal age.
Eur J Epidemiol. 2015;30(12):1229-61.

Μέτα-παλινδρόμηση (meta-regression)

- Μοντέλο το οποίο εξετάζει την επίδραση συνεχών (ή και κατηγορικών) μεταβλητών στο μέγεθος αποτελέσματος.
- Αποτελεί γενίκευση των αναλύσεων υποομάδων.

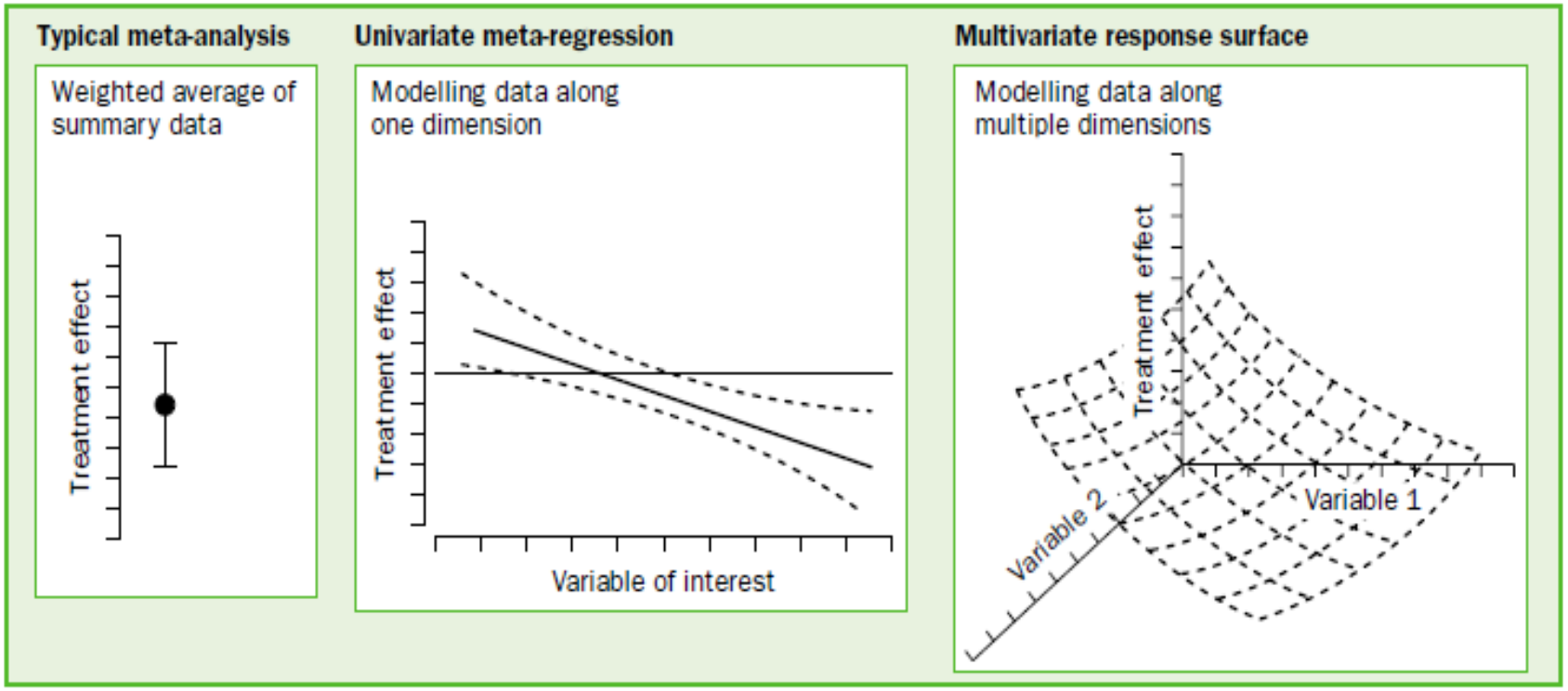
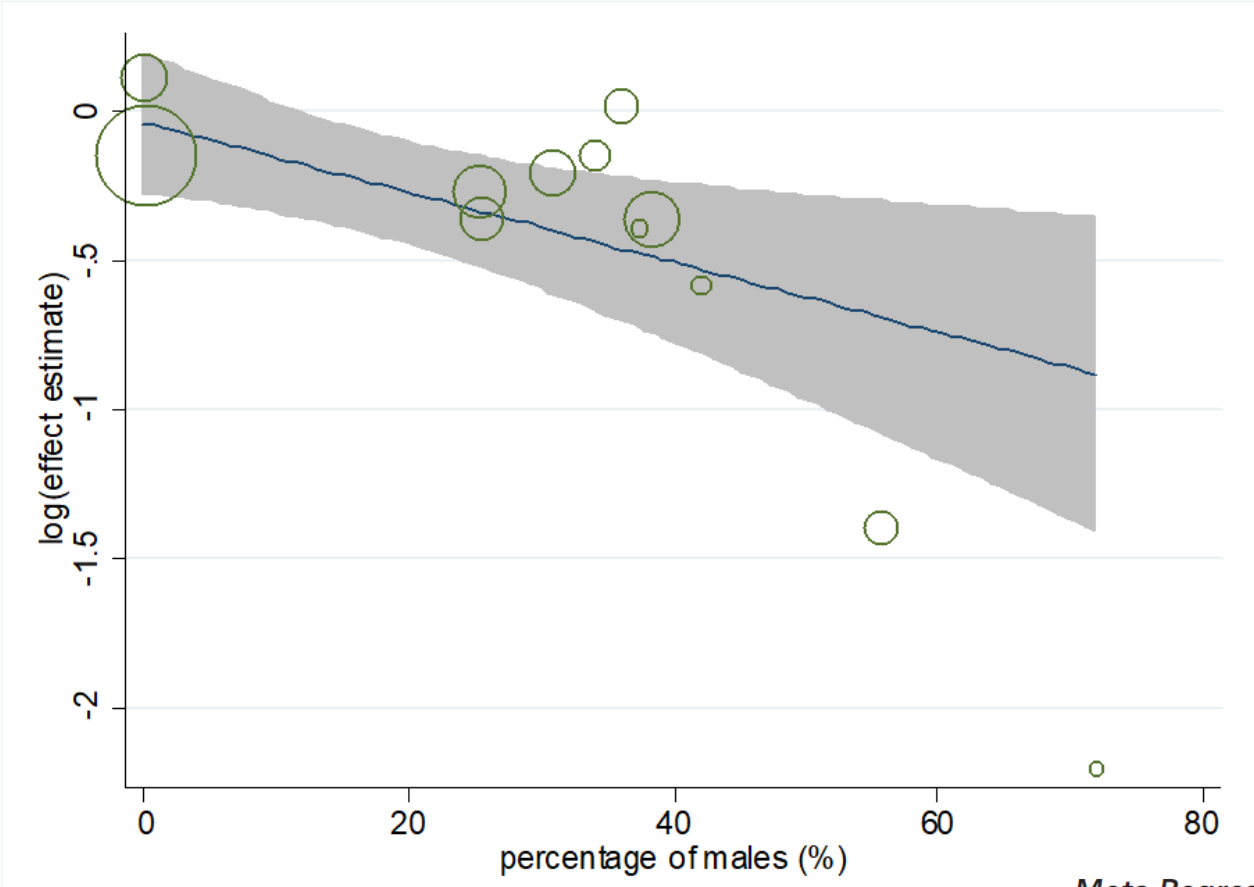


