Συστηματική ανασκόπηση και μετα-ανάλυση

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Επιδιωκόμενα μαθησιακά αποτελέσματα (ILOs)

- Να *γνωρίζετε* και να *ερμηνεύετε* τα διαγράμματα δάσους, τον κίνδυνο, τον σχετικό κίνδυνο, τα odds και το odds ratio
- Να *ορίζετε* τη συστηματική ανασκόπηση και τη μετα-ανάλυση
- Να *ερμηνεύετε* τα διαγράμματα δάσους
- Να *προβλέπετε* τα βήματα που θα πρέπει να ακολουθήσετε για τη διεξαγωγή μιας συστηματικής ανασκόπησης ή μετα-ανάλυσης κατά τα PRISMA guidelines
- Να *παρέχετε παραδείγματα* υποθέσεων για τις συστηματικές ανασκοπήσεις / μετα-αναλύσεις
- Να *προβλέπετε* και να *σχεδιάζετε* αλγορίθμους αναζήτησης για τη διεξαγωγή μιας συστηματικής ανασκόπησης ή μετα-ανάλυσης
- Να *σχεδιάζετε* διάγραμμα ροής κατά PRISMA
- Να *γνωρίζετε* την έννοια της ετερογένειας, καθώς επίσης τους τρόπους αντιμετώπισής της στο μετα-επίπεδο
- Να *γνωρίζετε* το συστηματικό σφάλμα δημοσίευσης και να *ερμηνεύετε* τα διαγράμματα χωνιού
- Να *κατανοείτε* τη σημασία της συστηματικής ανασκόπησης και μετα-ανάλυσης στη σύγχρονη Επιστήμη

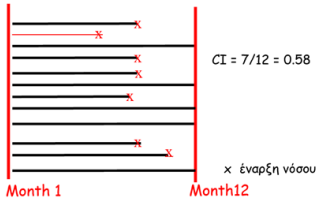
*στις συγχρονικές μελέτες, θα δείτε να εφαρμόζονται μέθοδοι επαγωγικής στατιστικής, ωστόσο θα τις ερμηνεύετε με περίσκεψη, δεδομένου του σχεδιασμού τους

Έννοιες υποβάθρου

Risk (κίνδυνος)

$$\text{Risk in group A} = \frac{a}{a+b}$$

(ποσοστό μιας ομάδας που εμφανίζει ένα αποτέλεσμα, ένα χαρακτηριστικό)



Cumulative incidence= Risk

Odds (λόγος συμπληρωματικών πιθανοτήτων)

$$\text{Odds in group A} = \frac{a}{b}$$

Οι στήλες εκφράζουν ένα «αποτέλεσμα»

	Event	No event	
Group A	a	b	a+b
Group B	c	d	c+d
	a+c	b+d	n

Οι γραμμές εκφράζουν έναν παράγοντα «έκθεσης»

	ΟΕΜ	Όχι ΟΕΜ	Σύνολο
Άνδρες	15	15	30
Γυναίκες	20	30	50
Σύνολο	35	45	80

ΟΕΜ: οξύ έμφραγμα του μυοκαρδίου

Risk (κίνδυνος)

$$\text{Risk in group A} = \frac{a}{a+b}$$

(ποσοστό μιας ομάδας που εμφανίζει ένα αποτέλεσμα, ένα χαρακτηριστικό)

Odds

(λόγος συμπληρωματικών πιθανοτήτων)

$$\text{Odds in group A} = \frac{a}{b}$$

	Event	No event	
Group A	a	b	$a+b$
Group B	c	d	$c+d$
	$a+c$	$b+d$	n

	ΟΕΜ	Όχι ΟΕΜ	Σύνολο
Άνδρες	15	15	30
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Σύνολο	35	45	80

- Με τι ισούται ο κίνδυνος (risk) ΟΕΜ στους άνδρες; Στις γυναίκες;
- Με τι ισούνται τα odds ΟΕΜ στους άνδρες; Στις γυναίκες;

	ΟΕΜ	Όχι ΟΕΜ	Σύνολο
Άνδρες	15	15	30
Γυναίκες	20	30	50
Σύνολο	35	45	80

- Κίνδυνος (risk) ΟΕΜ στους άνδρες = 15/30 = 0.5 (50%)
- Κίνδυνος (risk) ΟΕΜ στις γυναίκες = 20/50 = 0.4 (40%)

- Odds ΟΕΜ στους άνδρες = 15/15 = 1
- Odds ΟΕΜ στις γυναίκες = 20/30 = 0.67

OR (σχετικός λόγος συμπληρωματικών πιθανοτήτων) και RR (σχετικός κίνδυνος)

(Relative risk, σχετικός κίνδυνος)

$$RR_{A \text{ vs. } B} = \frac{\text{Risk in group A}}{\text{Risk in group B}}$$

Risk Ratio (RR)

(**Σχετικός** λόγος συμπληρωματικών πιθανοτήτων)

$$OR_{A \text{ vs. } B} = \frac{\text{Odds in group A}}{\text{Odds in group B}}$$

Odds Ratio (OR)

	Event	No event	
Group A	*a*	*b*	*a+b*
Group B	*c*	*d*	*c+d*
	a+c	*b+d*	*n*

$$RR_{A \text{ vs. } B} = \frac{a/(a+b)}{c/(c+d)} = \frac{a\,(c+d)}{c\,(a+b)}$$

$$OR_{A \text{ vs. } B} = \frac{a/b}{c/d} = \frac{a\,d}{c\,b}$$

	ΟΕΜ	Όχι ΟΕΜ	Σύνολο
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- Odds ΟΕΜ στους άνδρες = 15/15 = 1
- Odds ΟΕΜ στις γυναίκες = 20/30 = 0.67

- $RR_{\text{άνδρες vs. γυναίκες}} = ?$
- $RR_{\text{γυναίκες vs. άνδρες}} = ?$
- $OR_{\text{άνδρες vs. γυναίκες}} = ?$
- $OR_{\text{γυναίκες vs. άνδρες}} = ?$

	ΟΕΜ	Όχι ΟΕΜ	Σύνολο
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- Κίνδυνος (risk) ΟΕΜ στις γυναίκες = 20/50 = 0.4 (40%)

- Odds ΟΕΜ στους άνδρες = 15/15 = 1
- Odds ΟΕΜ στις γυναίκες = 20/30 = 0.67

- $RR_{\text{άνδρες vs. γυναίκες}} = 0.5 / 0.4 = 1.25$
- $RR_{\text{γυναίκες vs. άνδρες}} = 0.4 / 0.5 = 0.8$
- $OR_{\text{άνδρες vs. γυναίκες}} = 1 / 0.67 = 1.5$
- $OR_{\text{γυναίκες vs. άνδρες}} = 0.67 / 1 = 0.67$

Ερμηνεία RR και OR

Έννοιες υποβάθρου

	ΟΕΜ	Όχι ΟΕΜ	Σύνολο
Άνδρες	15	15	30
Γυναίκες	20	30	50
Σύνολο	35	45	80

- $RR_{\text{άνδρες vs. γυναίκες}} = 0.5 / 0.4 = 1.25$

Σε σχέση με τις γυναίκες, οι άνδρες έχουν κατά 25% μεγαλύτερο κίνδυνο ΟΕΜ

- $RR_{\text{γυναίκες vs. άνδρες}} = 0.4 / 0.5 = 0.8$
- $OR_{\text{άνδρες vs. γυναίκες}} = 1 / 0.67 = 1.5$

Σε σχέση με τις γυναίκες, οι άνδρες έχουν κατά 50% μεγαλύτερα odds ΟΕΜ

- $OR_{\text{γυναίκες vs. άνδρες}} = 0.67 / 1 = 0.67$

Ερμηνεία RR και OR

Έννοιες υποβάθρου

	ΟΕΜ	Όχι ΟΕΜ	Σύνολο
Άνδρες	15	15	30
Γυναίκες	20	30	50
Σύνολο	35	45	80

- $RR_{\text{άνδρες vs. γυναίκες}} = 0.5 / 0.4 = 1.25$
- $RR_{\text{γυναίκες vs. άνδρες}} = 0.4 / 0.5 = 0.8$
- $OR_{\text{άνδρες vs. γυναίκες}} = 1 / 0.67 = 1.5$
- $OR_{\text{γυναίκες vs. άνδρες}} = 0.67 / 1 = 0.67$

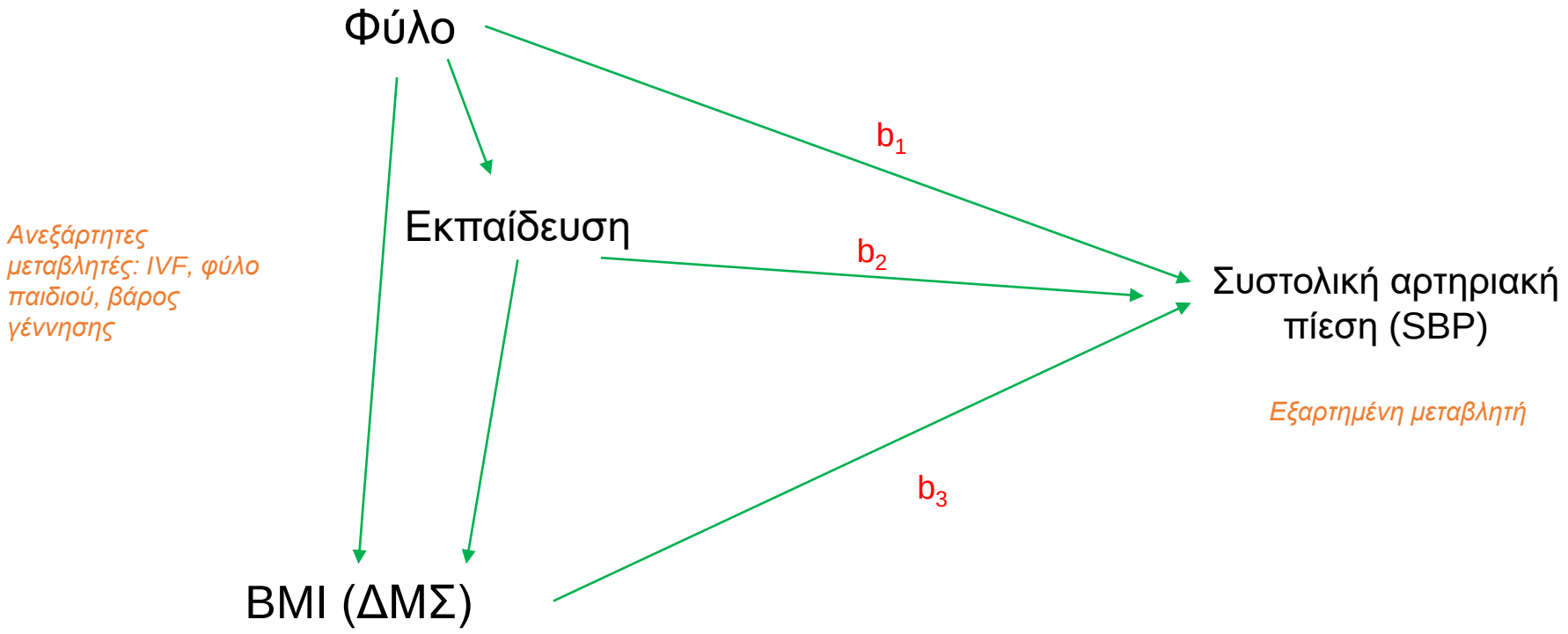
Σε σχέση με τις γυναίκες, οι άνδρες έχουν κατά 25% μεγαλύτερο κίνδυνο ΟΕΜ

Σε σχέση με τους άνδρες, οι γυναίκες έχουν κατά 20% μικρότερο κίνδυνο ΟΕΜ

Σε σχέση με τις γυναίκες, οι άνδρες έχουν κατά 50% μεγαλύτερα odds ΟΕΜ

Σε σχέση με τους άνδρες, οι γυναίκες έχουν κατά 33% μικρότερα odds ΟΕΜ

Πολυπαραγοντική γραμμική παλινδρόμηση (multivariate linear regression)

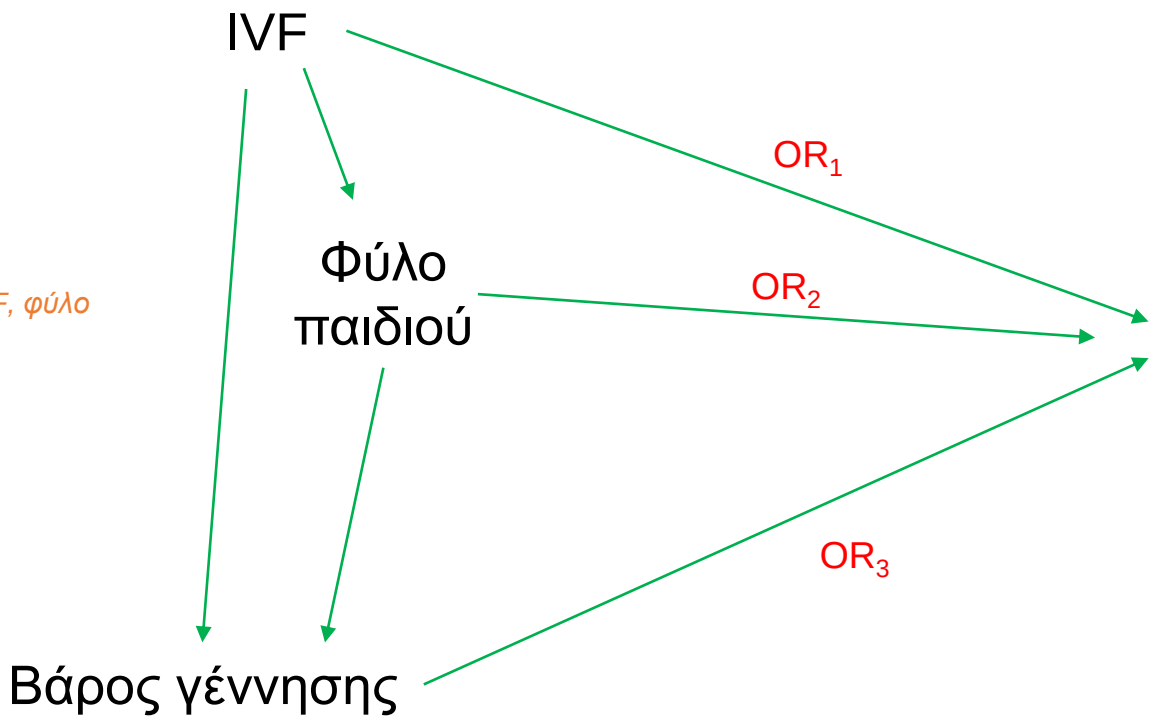


- Τα b_1 ,b_2 ,b_3 είναι “adjusted” (προσαρμοσμένα)

π.χ. το b_1 είναι *προσαρμοσμένο (adjusted)* για την επίδραση της εκπαίδευσης και του BMI (δηλώνει την επίδραση του φύλου στη συστολική αρτηριακή πίεση *ανεξάρτητα από το επίπεδο εκπαίδευσης και το BMI*)

το b_2 δηλώνει την επίδραση του επιπέδου εκπαίδευσης στη συστολική αρτηριακή πίεση, είναι *προσαρμοσμένο (adjusted)* για την επίδραση του φύλου και του BMI, κ.ο.κ.

Πολυπαραγοντική λογιστική παλινδρόμηση (multivariate logistic regression)



Ανεξάρτητες μεταβλητές: IVF, φύλο παιδιού, βάρος γέννησης

Εξαρτημένη μεταβλητή → OR

- Τα OR_1 ,OR_2 ,OR_3 είναι “adjusted” (προσαρμοσμένα)

π.χ. το OR_1 είναι *προσαρμοσμένο (adjusted)* για την επίδραση του φύλου και του βάρους γέννησης (δηλώνει την επίδραση της IVF στα odds των παιδικών νεοπλασιών *ανεξάρτητα από το φύλο και το βάρος γέννησης*)

το OR_2 είναι *προσαρμοσμένο (adjusted)* για την επίδραση της IVF και του βάρους γέννησης, κ.ο.κ.

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 μελετών που πληρούν τα κριτήρια επιλεξιμότητας

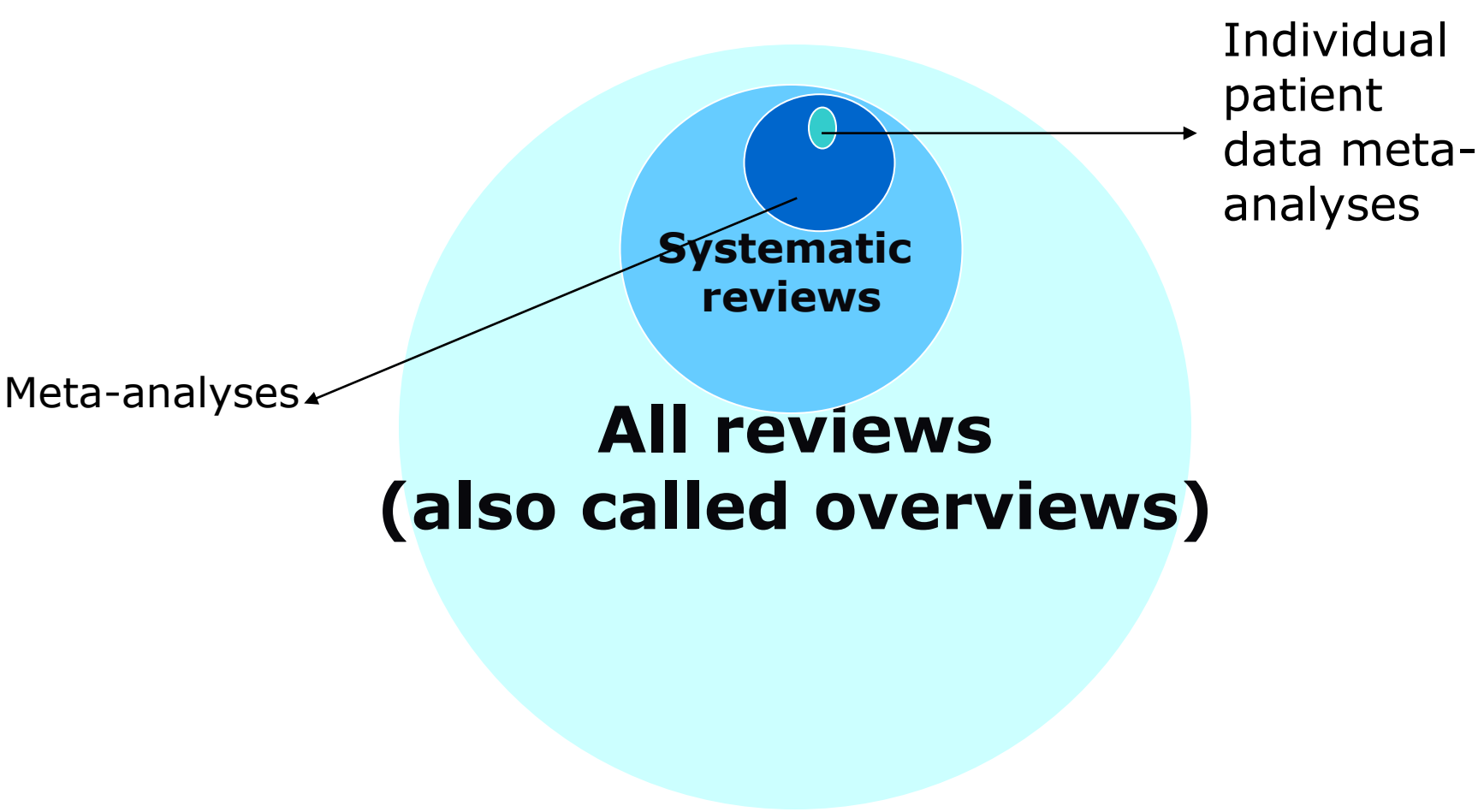
γ) αξιολόγηση της εγκυρότητας των μελετών - αξιολόγηση συστηματικών σφαλμάτων

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

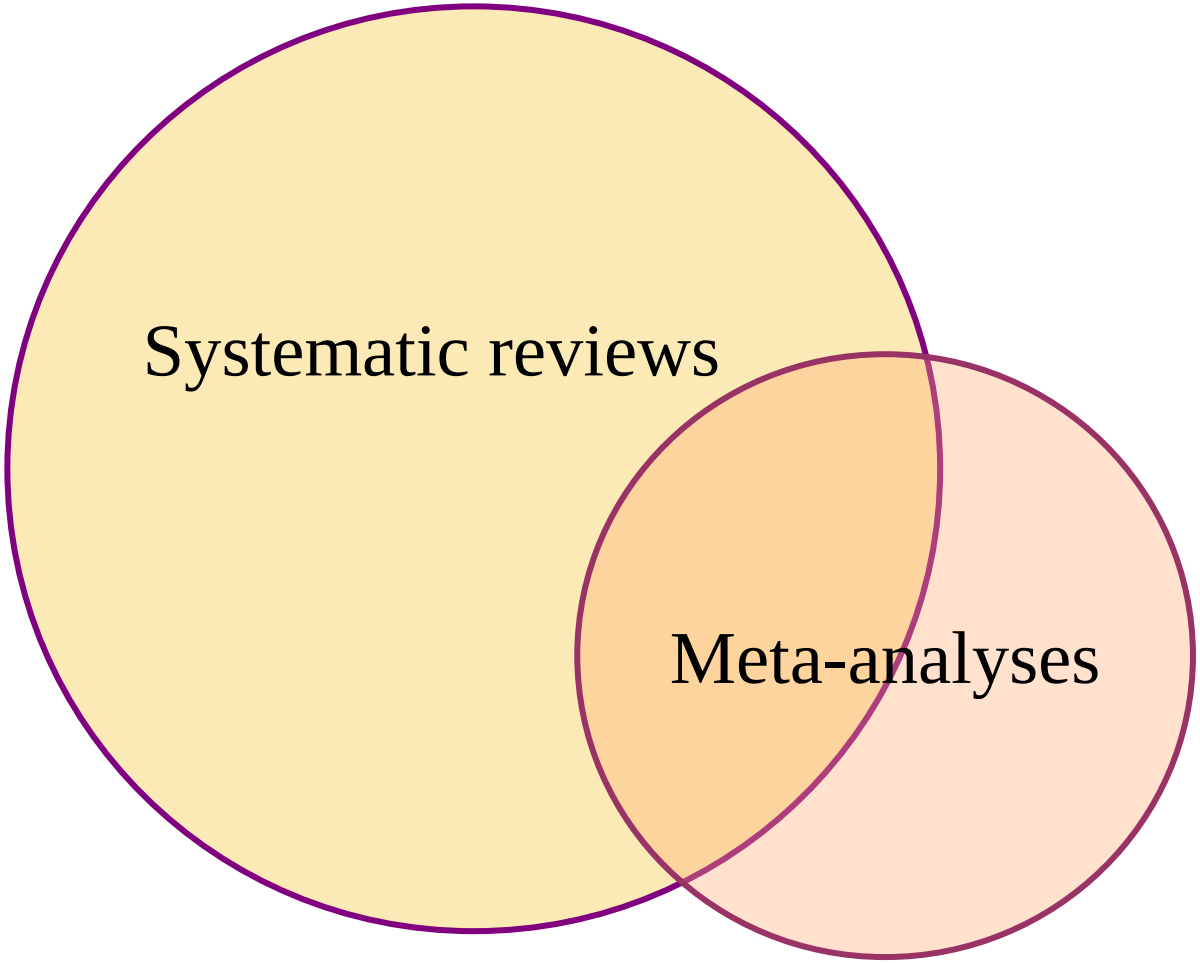
Μετα-ανάλυση (meta-analysis)

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

Κατηγορίες ανασκοπήσεων, μετα-αναλύσεων



Optional part of a systematic review



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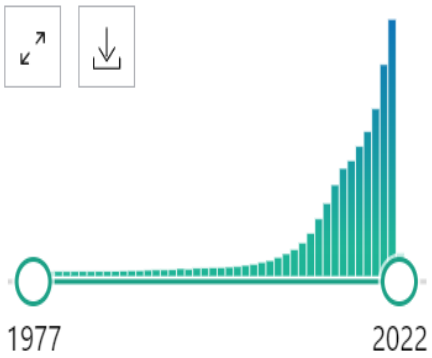

1 The Effect of Repetitive Transcranial Magnetic Stimulation on Suicidal Ideation in Treatment-Resistant Depression: A **Meta-Analysis**.

Cite

Mehta S, Konstantinou G, Weissman CR, Daskalakis ZJ, Voineskos D, Downar J, Mulsant BH, Blumberger DM.

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J Clin Psychiatry. 2022 Jan 18;83(2):21r13969. doi: 10.4088/JCP.21r13969.

PMID: 35044731

Η έννοια του “effect size”

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

Συνεπώς

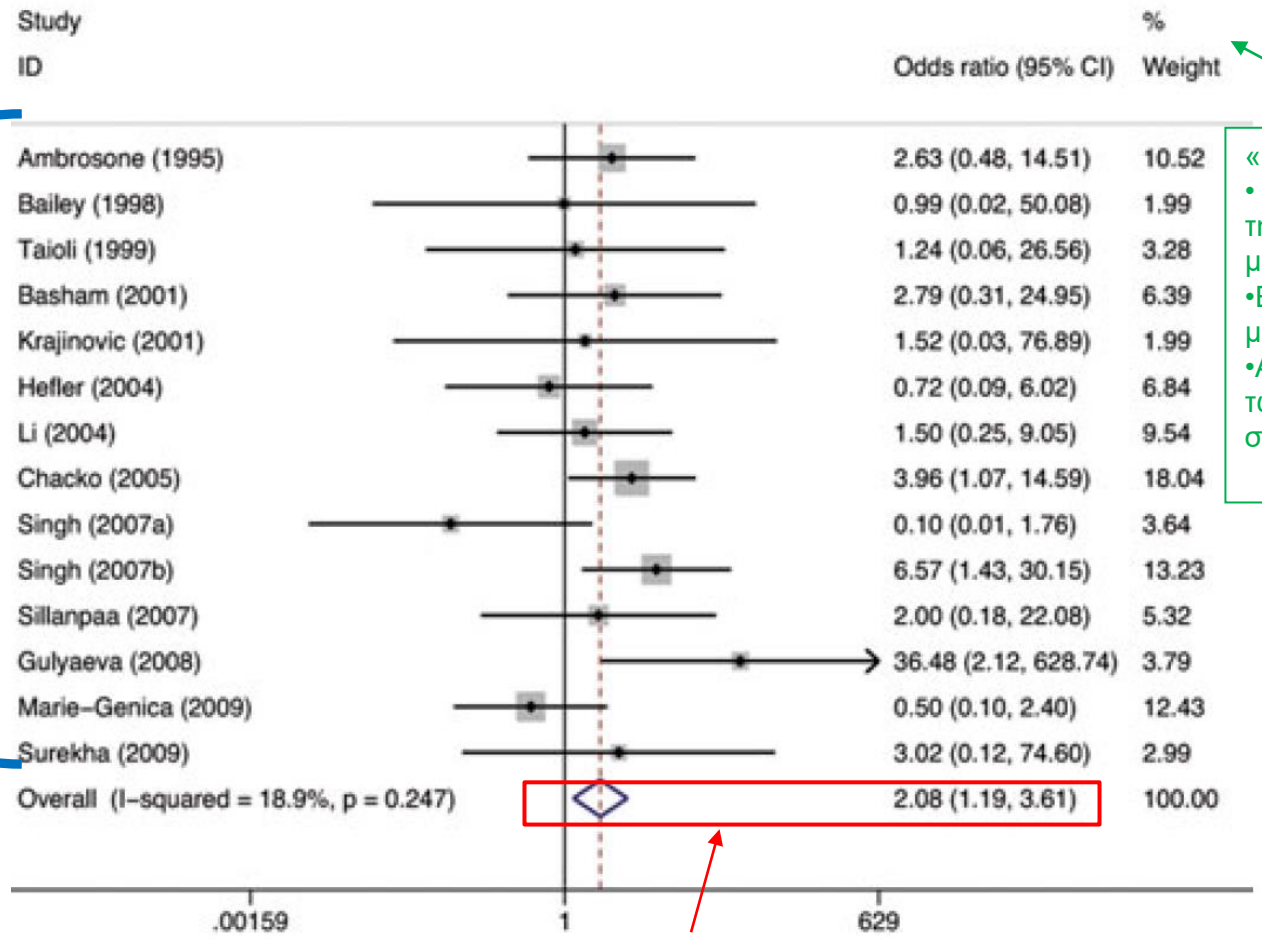
- Αναγκαία η ταυτοποίηση ενός κοινού **«μεγέθους αποτελέσματος» (effect size)**

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)



Επιμέρους μελέτες

«Βάρη» (weights):
- Σχετίζονται αντίστροφα με τη διακύμανση της κάθε μελέτης.
- Εκφράζουν έμμεσα το μέγεθος της μελέτης.
- Αντιστοιχούν στο μέγεθος των τετραγώνων του σχήματος.

Pooled effect size as a diamond

Sergentanis TN, Economopoulos KP.
Four polymorphisms in cytochrome P450 1A1 (CYP1A1) gene and breast cancer risk: a meta-analysis.
Breast Cancer Res Treat 2010;122(2):459-69.