Figure 2: **Summing-up evidence in single and multiple dimensions**

Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not always enough. *Lancet* 1998;351(9096):123-7.

Supplementary Figure 29. Plot depicting the modifying effect mediated by the percentage of males upon the association between stroke and adherence to Mediterranean diet. The circle sizes represent the inverse of each within-study variance.

(A): High adherence

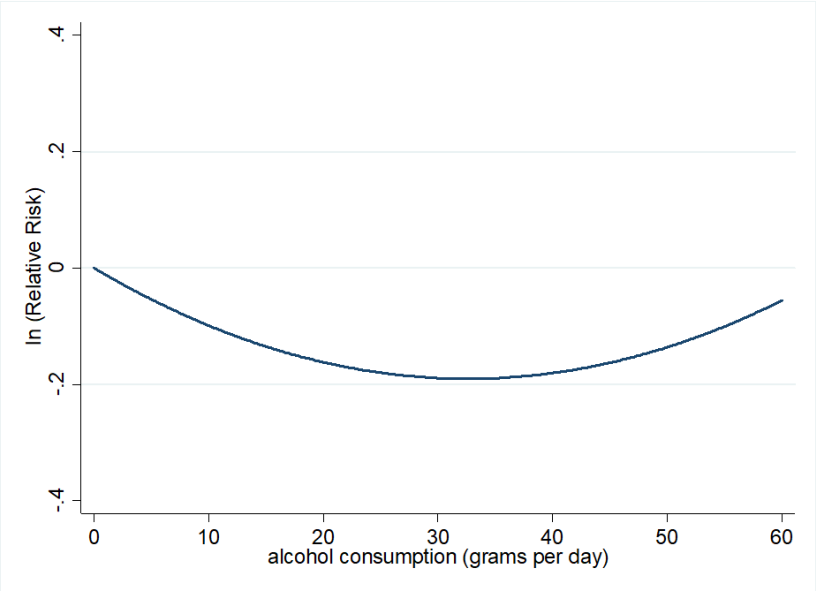


Meta-Regression Analysis

Table 3 presents the results of meta-regression analyses. The protective effects mediated by high adherence to Mediterranean diet in terms of risk for stroke seemed more pronounced among males (exponentiated coefficient = 0.84, 95% CI = 0.74–0.94; Supplementary Fig 29A).

Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. Ann Neurol 2013;74(4):580-91.