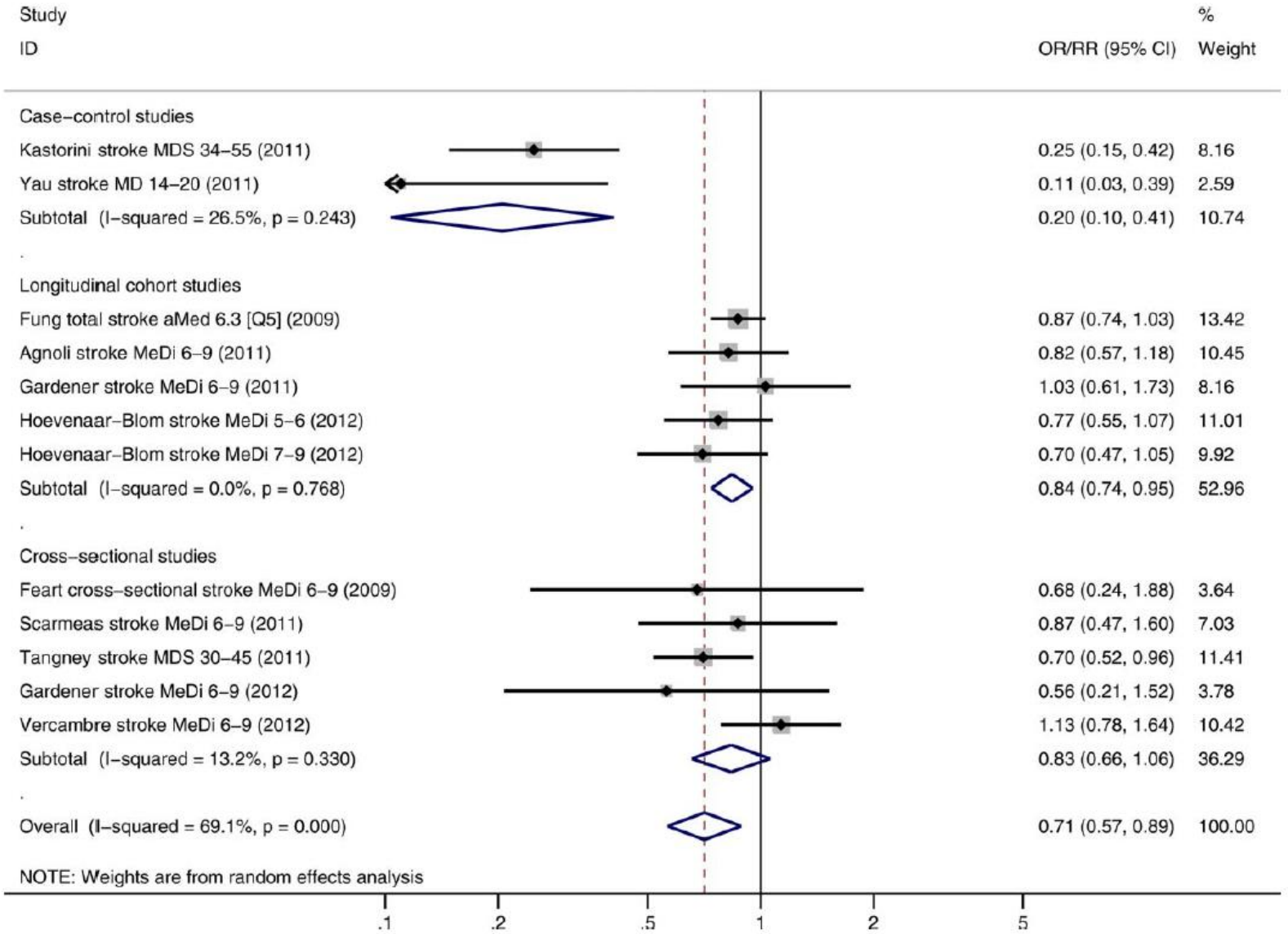


FIGURE 1: Forest plot describing the association between high adherence to Mediterranean diet and risk for stroke. Apart from the overall analysis, the subanalyses on case–control (upper rows), longitudinal cohort (middle rows), and cross-sectional studies (lower rows) are presented.

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.

Εθελοντής για ερμηνεία του Σχήματος;

Mean difference (→Difference in means)	Standardized mean difference
Measures the **absolute difference between the mean value** in two groups.	$\text{SMD} = \frac{\text{Difference in mean outcome between groups}}{\text{Standard deviation of outcome among participants}}$
Estimates the amount by which the experimental intervention changes the **outcome on average** compared with the control.	Expresses the size of the intervention effect in each study **relative to the variability** observed in that study.
Can be used as a summary statistic in meta-analysis when outcome measurements in all studies are made on the **same scale.**	Studies for which the difference in means is the same proportion of the standard deviation will have the same SMD, **regardless of the actual scales** used to make the measurements.
*Analyses based on this effect measure have historically been termed **weighted mean difference (WMD)** analyses in the* Cochrane Database of Systematic Reviews *(*CDSR*). This name is potentially confusing: although the meta-analysis computes a weighted average of these differences in means, no weighting is involved in calculation of a statistical summary of a single study.*	

Κατευθυντήριες οδηγίες για συστηματικές ανασκοπήσεις και μετα-αναλύσεις

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]

The PRISMA 2020 statement: an updated guideline for reporting systematic reviews

Matthew J Page,[1] Joanne E McKenzie,[1] Patrick M Bossuyt,[2] Isabelle Boutron,[3] Tammy C Hoffmann,[4] Cynthia D Mulrow,[5] Larissa Shamseer,[6] Jennifer M Tetzlaff,[7] Elie A Akl,[8] Sue E Brennan,[1] Roger Chou,[9] Julie Glanville,[10] Jeremy M Grimshaw,[11] Asbjørn Hróbjartsson,[12] Manoj M Lalu,[13] Tianjing Li,[14] Elizabeth W Loder,[15] Evan Mayo-Wilson,[16] Steve McDonald,[1] Luke A McGuinness,[17] Lesley A Stewart,[18] James Thomas,[19] Andrea C Tricco,[20] Vivian A Welch,[21] Penny Whiting,[17] David Moher[22]

For numbered affiliations see end of the article.

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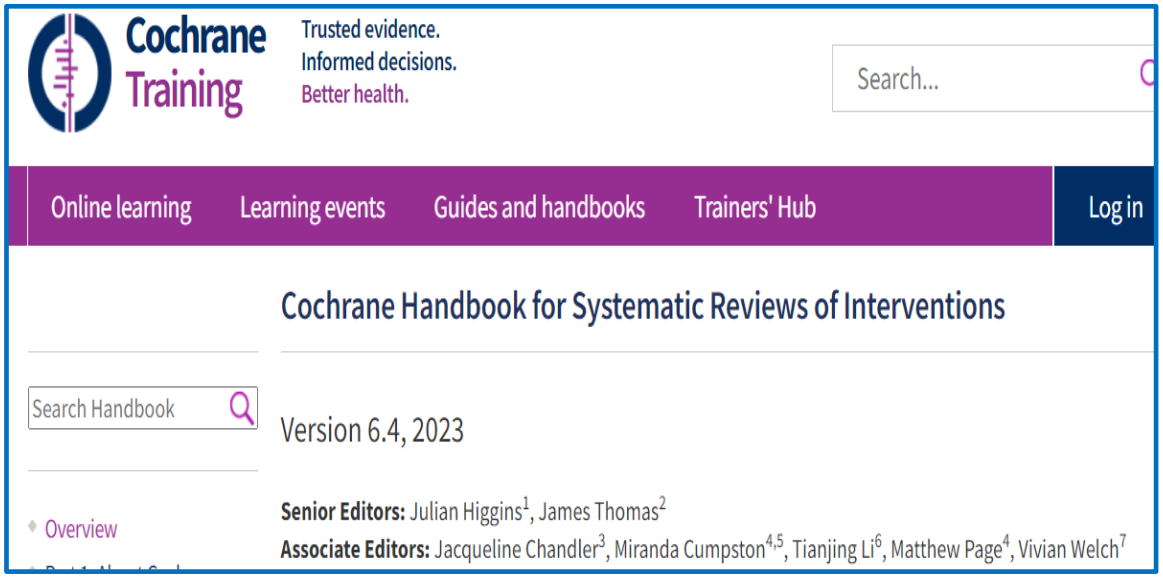
http://dx.doi.org/10.1136/bmj.n71

Στάδια κατά τη διεξαγωγή μιας συστηματικής ανασκόπησης και μετα-ανάλυσης

https://training.cochrane.org/handbook/current

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AKISA "Attikon" University Hospital
Athens, 28th & 29th September 2018


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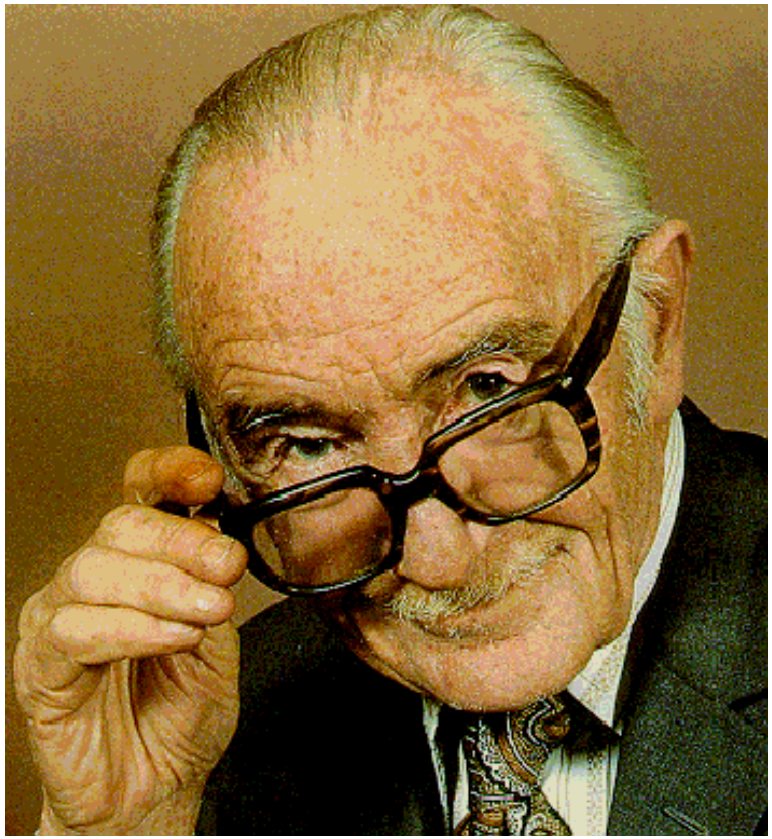
Date: 6 March 2020 to 7 March 2020

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"*



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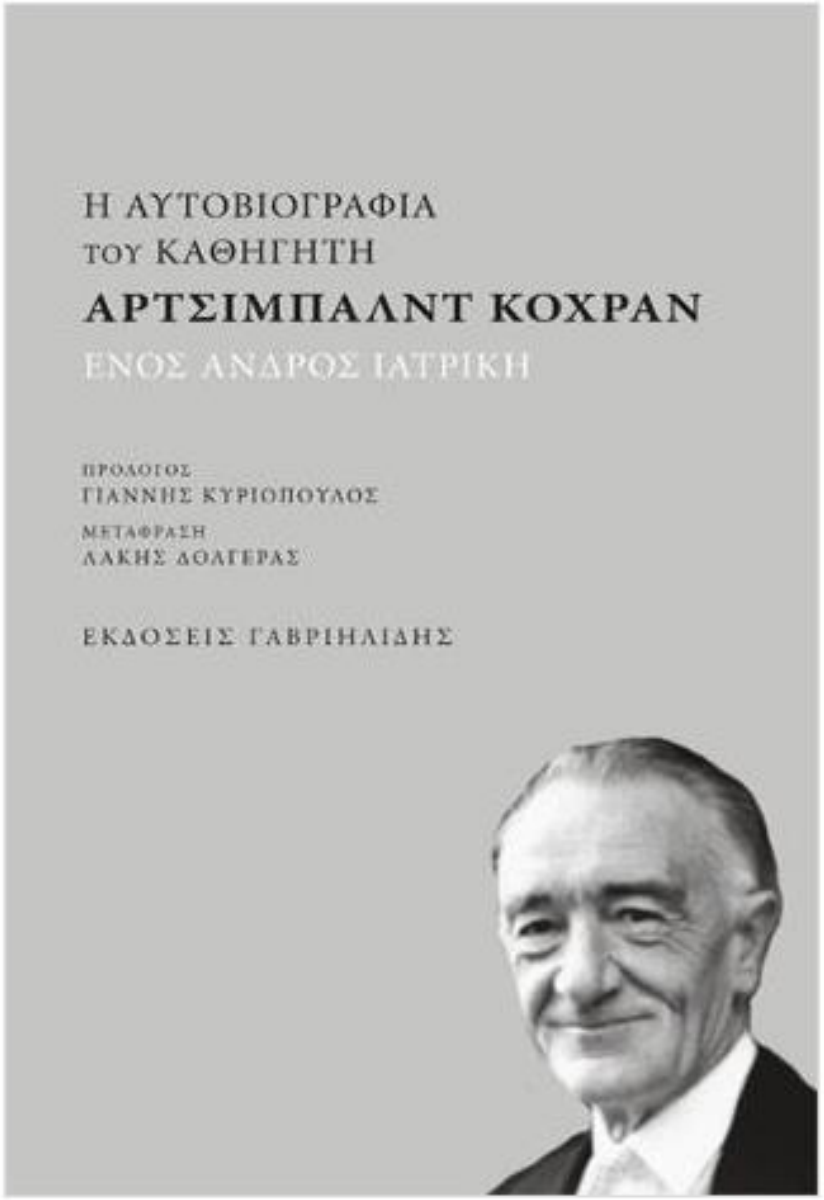
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"The Cochrane Collaboration is an enterprise that rivals the Human Genome Project in its potential implications for modern medicine."
- The Lancet

Cochrane in the News

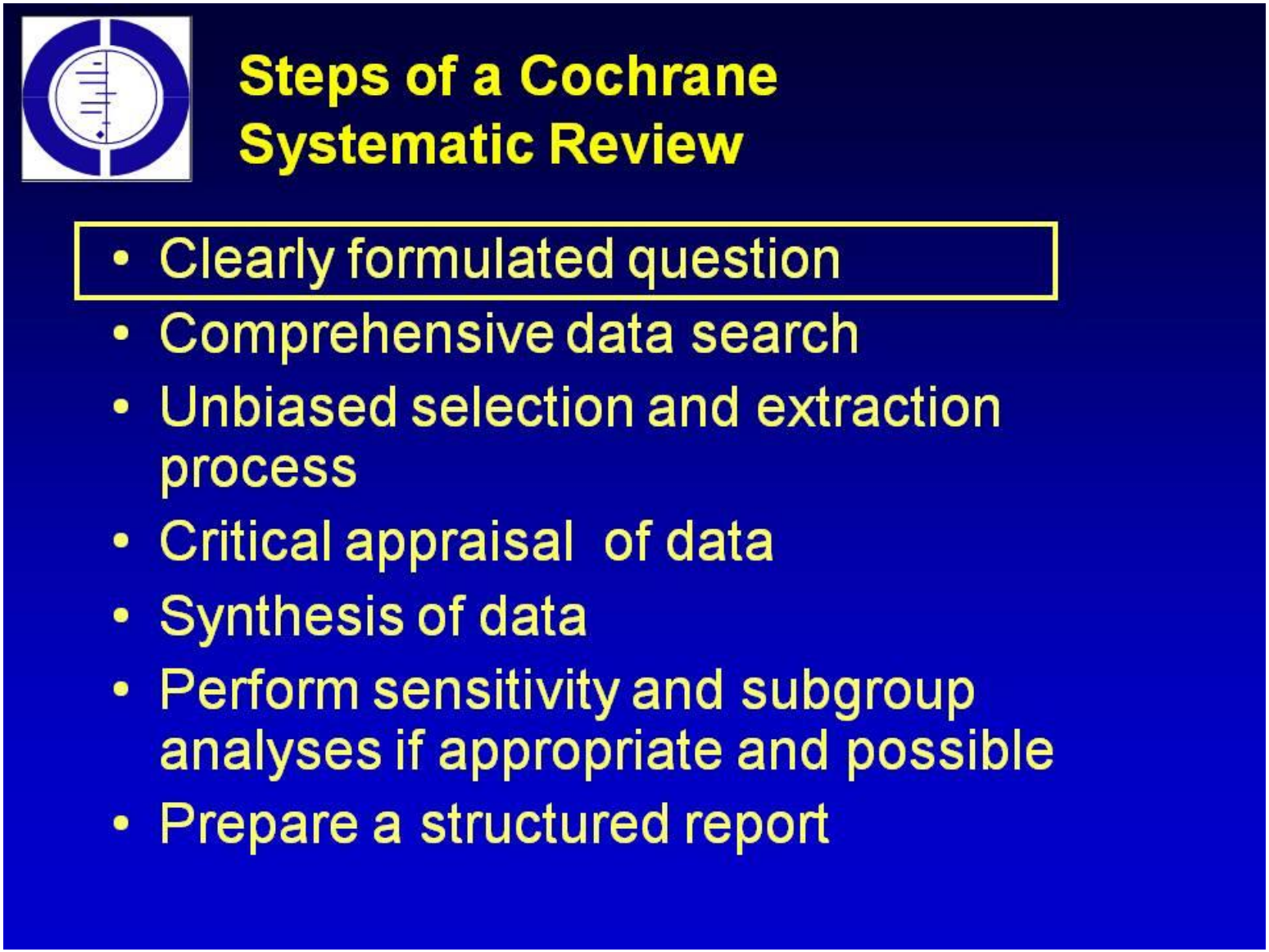
Examiner.com (US) spotlights a new Cochrane review in an article on how smoking bans in public places reduce exposure to secondhand smoke and associated health impacts.

1 of 91 ››

All news

Cochrane Multimedia

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

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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.

Στάδιο 1: η υπόθεση, κατά PRISMA

Participants (συμμετέχοντες)

Interventions (παρεμβάσεις)

Comparators (συγκρίσεις)

Outcomes (εκβάσεις)

Study Design (σχεδιασμός των επιλέξιμων μελετών)

Άσκηση - Παράδειγμα

- Ποιο είναι το PICOS για τη διερεύνηση της υπόθεσης:

«Συσχετίζεται η κατανάλωση ελαιολάδου με τον κίνδυνο εμφάνισης καρκίνου σε ενηλίκους, σύμφωνα με προοπτικές μελέτες παρατήρησης;»*

**[προστατευτικά]*

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.

Άσκηση – Παράδειγμα

- Δομήστε αλγόριθμο αναζήτησης στη βάση PubMed για συστηματική ανασκόπηση με τίτλο:

«Παχυσαρκία σε παιδιά και εφήβους κατά την πανδημία COVID-19: συστηματική ανασκόπηση»

«Παγίδες» κατά την αναζήτηση των δεδομένων

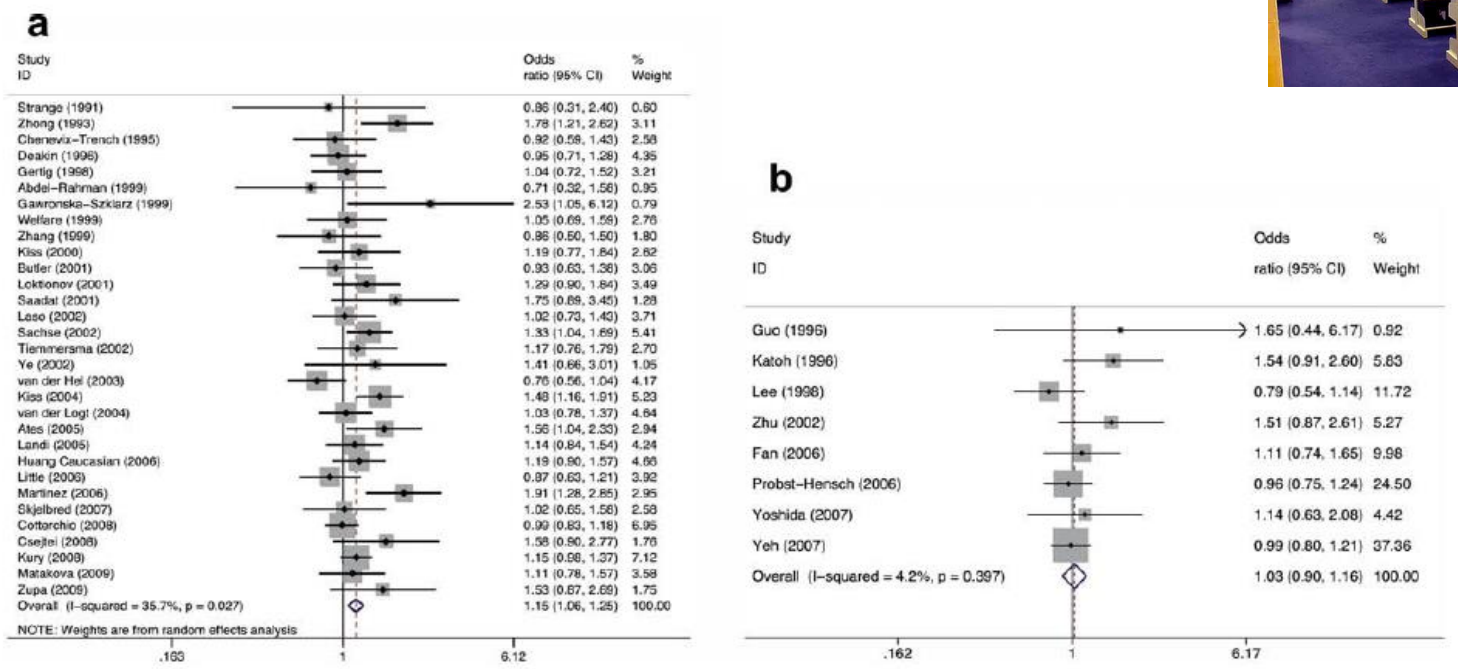

Fig. 2 – Forest plot for the overall association between null GSTM1 genotype and colorectal cancer risk for (a) Caucasian and (b) Chinese subjects. Each study is shown by the point estimate of the Odds Ratio (OR) (the size of the square is proportional to the weight of each study) and 95% confidence 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.

Το πρόβλημα του συστηματικού σφάλματος δημοσίευσης (publication bias)

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

Αντιμετώπιση του publication bias και της “fugitive literature” κατά το δυνατό

- conference indexes, abstracts
- unpublished theses and dissertations
- clinical trial registries, industry

➢Στην πράξη πολύ δύσκολο

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 των μελετών στη συστηματική ανασκόπηση / μετα-ανάλυση (inclusion criteria), βάσει του ***PICOS,*** με περισσότερες λεπτομέρειες (π.χ. έτη αναζήτησης, γλώσσα δημοσίευσης, κατάσταση δημοσίευσης)

•Πληθυσμός

•Παρεμβάσεις (interventions)

•Συγκρίσεις

•Αυστηρός ορισμός του «αποτελέσματος» (outcome)

•Σχεδιασμός μελέτης

➢ Εργασία ερευνητών σε ζεύγη, τυφλοποιημένα ο ένας ως προς τον άλλον - Οι διαφορές λύνονται με συμφωνία (consensus) με τρίτο κριτή ή το σύνολο της ομάδας

Το διάγραμμα ροής (flow chart) της συστηματικής ανασκόπησης

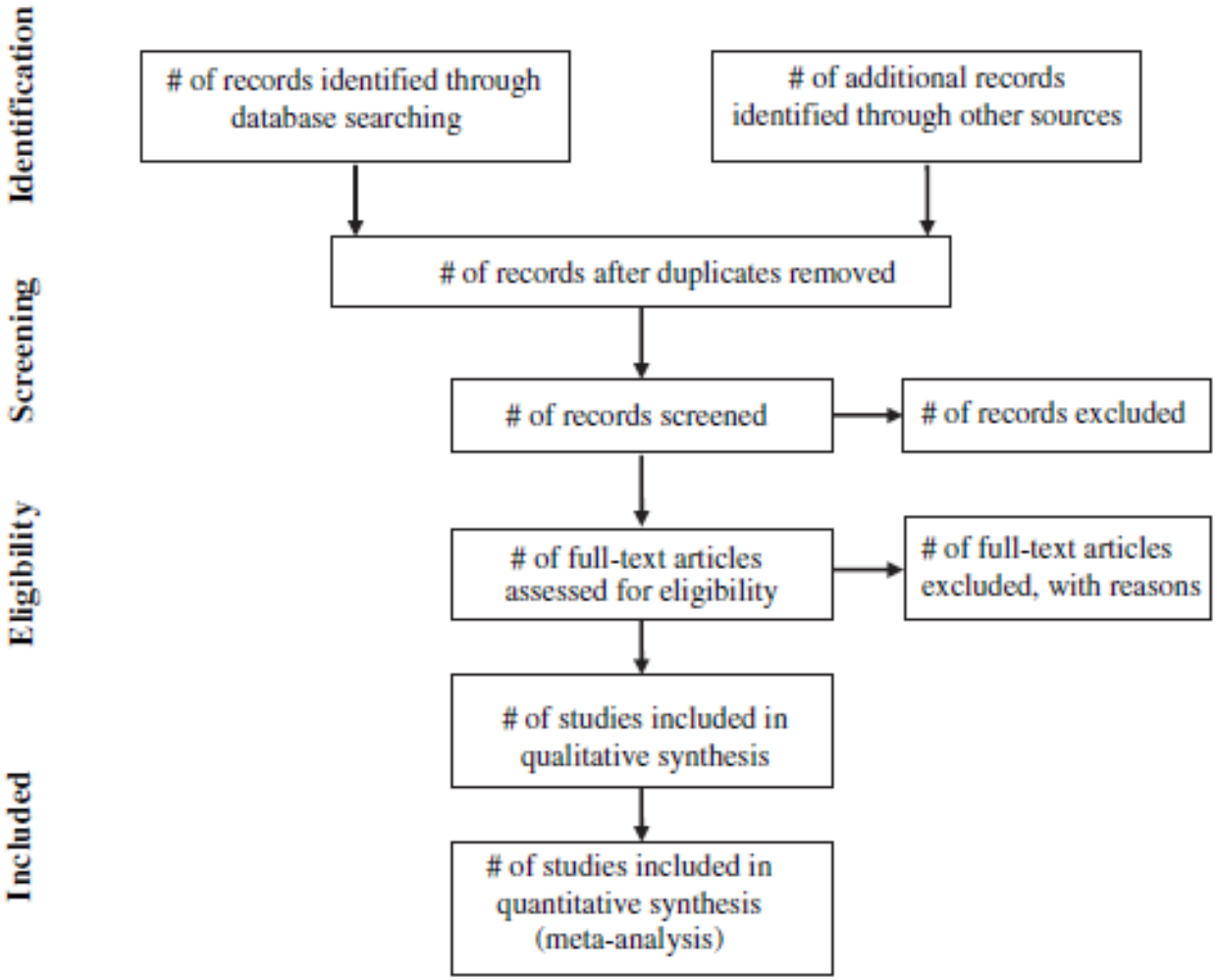

Fig. 1. Flow of information through the different phases of a systematic review.

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

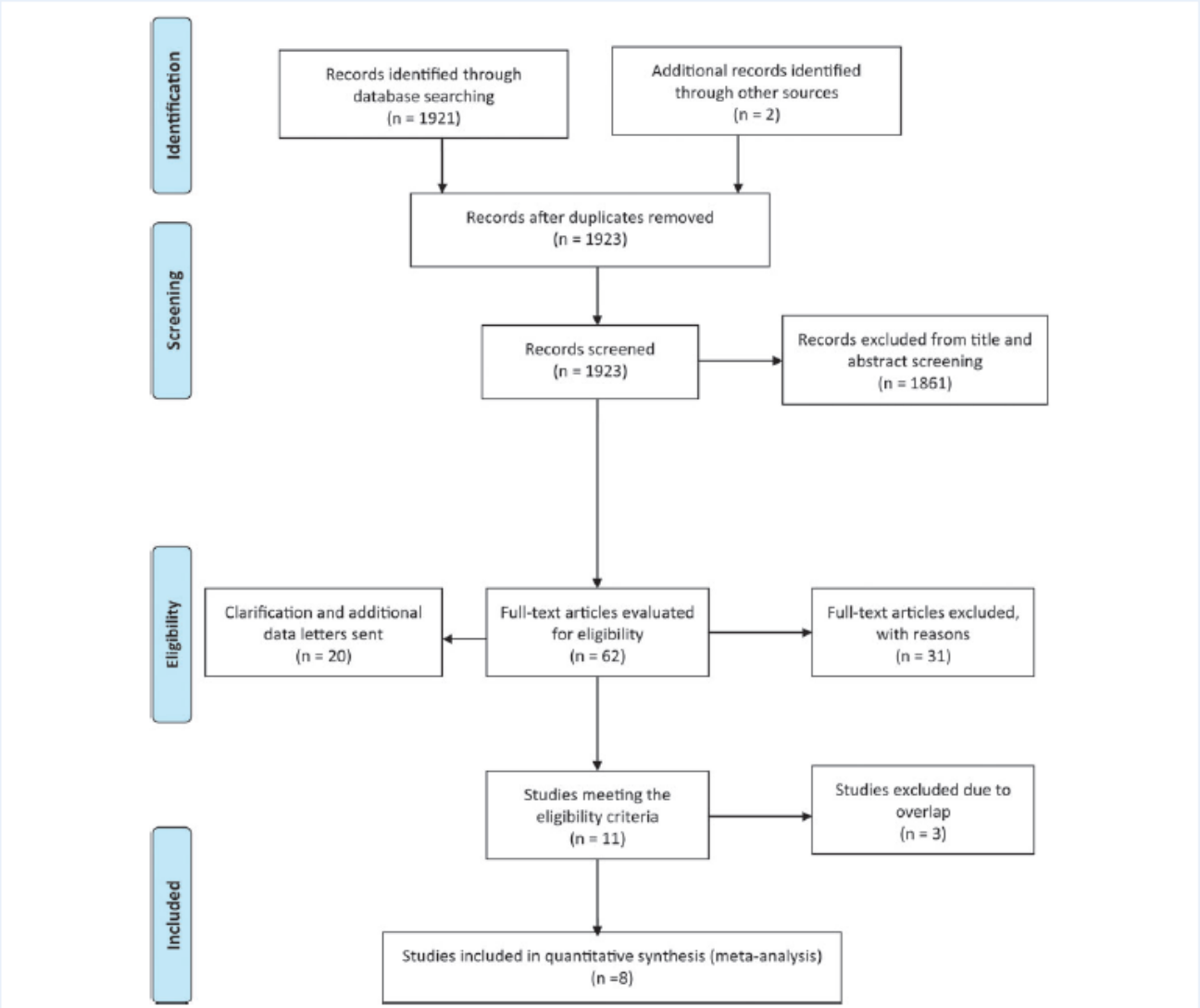

Figure 1 PRISMA flow chart for systematic review of IVF and breast cancer.