Supplemental Figure 15. Graphical representation of the second-order equation describing the association between Relative Risk for multiple myeloma and alcohol consumption.

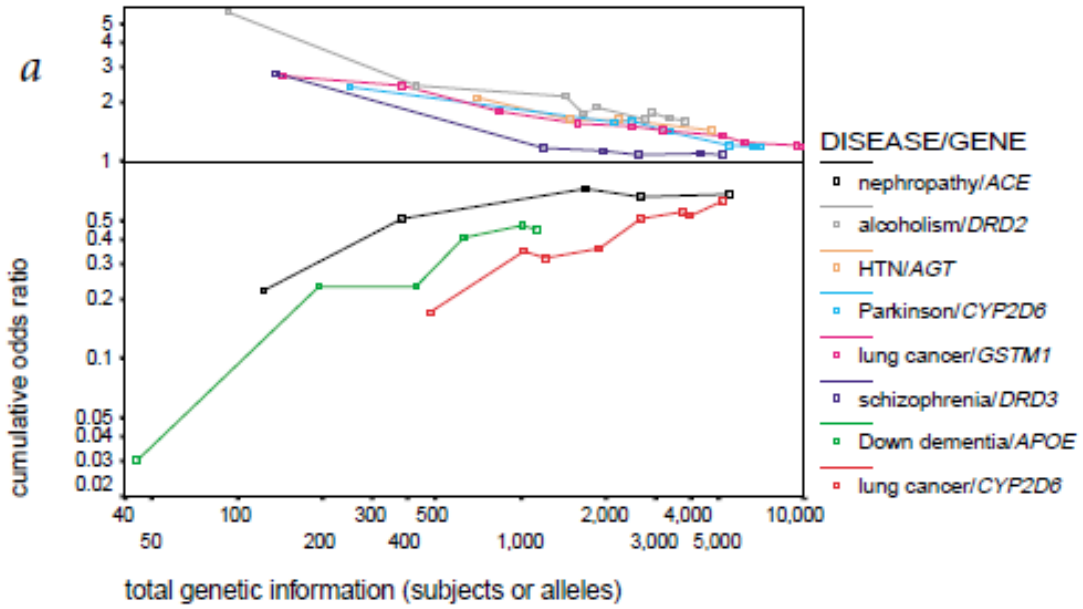


Higher order meta-regression analysis pointed to the following equation as the best fitting curve: $RR = e^{(-0.0116727*x + 0.00179*x2)}$, with statistical significance for the first-order ($p = 0.032$) but only a marginal effect for the second-order coefficient ($p = 0.11$) and x representing the amount of alcohol grams ingested per day. The global minimum of the parabola, denoting maximum protection, corresponded to 32.6 gpd; the respective U-shaped curve is presented in Supplementary Figure 15 available online at http://informahealthcare.com/doi/abs/10.3109/10428194.2014.956312.

Psaltopoulou T, Sergentanis TN, Sergentanis IN, Karadimitris A, Terpos E, Dimopoulos MA.
Alcohol intake, alcoholic beverage type and multiple myeloma risk: a meta-analysis of 26 observational studies.
Leuk Lymphoma. 2015;56(5):1484-501.

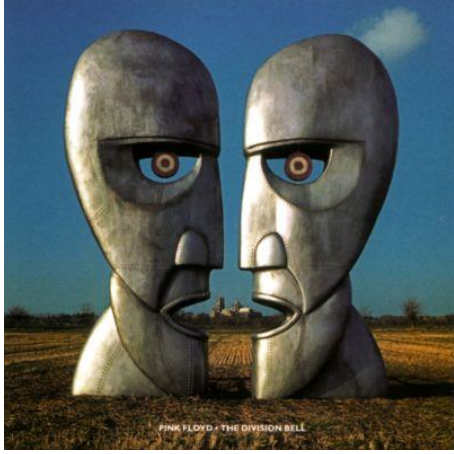
Μέτα-παλινδρόμηση (meta-regression) ως προς το χρόνο

"The first study effect": η μεγαλύτερη συσχέτιση παρατηρείται στην πρώτη μελέτη – η συσχέτιση φθίνει στις μελλοντικές μελέτες



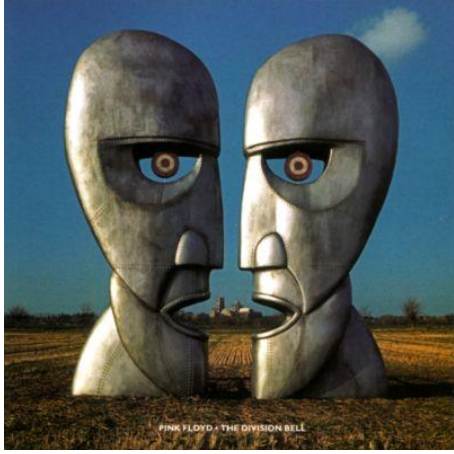
Ioannidis JP, et al. Replication validity of genetic association studies. *Nat Genet* 2001;29:306-9.

Ανάλυση ευαισθησίας



- **Ανάλυση ευαισθησίας** (sensitivity analysis): *«η εξαίρεση ορισμένων μελετών επηρεάζει τα αποτελέσματα της μετα-ανάλυσης;»*

Ανάλυση ευαισθησίας



Breast Cancer Res Treat
DOI 10.1007/s10549-009-0694-5

EPIDEMIOLOGY

Four polymorphisms in cytochrome P450 1A1 (CYP1A1) gene and breast cancer risk: a meta-analysis

Theodoros N. Sergentanis ·
Konstantinos P. Economopoulos

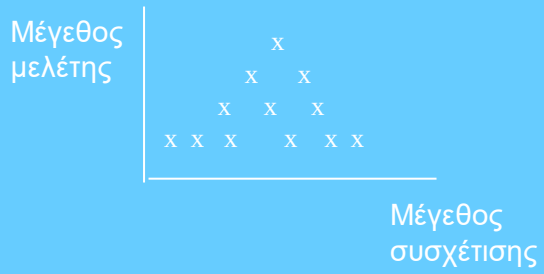
Examining genotype frequencies in controls, significant deviation from HWE was detected in two studies [48, 69], which were both performed on Caucasian subjects. After the exclusion of the two studies significantly departing from HWE the associations demonstrated in Caucasian populations retained their statistical significance. Specifi-

Το πρόβλημα του συστηματικού σφάλματος δημοσίευσης (publication bias)

- Τα **στατιστικά σημαντικά** αποτελέσματα **δημοσιεύονται**, ενώ τα στατιστικά μη σημαντικά τείνουν να μη δημοσιεύονται

Αξιολόγηση του Publication bias – Διάγραμμα χωνιού (Funnel Plot)

- Αδρά: Παριστά το effect estimate (π.χ. OR) σε σχέση με το μέγεθος της μελέτης
- Απουσία σφάλματος, συμμετρικό, ανεστραμμένο χωνί (inverted funnel)



- Επί σφάλματος: ασυμμετρία

Αξιολόγηση του Publication bias – Διάγραμμα χωνιού (Funnel Plot)

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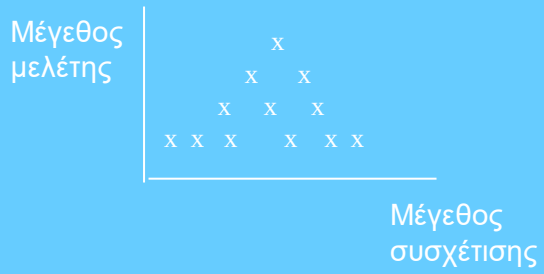