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,*]

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

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

Περιγραφή των μελετών

Table I. Characteristics of eligible cohort studies.

Study	Cohort size	Incident cases	Follow-up (years, median or mean)	Study period	Region	Males (%)	Mean age	Age range	Cohort characteristics	Definition/features of myeloma in cohort	Alcoholic beverages studied	Definition of alcohol intake in time	Adjusting factors
Blair (2005)	37 083	95	14.3	1986–2001	Iowa, USA	0.0	61.7	55–69	Iowa Women's Health Study, population-based cohort; subjects were excluded at baseline if they reported cancer other than skin cancer, were premenopausal or were classified as underweight	Incident cases ascertained through linkage to State Health Registry of Iowa, which participates in National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program; coded according to ICD-O-3	Total alcohol	Ever: NR	None
Gapstur (2012)	143 124	337	12.7	1992–2007	21 states in USA	47.7	62.9	50–74	American Cancer Society's Cancer Prevention Study II (CPS-II) Nutrition Cohort; participants residing in states with population-based cancer registries; excluded were participants who were lost to follow-up, reported a personal history of cancer other than non-melanoma skin cancer in 1992, reported a diagnosis of lymphoma on first survey that could not be verified through medical or cancer registry records, or were missing information on alcohol intake in 1992	Beginning in 1997, follow-up questionnaires were sent to cohort members every 2 years to ascertain self-reported, newly diagnosed cancers. Cases were subsequently verified from medical records, linkage with state cancer registries or identified as interval deaths through automated linkage of entire cohort with National Death Index, and these cases were verified through linkage with state cancer registries. InterLymph Pathology Working Group classification was used based on ICD-O-2 and O-3 codes	Total alcohol	Ever: consuming alcohol more than once a month; current: NR; former: NR	Age, sex, education, body mass index, height, physical activity, smoking status, family history of hematopoietic cancer

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.

Περιγραφή των μελετών

Table II. Characteristics of eligible case–control studies.

Study	Cases (*n*)	Controls (*n*)	Study period	Region	Males (%)	Mean age	Age range	Definition/features of cases	Definition of controls	Matching factors	Alcoholic beverages studied	Definition of alcohol consumption in time	Adjusting factors
Boffetta (1989)	282	1128	1982–1986	All 50 of United States, District of Columbia and Puerto Rico	55.7	NR	30+	Incident or prevalent American Cancer Society (ACS) Cancer Prevention Study II cases; subjects who died, with multiple myeloma (coded according to ICD-9) reported on death certificate as either underlying or contributing cause of death	Randomly selected ACS Cancer Prevention Study II subjects	Sex, ACS division, year of birth, ethnic group	Total alcohol	Ever: ever regular drinker	Age, sex, ethnic group, ACS division, education, history of diabetes, X-ray treatment, pesticide and herbicide exposure, farming
Brown (1992)	173	452	1981–1984	Iowa, USA	100.0	NR	30+	Newly diagnosed, pathologic material and laboratory reports reviewed by expert pathologist; not included in analyses were cases of myeloma for whom adequate information for diagnostic confirmation was unavailable	Population-based stratified sample of white men without lymphatic or hematopoietic cancer: random digit dialing for living controls under age 65 and Medicare records provided by Health Care Financing Administration for living controls aged 65 and over; in addition, state death certificate files were used to select deceased controls	5-year age group, vital status at time of interview, state of residence	Total, beer or wine, hard liquor, other combinations	Ever: ever consumed any alcoholic beverage on at least a weekly basis	Age, state, daily use of tobacco

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.

Περιγραφή των μελετών

Table 1 – Characteristics of the eligible studies.

Study	Country	Ethnicity	Polymorphisms studied	Source and ascertainment of cases	Source of controls	Method	Tumour Stage	Prevalence of risk factors in cases	Prevalence of risk factors in controls	Factor taken into account during OR adjustment
Strange[55]	UK	Caucasian	GSTM1	Individuals with histologically confirmed adenocarcinomas who attended the Surgery Clinic	Post-mortem individuals who died primarily from cardiovascular disease and had no evidence of cancer	Starch gel electrophoresis	N/A	N/A	N/A	N/A
Zhong[56]	UK	Caucasian	GSTM1	Individuals with histologically confirmed diagnosis from one hospital	Randomly selected from two hospitals and a group of volunteers	PCR	N/A	N/A	N/A	N/A
Chenevix-Trench[93]	Australia	Caucasian	GSTM1, GSTT1	Individuals with histologically confirmed adenocarcinomas	Unselected and geriatric healthy individuals without cancer or family history of cancer	PCR	N/A	N/A	N/A	N/A
Dealin[92]	UK	Caucasian	GSTM1, GSTT1	Individuals who attended one hospital (ANC)	Unrelated healthy individuals from the same	PCR	N/A	N/A	N/A	N/A

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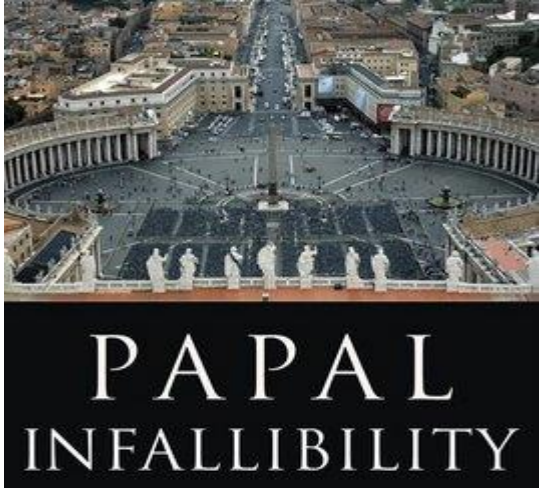
available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

GSTM1, GSTT1, GSTP1, GSTA1 and colorectal cancer risk: A comprehensive meta-analysis

Konstantinos P. Economopoulos [a,b,*], *Theodoros N. Sergentanis* [a,b]



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

Critical appraisal of methodological aspects in the recent meta-analysis evaluating the association between cyclin D1 G870A polymorphism and risk of breast cancer.
Sergentanis TN, **Sarafis** P.
J Cell Biochem. 2020 Jun;121(5-6):3029-3030. doi: 10.1002/jcb.29694. Epub 2020 Feb 25. No abstract available.
PMID: 32100336
Similar articles

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 συστηματικών σφαλμάτων για τις επιλέξιμες μελέτες

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

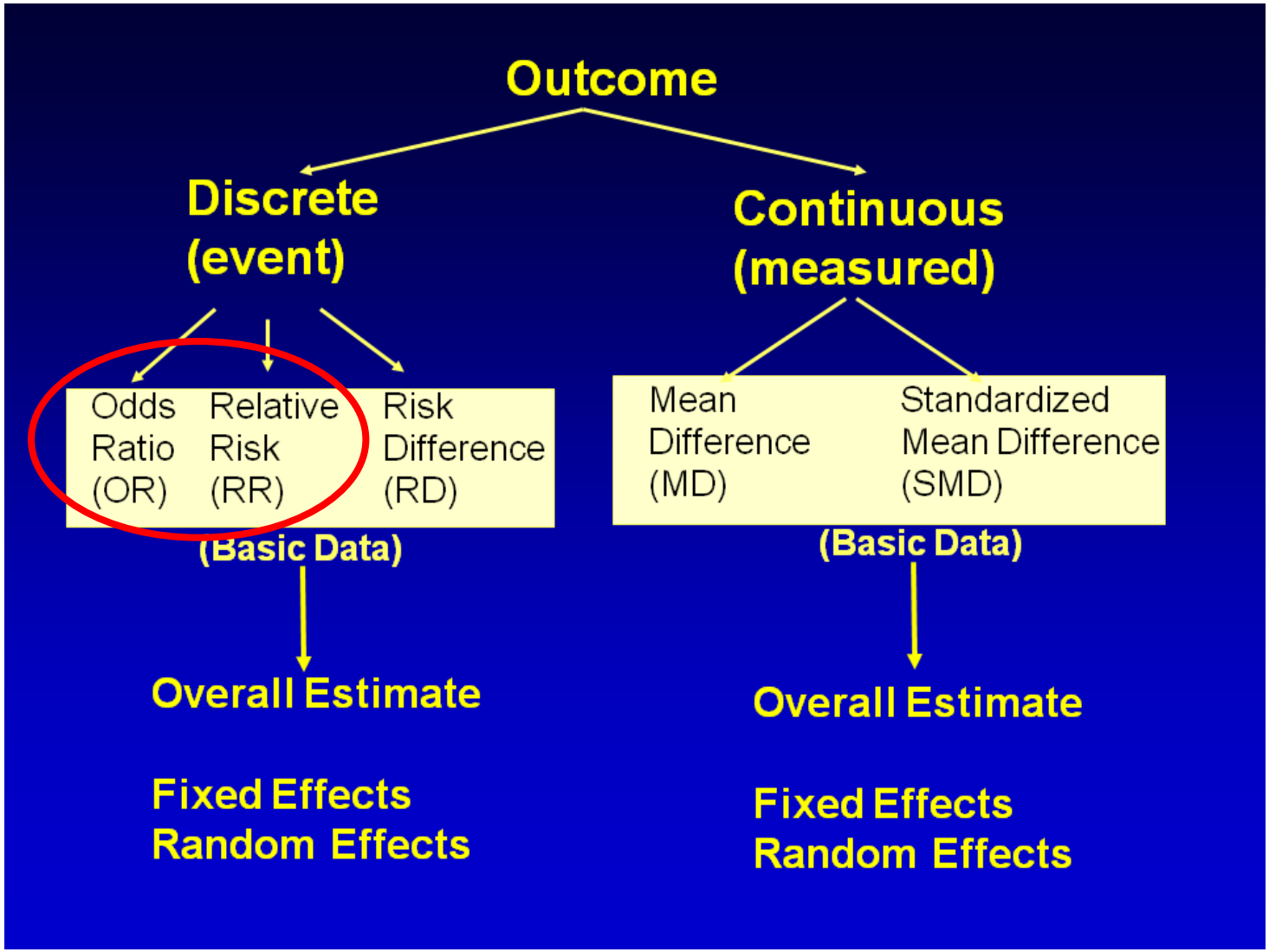
CTS: California Teachers Study

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

Στάδιο 5: η στατιστική σύνθεση των επιμέρους αποτελεσμάτων



Αναγκαία η αναζήτηση της ετερογένειας

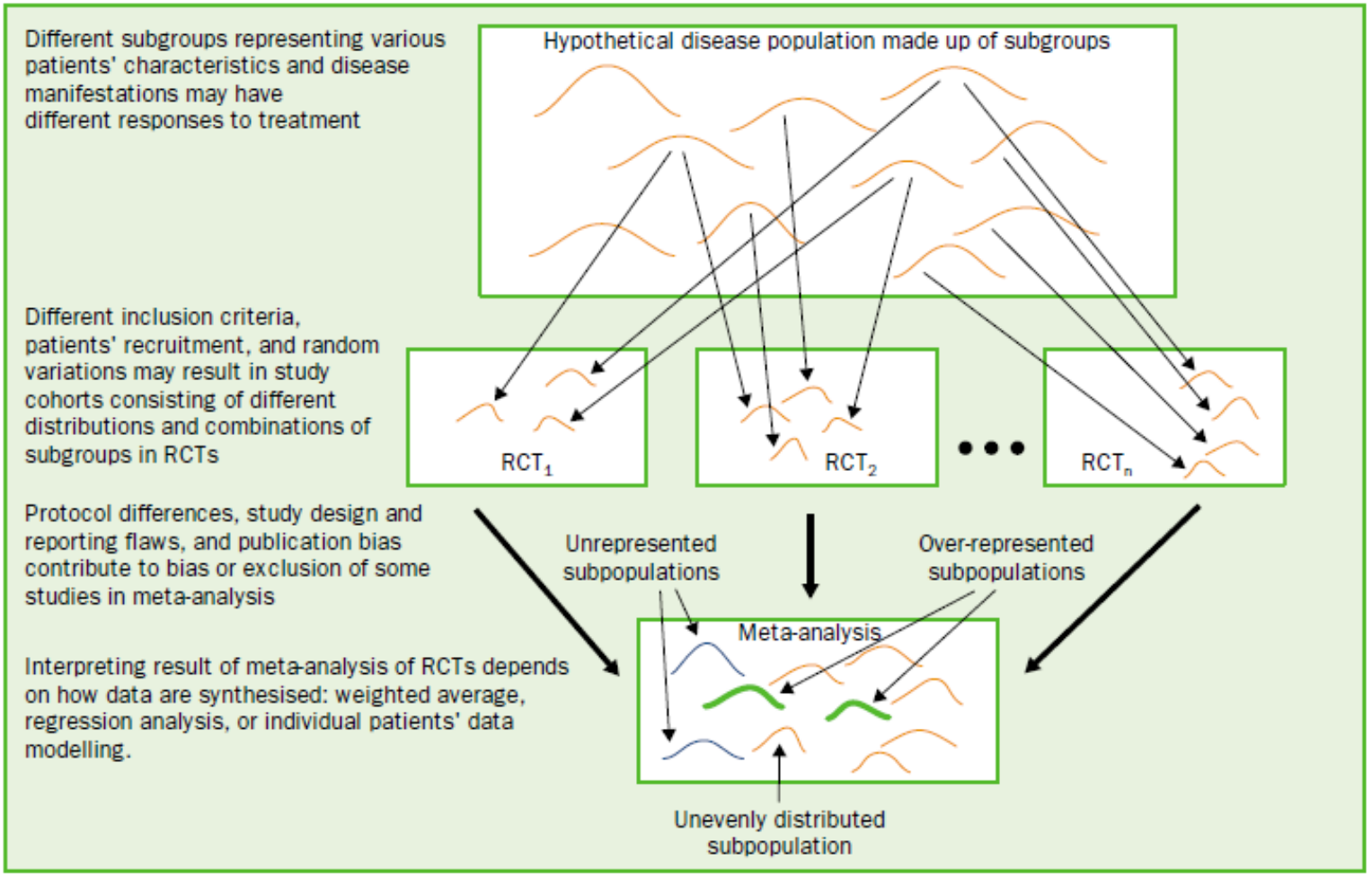


Figure 1: **Diversity in populations of patients in clinical trials and meta-analyses**

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

Types of heterogeneity

- **Statistical heterogeneity**
  - observed intervention effects being more different from each other than one would expect due to **random error** (chance) alone
- **Methodological heterogeneity (methodological diversity)**
  - variability in **study design** and risk of bias (e.g. quality of allocation concealment)
- **Clinical heterogeneity (clinical diversity)**
  - variability in participants, interventions and outcomes studied

Πηγές μεθοδολογικής και κλινικής 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)

Στατιστικές δοκιμασίες για την αξιολόγηση της ετερογένειας

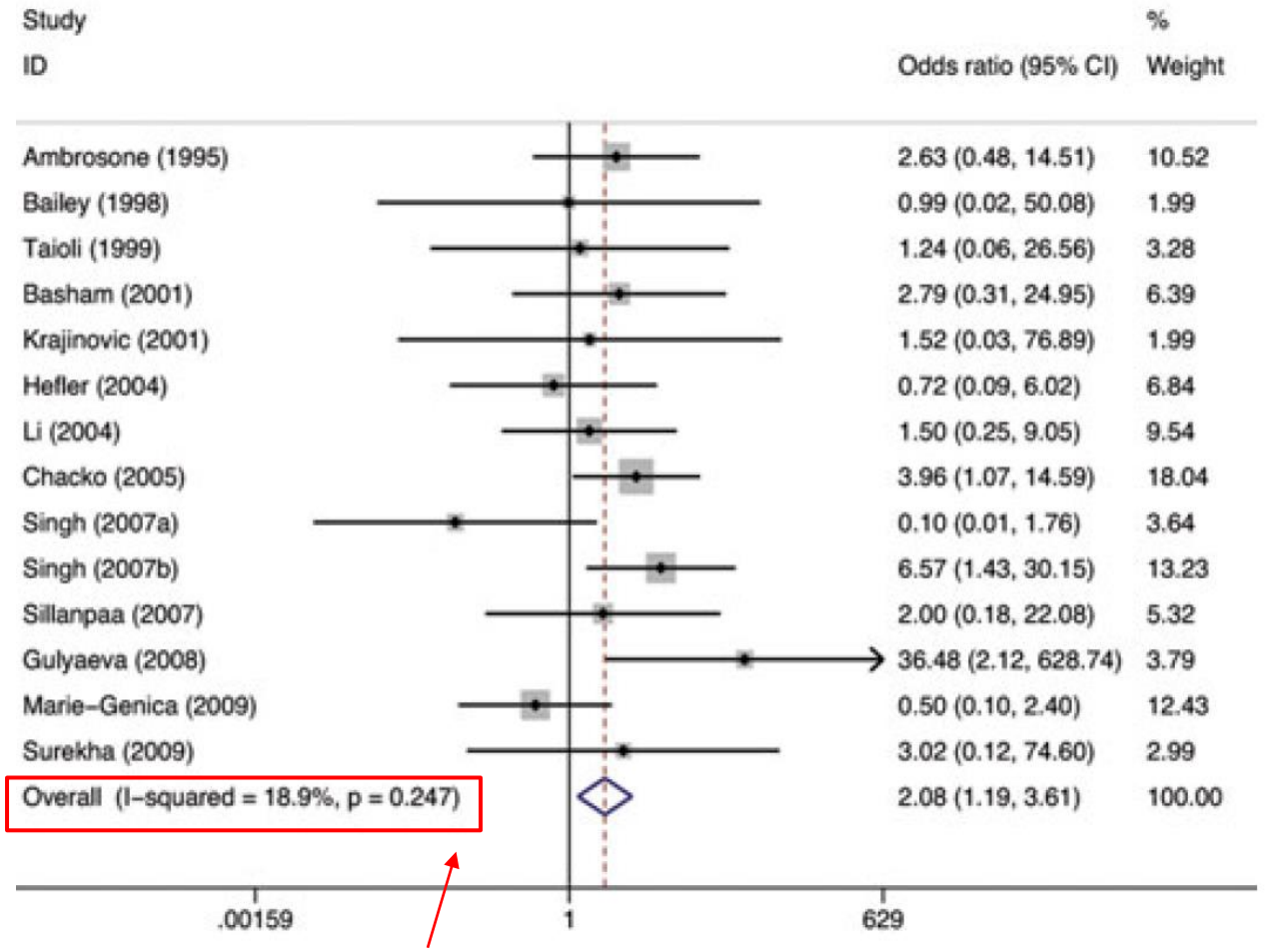
1. Mantel-Haenszel Q (αξιολογείται στο 0.05)

2. I^2 for inconsistency (εκφράζεται ως %)
   - Εμπειρικά >50%: σημαντική ετερογένεια

Thresholds for the interpretation of I^2 can be misleading, since the importance of inconsistency depends on several factors. A rough guide to interpretation is as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;
- 75% to 100%: considerable heterogeneity*.

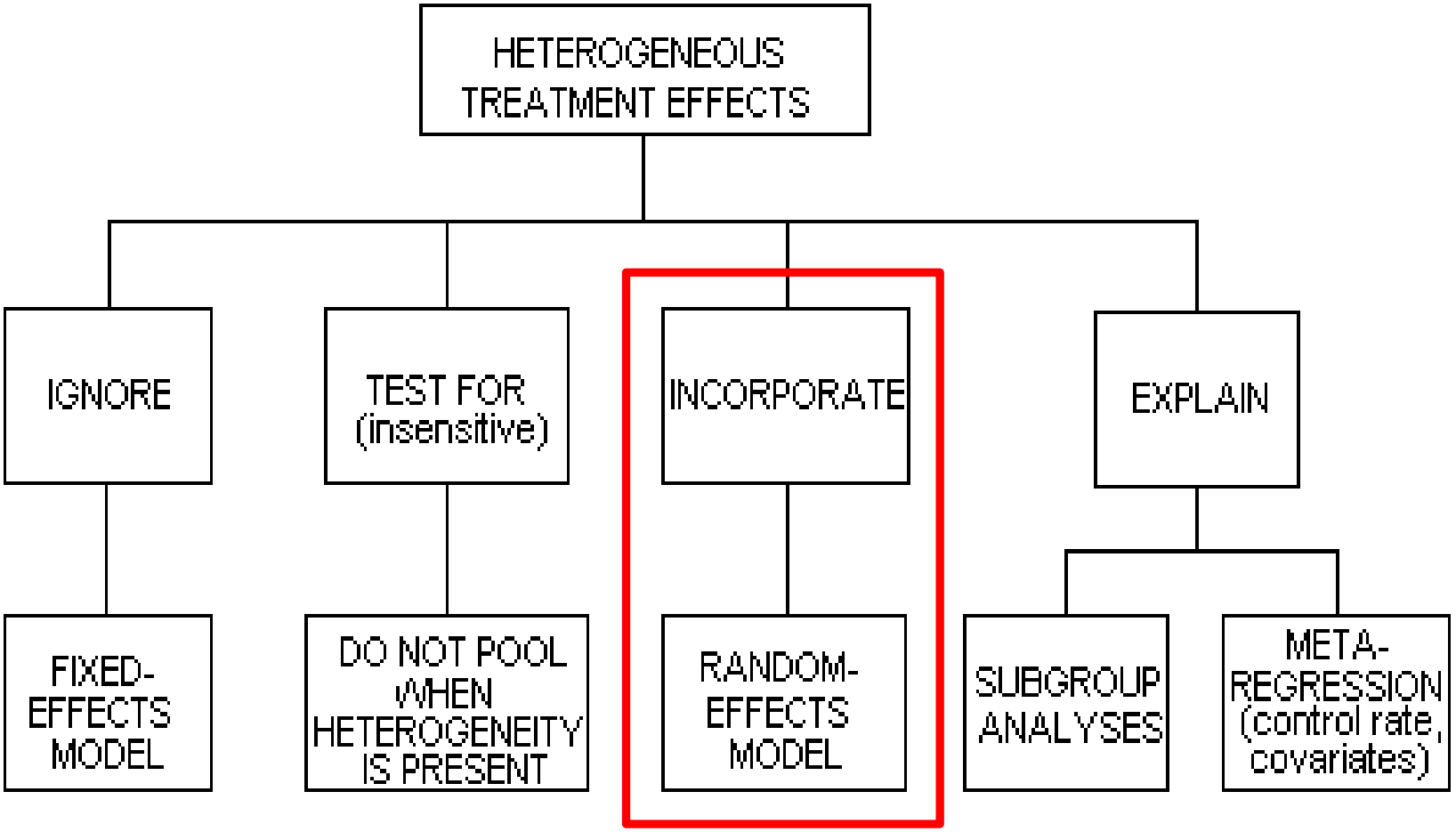
Ο «πυρήνας» της μετα-ανάλυσης: Διάγραμμα δάσους (forest plot)



Αξιολόγηση της ετερογένειας

Sergentanis TN, Economopoulos KP.
Four polymorphisms in cytochrome P450 1A1 (CYP1A1) gene and breast cancer risk: a meta-analysis.
Breast Cancer Res Treat 2010;122(2):459-69.

Ετερογένεια: κομβική στην ανάλυση

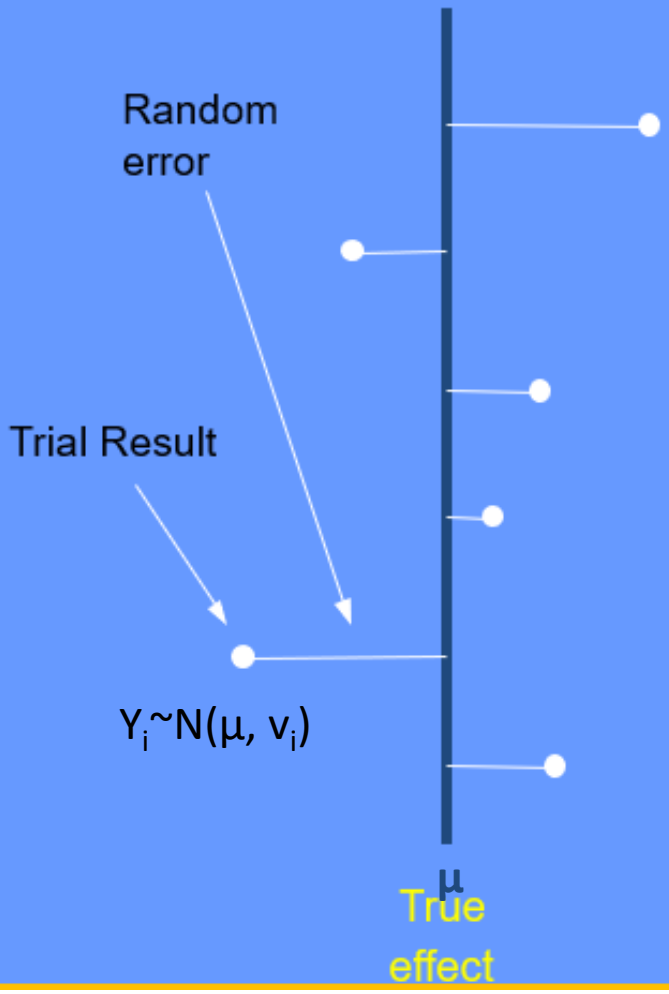


Πιθανά μοντέλα μετα-αναλύσεων
Fixed-Effects Model

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

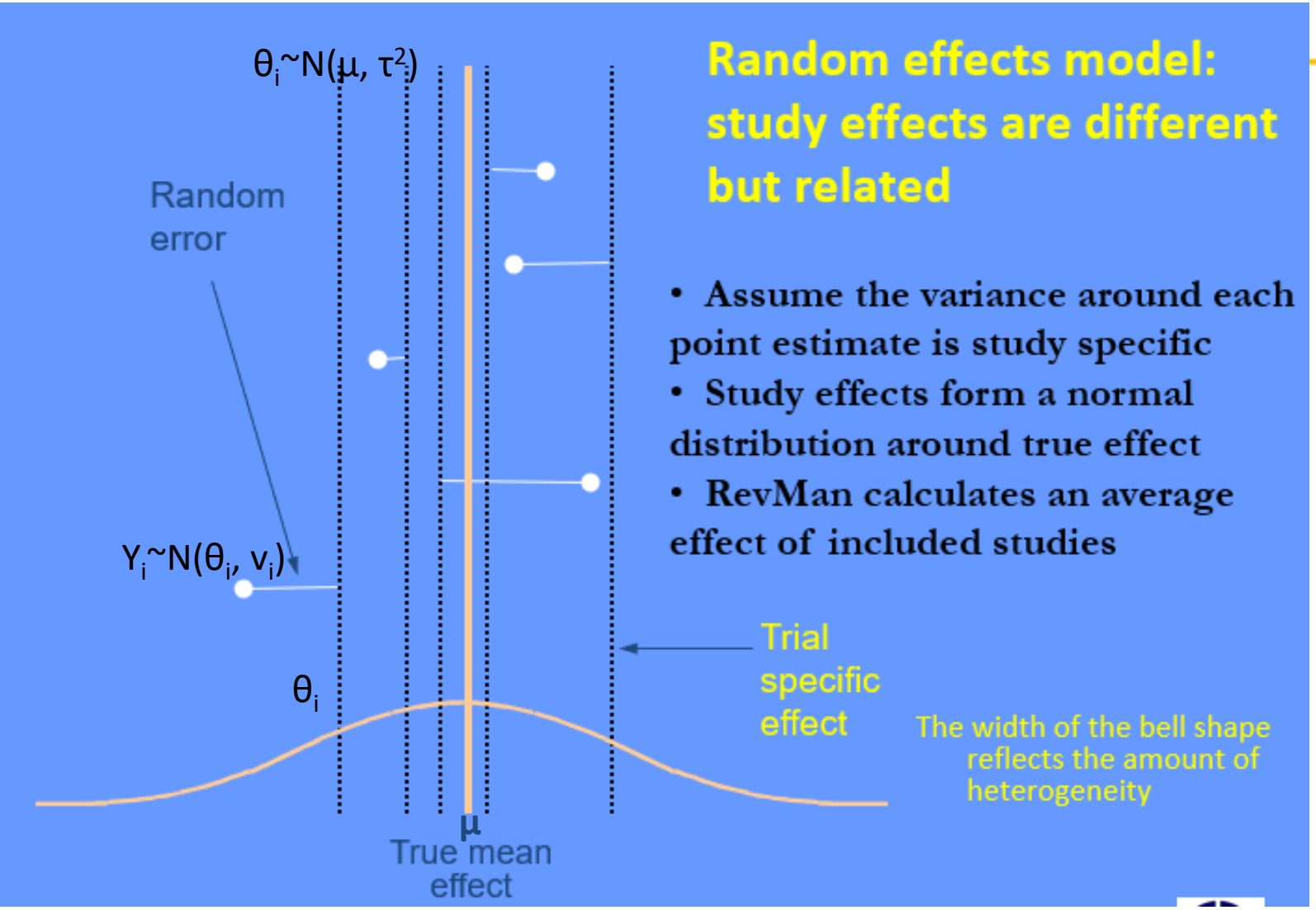
Πιθανά μοντέλα μετα-αναλύσεων
Random-Effects Model

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



Fixed effect model –

- Assumes that the estimate of treatment effect in each study included in a meta-analysis is the same
- Assumes any variation between studies would disappear if all the studies were infinitely large



- For any particular set of studies in which heterogeneity is present, a confidence interval around the random-effects pooled estimate is **wider** than a confidence interval around a fixed-effect pooled estimate.
- RevMan implements a version of random-effects meta-analysis that is described by DerSimonian and Laird (1986).