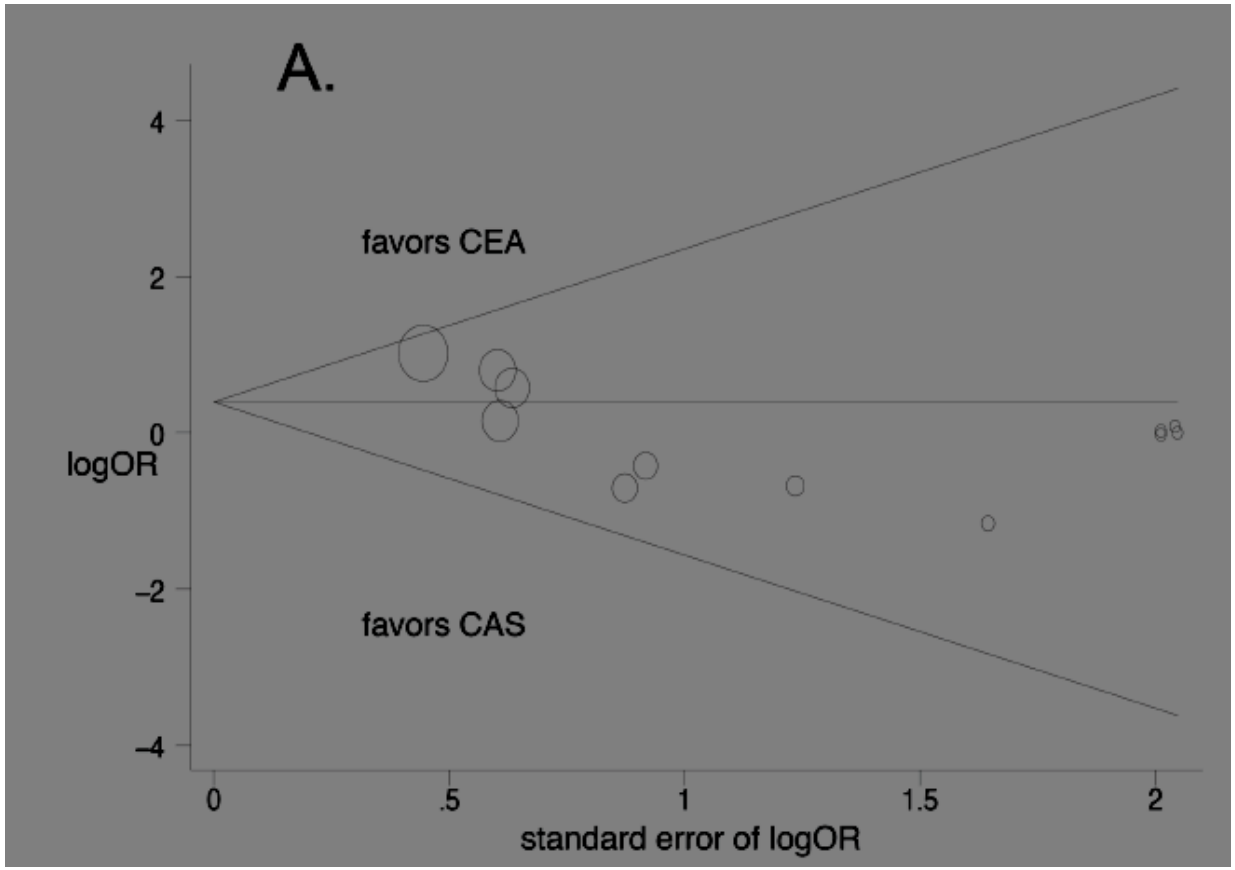
- Επί σφάλματος: ασυμμετρία

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Stroke Association
A Division of American Heart Association

Carotid Artery Stenting Versus Carotid Endarterectomy: A Comprehensive Meta-Analysis of Short-Term and Long-Term Outcomes

Konstantinos P. Economopoulos, Theodoros N. Sergentanis, Georgios Tsivgoulis, Anargiros D. Mariolis and Christodoulos Stefanadis

Stroke published online Jan 13, 2011;
DOI: 10.1161/STROKEAHA.110.606079



Στατιστικές δοκιμασίες για την αξιολόγηση του συστηματικού σφάλματος δημοσίευσης:

- Begg's test
- Egger's test

Στάδιο 7:
“the structured report”

ELSEVIER

Journal of Clinical Epidemiology 62 (2009) e1–e34

Journal of Clinical Epidemiology

The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration

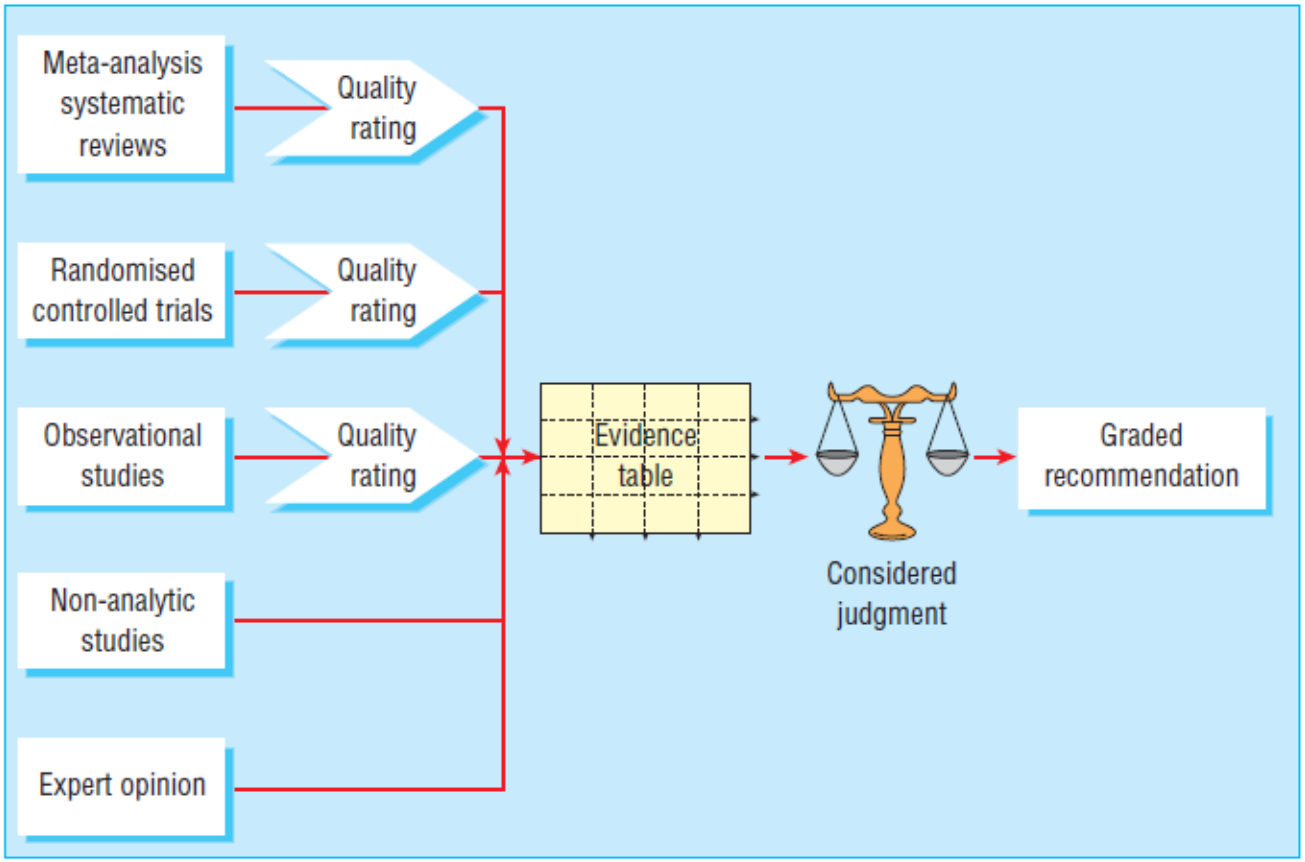
Alessandro Liberati[1,2,*], Douglas G. Altman[3], Jennifer Tetzlaff[4], Cynthia Mulrow[5], Peter C. Gøtzsche[6], John P.A. Ioannidis[7], Mike Clarke[8,9], P.J. Devereaux[10], Jos Kleijnen[11,12], David Moher[4,13]

Στάδιο 7:
“the structured report”

Εν κατακλείδι

- Αναλυτική περιγραφή υπόθεσης, μεθοδολογίας και στρατηγικής
- Αναλυτικός πίνακας
- Flow chart, Forest plots, Funnel plot
- Ενδελεχής ανάλυση και υποαναλύσεις

Μετα-ανάλυση και ο «Ζυγός» της Τεκμηριωμένης Ιατρικής (evidence-based medicine)



Overview of the process for developing and grading guideline recommendations

Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001;323(7308):334-6.

Μετα-ανάλυση: **πρωτείο** στην ιεραρχία της τεκμηριωμένης ιατρικής (evidence-based medicine)

Box 1 Hierarchy of study types

- Systematic reviews and meta-analyses of randomised controlled trials
- Randomised controlled trials
- Non-randomised intervention studies
- Observational studies
- Non-experimental studies
- Expert opinion

Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001;323(7308):334-6.

Μετα-ανάλυση: **πρωτείο** στην ιεραρχία της τεκμηριωμένης ιατρικής (evidence-based medicine)

Box 3 Revised grading system for recommendations in evidence based guidelines

Levels of evidence

1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1– Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias

2++ High quality systematic reviews of case-control or cohort studies *or*

High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal

2+ Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal

2– Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal

3 Non-analytic studies, eg case reports, case series

4 Expert opinion

Grades of recommendations

A At least one meta-analysis, systematic review, or RCT rated as 1 + + and directly applicable to the target population *or*

A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1 + directly applicable to the target population and demonstrating overall consistency of results

B A body of evidence including studies rated as 2 + + directly applicable to the target population and demonstrating overall consistency of results *or*

Extrapolated evidence from studies rated as 1 + + or 1 +

C A body of evidence including studies rated as 2 + directly applicable to the target population and demonstrating overall consistency of results *or*

Extrapolated evidence from studies rated as 2 + +

D Evidence level 3 or 4 *or*

Extrapolated evidence from studies rated as 2 +

Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001;323(7308):334-6.