Random-Effects Model (DerSimonian-Laird approach)

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

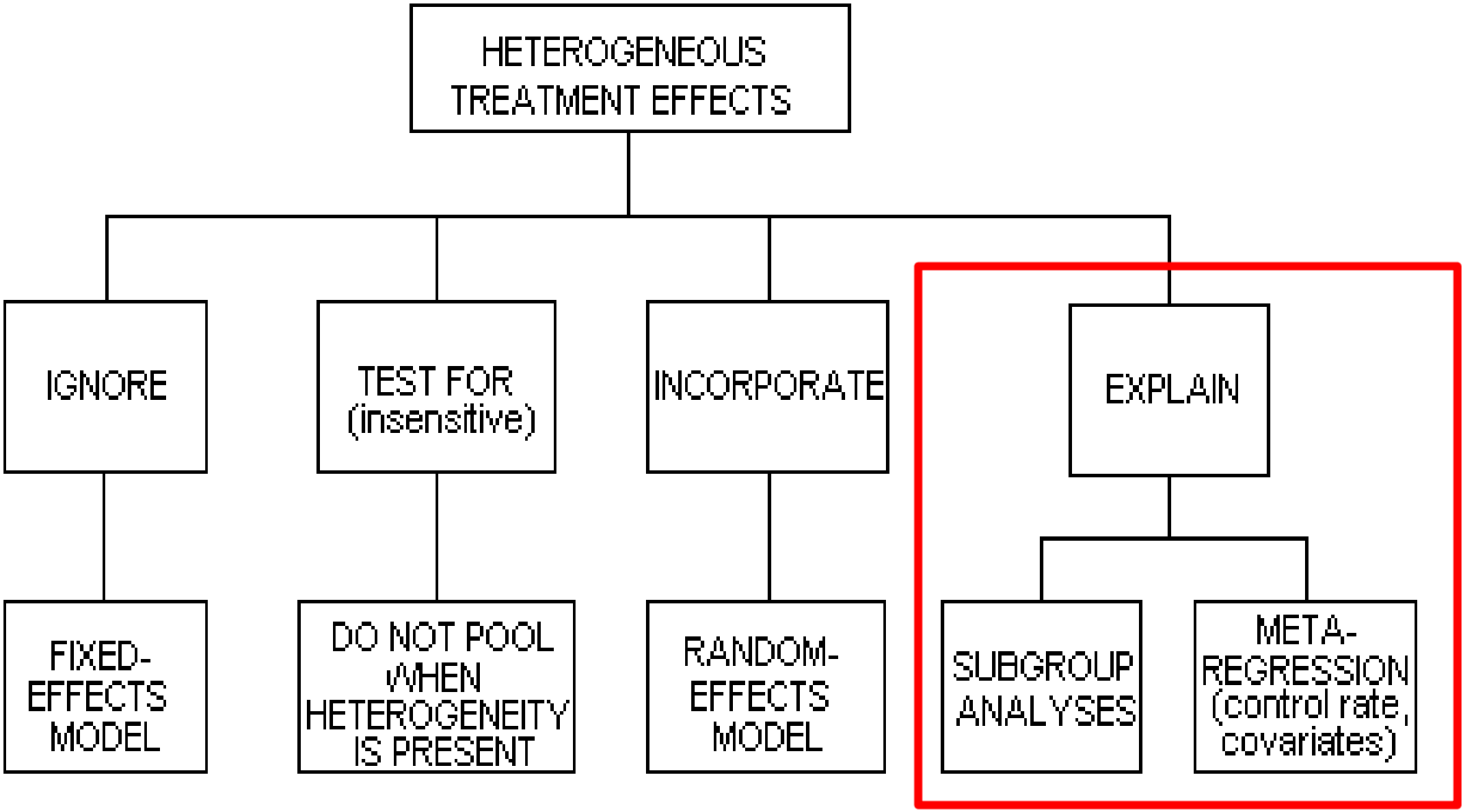
- **Λαμβάνουμε**
  - **διαφορετικό pooled estimate**
  - **ευρύτερα διαστήματα εμπιστοσύνης (CI)**
  - **μεγαλύτερο *p*-value**

  - **Άρα «πιο συντηρητικά» αποτελέσματα**

Αναγκαιότητα για επεξήγηση της ετερογένειας

- Αναλύσεις υποομάδων (subgroup analyses)
- Μετα-παλινδρόμηση

} ώστε να «εξηγηθεί» η ετερογένεια



Αναλύσεις υποομάδων

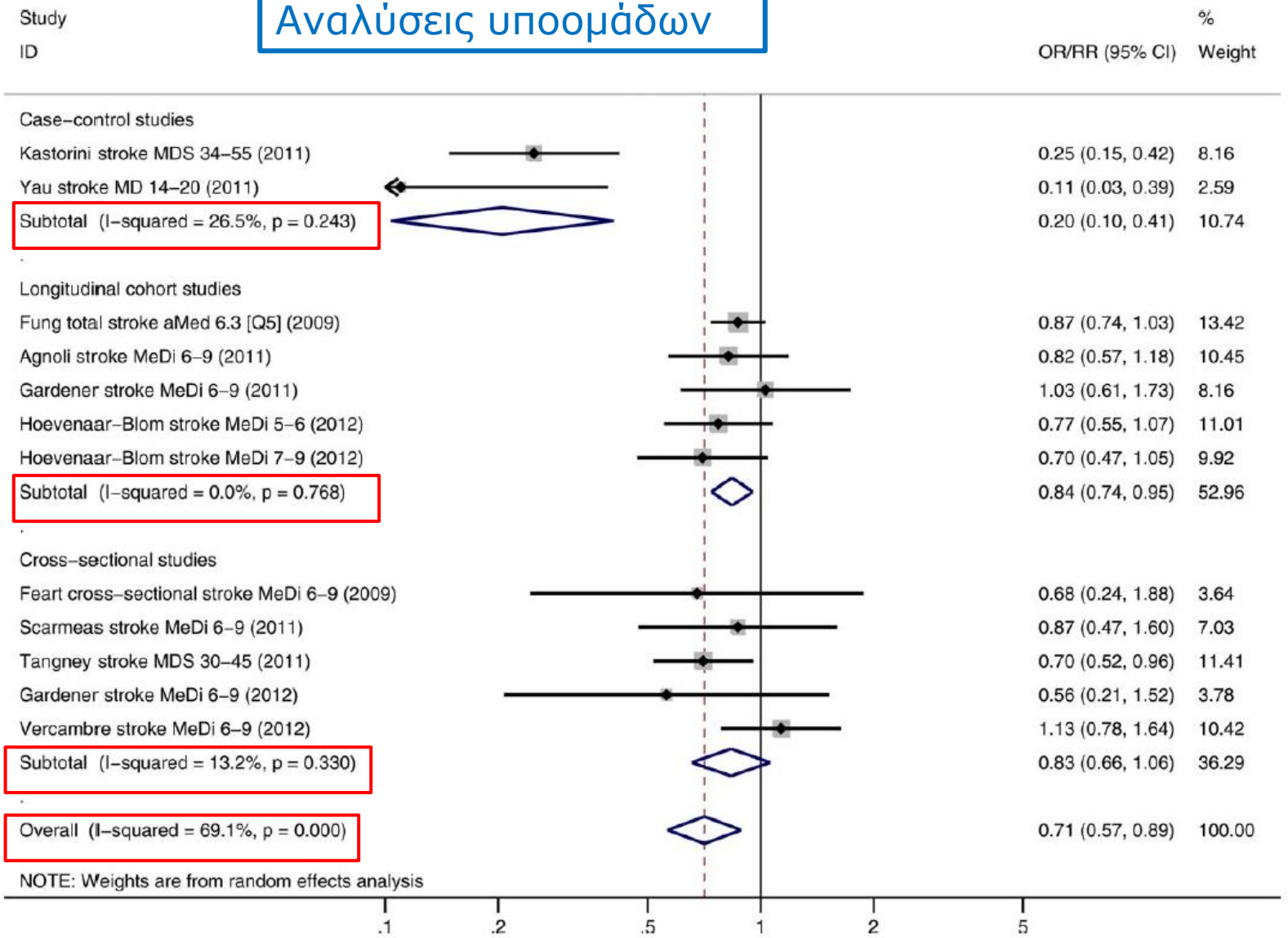
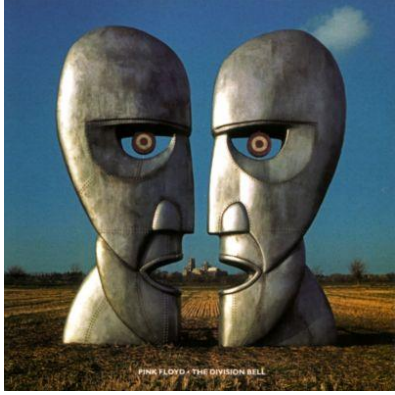


FIGURE 1: Forest plot describing the association between high adherence to Mediterranean diet and risk for stroke. Apart from the overall analysis, the subanalyses on case–control (upper rows), longitudinal cohort (middle rows), and cross-sectional studies (lower rows) are presented.

Στη συγκεκριμένη μετα-ανάλυση, ο σχεδιασμός αποτελεί αίτιο ετερογένειας;

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.

Αναλύσεις υποομάδων



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.

Μετα-παλινδρόμηση (meta-regression)

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

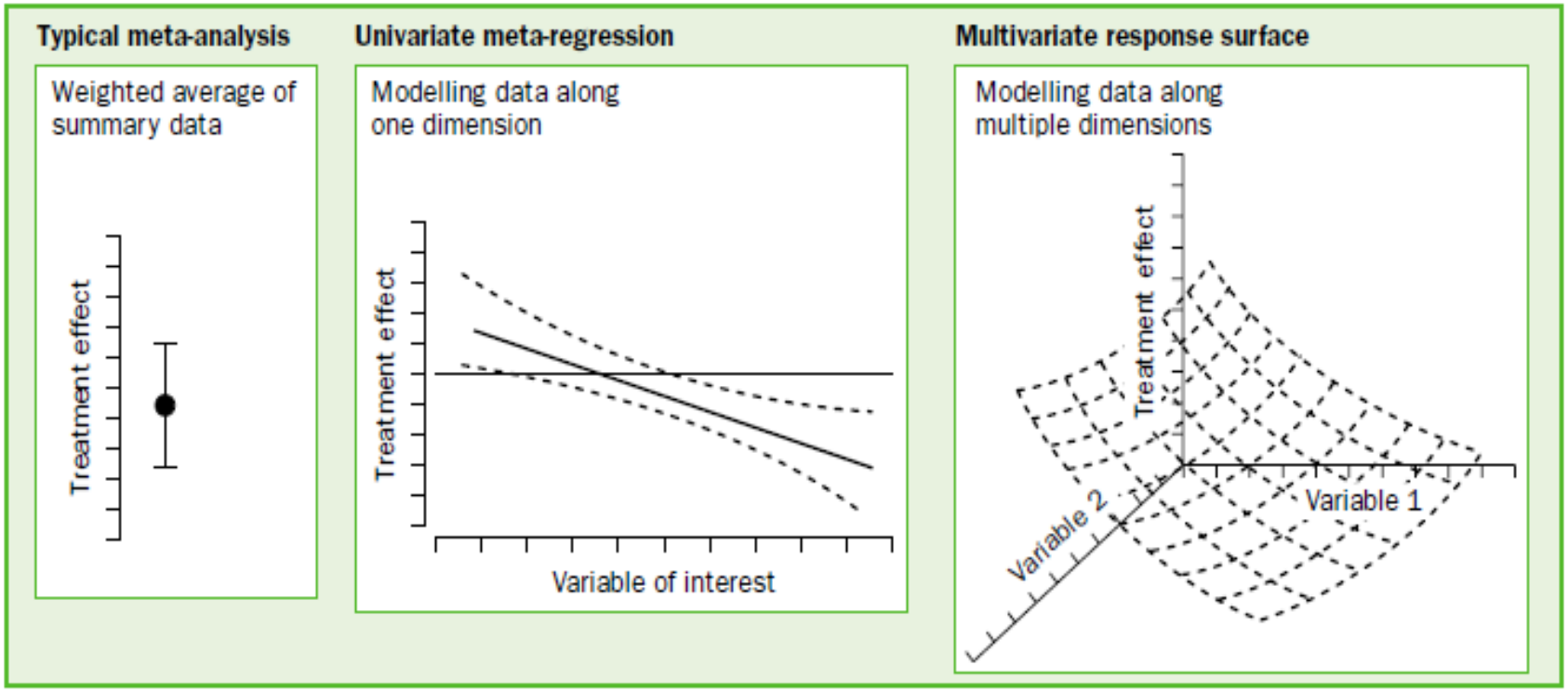
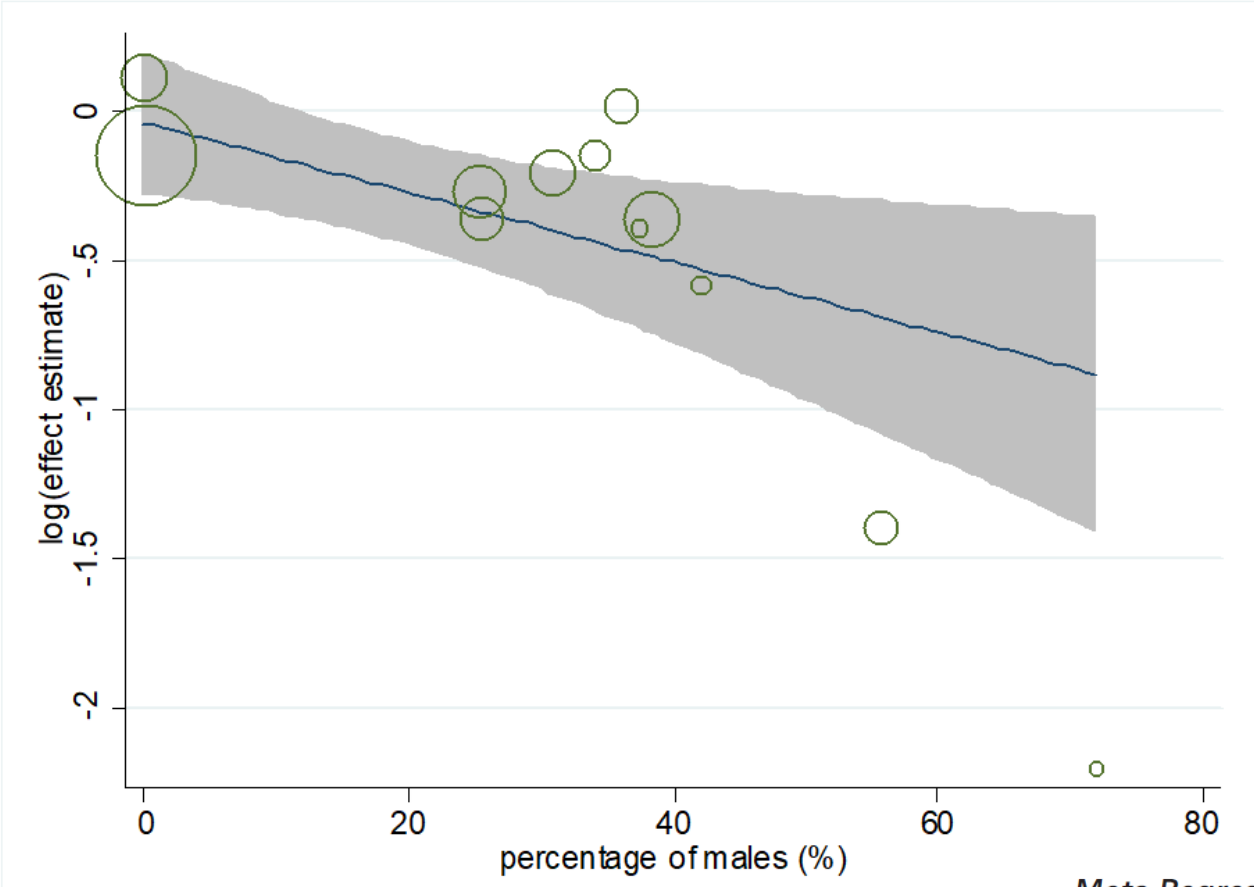