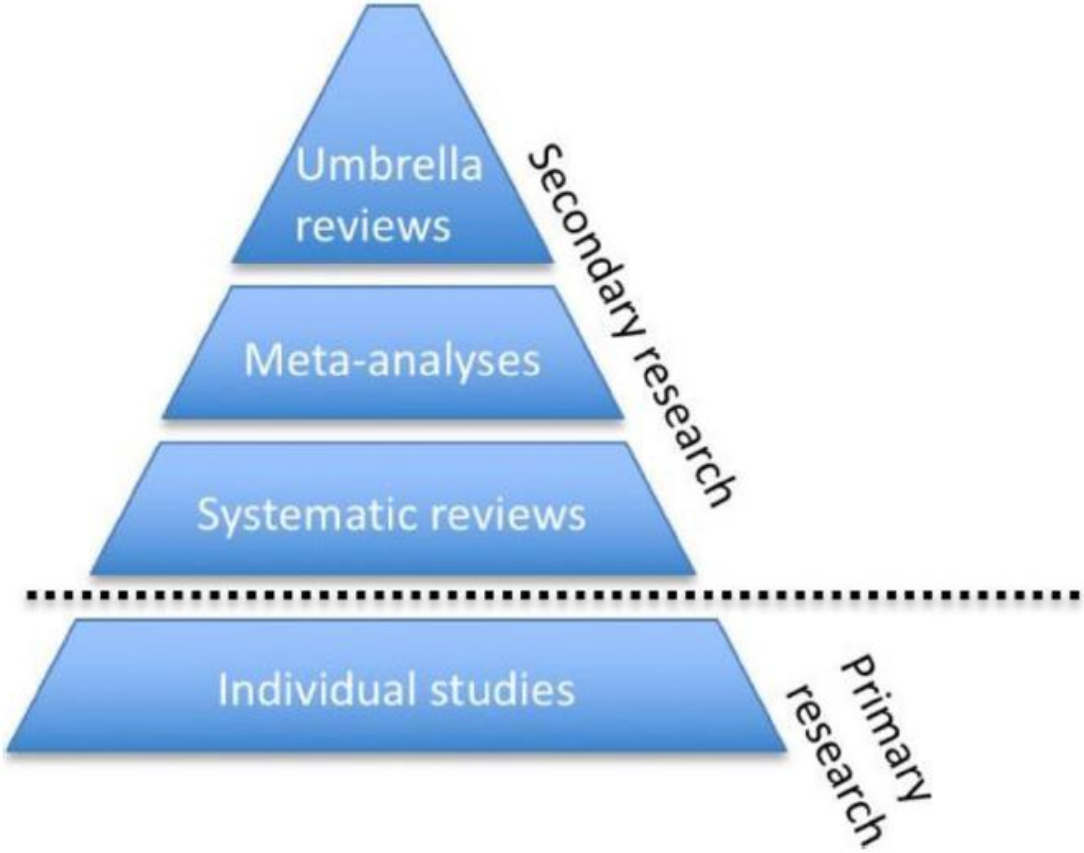


Figure 1 Hierarchy of evidence synthesis methods.

Μετα-Μετα-Επιδημιολογία

Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. Evid Based Ment Health. 2018 Aug;21(3):95-100.

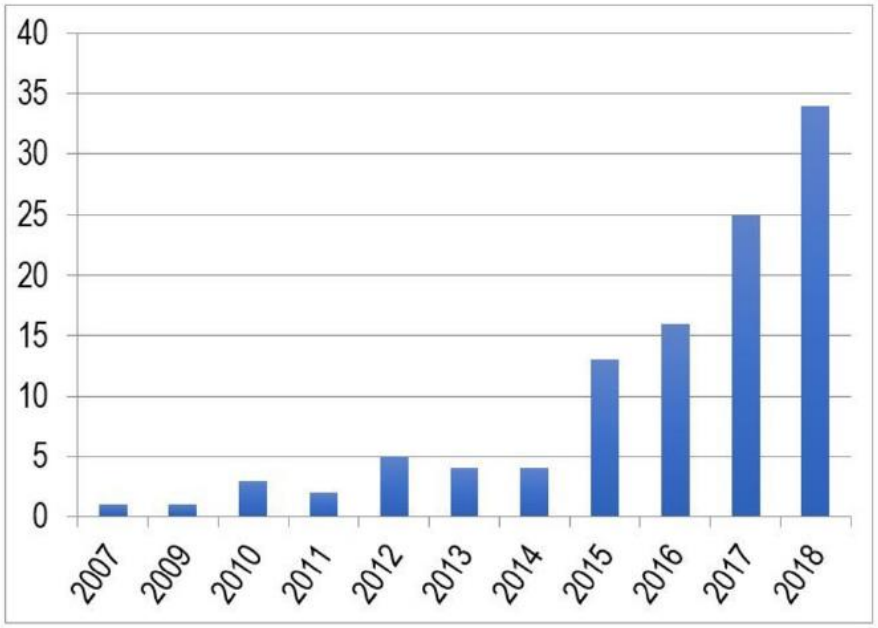


Figure 2 Web of Knowledge records containing 'umbrella review' in their title up to April 2018.

Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. Evid Based Ment Health. 2018 Aug;21(3):95-100

thebmj

BMJ 2014;350:g7607 doi: 10.1136/bmj.g7607 (Published 2 January 2015)

RESEARCH

Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies

Konstantinos K Tsilidis *assistant professor*[1,2], John C Kasimis *PhD student*[1], David S Lopez *assistant professor*[3], Evangelia E Ntzani *assistant professor*[1], John P A Ioannidis *professor*[4]

Table 1| Description of 27 meta-analyses of type 2 diabetes and cancer incidence or mortality included in umbrella review

Study	Association between diabetes and*	No of cases/population	Summary relative risk (95% CI)			Fixed P value‡	Random P value§	95% prediction interval
			Fixed effects	Random effects	Largest study†			
Zhu, 2013[32]	Bladder cancer	50 676/12 500 000	1.26 (1.22 to 1.29)	1.35 (1.17 to 1.56)	0.96 (0.92 to 1.01)	<0.001	<0.001	0.61 to 3.02
Larsson, 2007[33]	Breast cancer	30 859/1 422 788	1.19 (1.16 to 1.23)	1.20 (1.12 to 1.28)	1.20 (1.10 to 1.20)	<0.001	<0.001	1.01 to 1.43
Larsson, 2007[33]	Breast cancer mortality	4442/1 090 597	1.21 (1.10 to 1.34)	1.24 (0.95 to 1.62)	1.27 (1.11 to 1.45)	<0.001	0.11	0.49 to 3.16

Table 2| Evaluation of bias and heterogeneity in 27 meta-analyses of type 2 diabetes and cancer incidence or mortality

Author, year	Association of diabetes with	No of studies	Egger's P value*	RR for SE=0†	I^2 (95% CI; P value)‡	Observed§	Expected§	P value¶
Zhu, 2013[32]	Bladder cancer incidence	36	0.27	1.17	95 (94 to 95; <0.01)	19	4.4	<0.01
Larsson, 2007[33]	Breast cancer incidence	20	0.94	1.19**	48 (0 to 68; <0.01)	8	11.9	NR
Larsson, 2007[33]	Breast cancer mortality	5	0.89	1.16	81 (40 to 90; <0.01)	3	1.40	0.14
Jing, 2012[34]	ICC incidence	9	0.63	2.10**	54 (0 to 77; 0.02)	4	7.40	NR

PLOS ONE

RESEARCH ARTICLE

Primary health care quality indicators: An umbrella review

André Ramalho[1,2]*, Pedro Castro[3], Manuel Gonçalves-Pinho[1,2], Juliana Teixeira[1], João Vasco Santos[1,2,4], João Viana[1,2], Mariana Lobo[1,2], Paulo Santos[1,2], Alberto Freitas[1,2]

1 MEDCIDS–Department of Community Medicine, Information and Health Decision Sciences, Faculty of Medicine, University of Porto, Porto, Portugal, **2** CINTESIS–Centre for Health Technology and Services Research, Porto, Portugal, **3** USF Camélias, ACeS Grande Porto VII (ARS Norte)–Vila Nova de Gaia, Portugal, **4** Public Health Unit, ACeS Grande Porto VIII (ARS Norte)–Espinho/Gaia, Portugal

* andrelcramalho@gmail.com

PLoS One. 2019; 14(8): e0220888.

J Antimicrob Chemother 2019; **74**: 2139–2152
doi:10.1093/jac/dkz152 Advance Access publication 19 April 2019

Journal of Antimicrobial Chemotherapy

Factors associated with antibiotic prescribing for adults with acute conditions: an umbrella review across primary care and a systematic review focusing on primary dental care

W. Thompson [1]*, S. Tonkin-Crine [2], S. H. Pavitt[1], R. R. C. McEachan[3], G. V. A. Douglas[1], V. R. Aggarwal[1] and J. A. T. Sandoe[4]

Reflections on a healthy way of life and healthy planet

Contact

Umbrella review of umbrella reviews. Physical activity in community / General Practice.

Μετα-Μετα-Μετα-Επιδημιολογία!!!

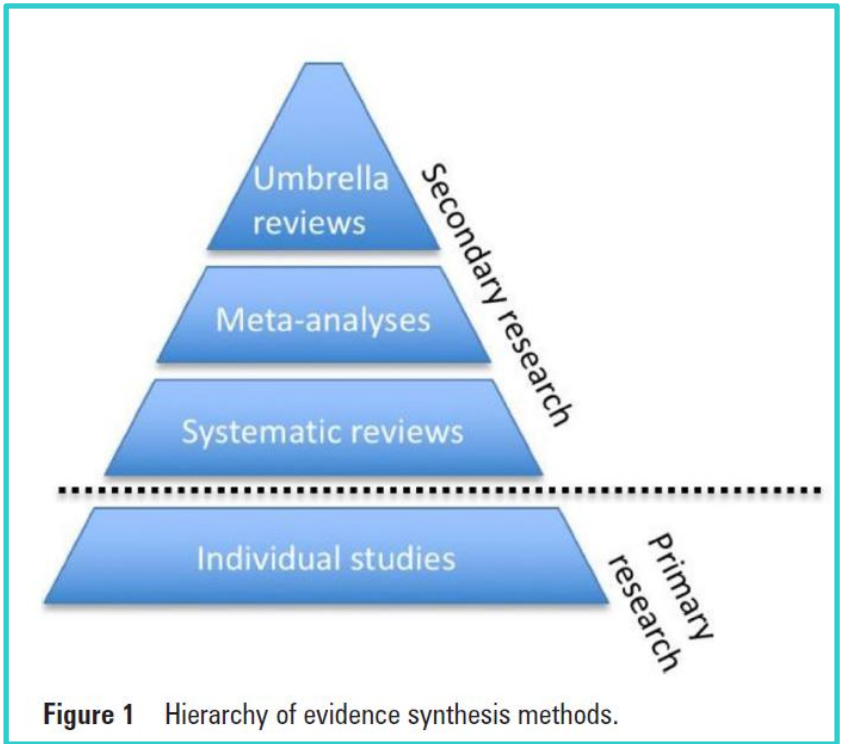


Figure 1 Hierarchy of evidence synthesis methods.

Ποια η θέση της (Μετα)^{ν}-Επιδημιολογίας;

- Μετα-μοντέρνο
- Μετα-γνώση (Winnicott)
- *"Υπέρ της των πάντων ενώσεως του Κυρίου δεηθώμεν…"*