Figure 2: **Summing-up evidence in single and multiple dimensions**

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

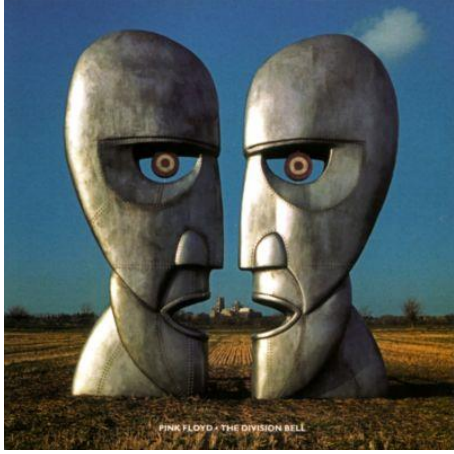


Meta-Regression Analysis

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).

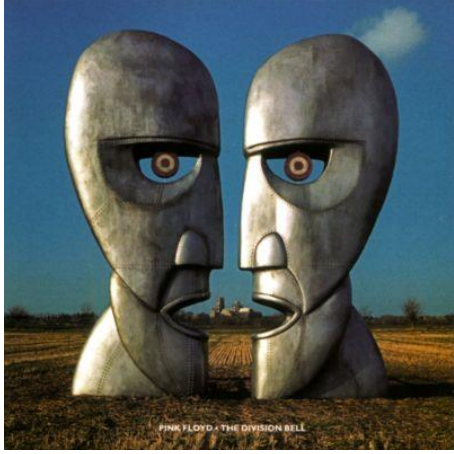
Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. Ann Neurol 2013;74(4):580-91.

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-

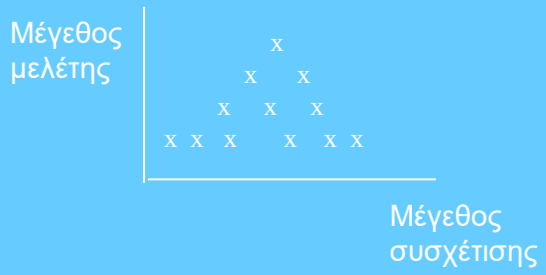
Αναλύσεις υποομάδων vs. αναλύσεις ευαισθησίας

- Ορισμένες φορές δημιουργείται σύγχυση ανάμεσα στις αναλύσεις υποομάδων και τις αναλύσεις ευαισθησίας. Παρόλο που οι αναλύσεις ευαισθησίας αφορούν στον περιορισμό της ανάλυσης σε υποσύνολο των μελετών, οι δυο μέθοδοι διαφέρουν.

Αναλύσεις υποομάδων	Sensitivity analyses
Εκτιμήσεις παρέχονται **για κάθε υποομάδα**	• **Δεν** πραγματοποιείται εκτίμηση για την/τις μελέτες που **απομακρύνεται/νονται από την ανάλυση.**
Στατιστικές συγκρίσεις μπορούν να γίνουν ανάμεσα στις υποομάδες.	• **Έμμεσες** συγκρίσεις/συμπεράσματα λαμβάνουν χώρα.

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)

- Αδρά: Παριστά το effect estimate (π.χ. OR) σε σχέση με το μέγεθος της μελέτης
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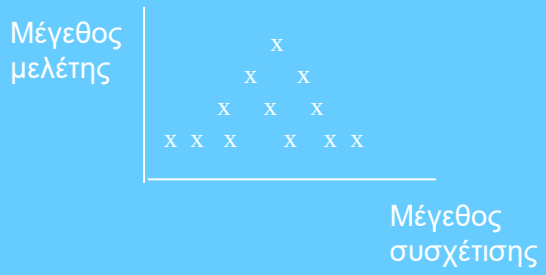


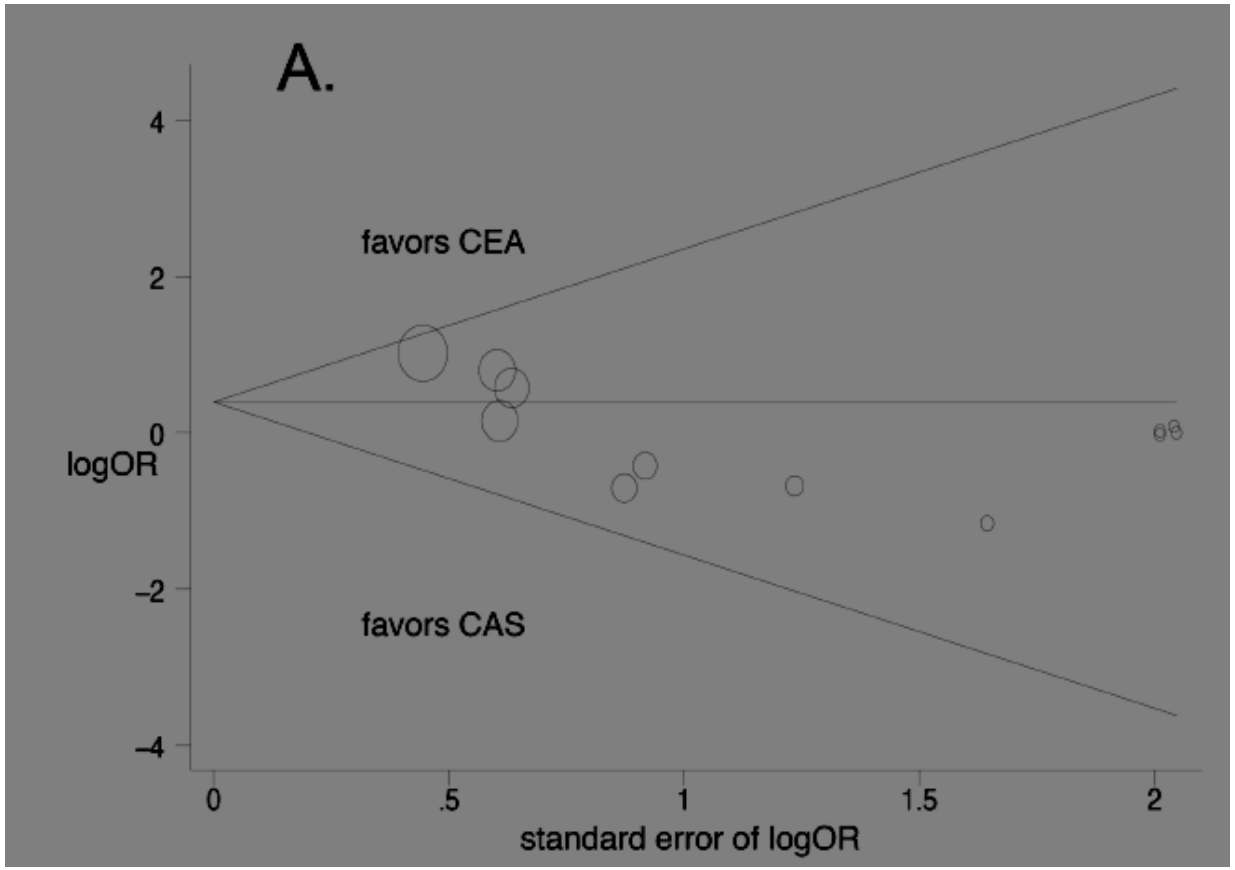
- Επί σφάλματος: ασυμμετρία

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

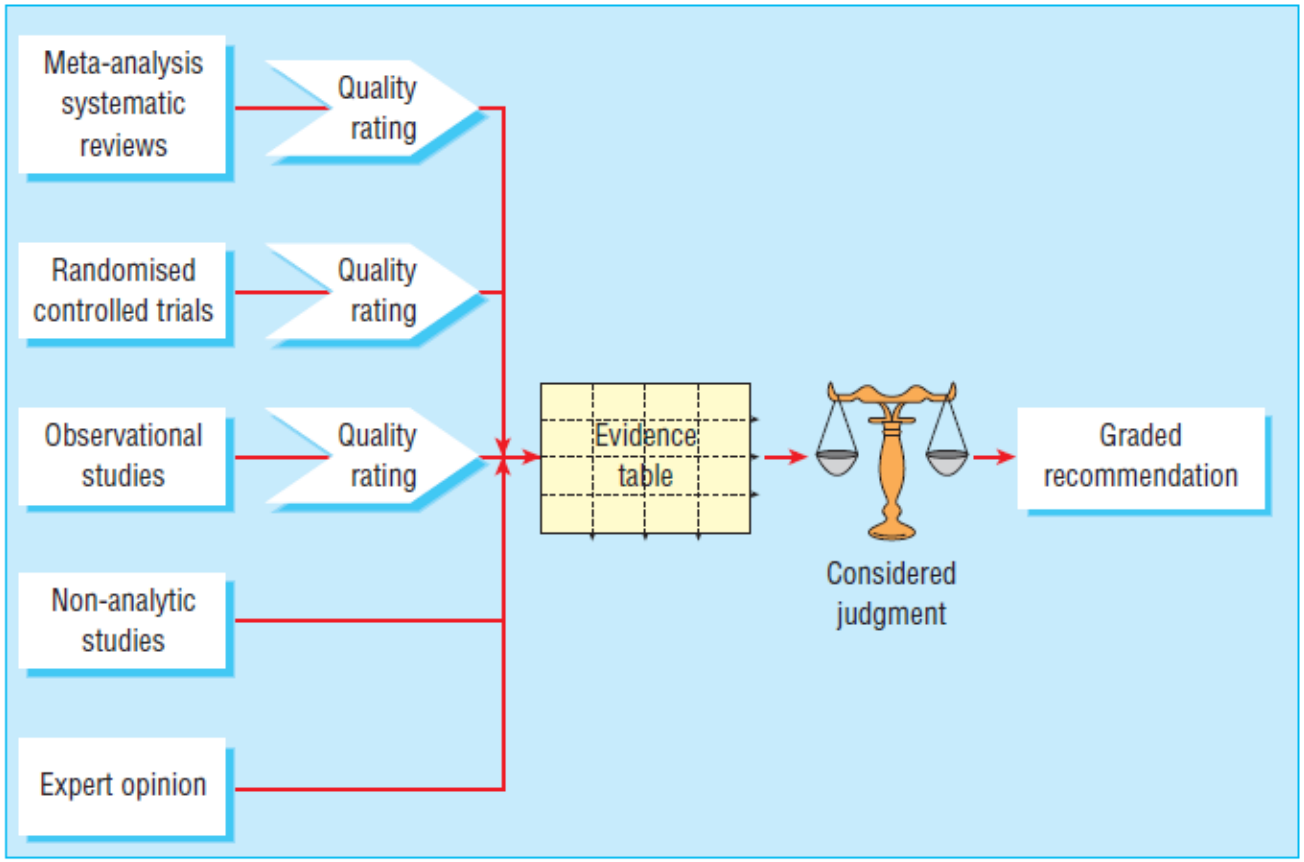
Alessandro Liberati[1,2,*], Douglas G. Altman[3], Jennifer Tetzlaff[4], Cynthia Mulrow[5], Peter C. Gøtzsche[6], John P.A. Ioannidis[7], Mike Clarke[8,9], P.J. Devereaux[10], Jos Kleijnen[11,12], David Moher[4,13]

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.

Table 1
Checklist of items to include when reporting a systematic review (with or without meta-analysis).

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Συζήτηση και διασύνδεση της μετα-ανάλυσης βάσει της λίστας PRISMA

Section/Topic	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		

METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
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Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
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Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
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Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
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Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

The PRISMA 2020 statement: an updated guideline for reporting systematic reviews

Matthew J Page,[1] Joanne E McKenzie,[1] Patrick M Bossuyt,[2] Isabelle Boutron,[3] Tammy C Hoffmann,[4] Cynthia D Mulrow,[5] Larissa Shamseer,[6] Jennifer M Tetzlaff,[7] Elie A Akl,[8] Sue E Brennan,[1] Roger Chou,[9] Julie Glanville,[10] Jeremy M Grimshaw,[11] Asbjørn Hróbjartsson,[12] Manoj M Lalu,[13] Tianjing Li,[14] Elizabeth W Loder,[15] Evan Mayo-Wilson,[16] Steve McDonald,[1] Luke A McGuinness,[17] Lesley A Stewart,[18] James Thomas,[19] Andrea C Tricco,[20] Vivian A Welch,[21] Penny Whiting,[17] David Moher[22]

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PRISMA, 2020

Box 2: Noteworthy changes to the PRISMA 2009 statement

- Inclusion of the abstract reporting checklist within PRISMA 2020 (see item #2 and table 2).
- Movement of the 'Protocol and registration' item from the start of the Methods section of the checklist to a new Other section, with addition of a sub-item recommending authors describe amendments to information provided at registration or in the protocol (see item #24a-24c).
- Modification of the 'Search' item to recommend authors present full search strategies for *all* databases, registers and websites searched, not just at least one database (see item #7).
- Modification of the 'Study selection' item in the Methods section to emphasise the reporting of how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process (see item #8).
- Addition of a sub-item to the 'Data items' item recommending authors report how outcomes were defined, which results were sought, and methods for selecting a subset of results from included studies (see item #10a).
- Splitting of the 'Synthesis of results' item in the Methods section into six sub-items recommending authors describe: the processes used to decide which studies were eligible for each synthesis; any methods required to prepare the data for synthesis; any methods used to tabulate or visually display results of individual studies and syntheses; any methods used to synthesise results; any methods used to explore possible causes of heterogeneity among study results (such as subgroup analysis, meta-regression); and any sensitivity analyses used to assess robustness of the synthesised results (see item #13a-13f).
- Addition of a sub-item to the 'Study selection' item in the Results section recommending authors cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded (see item #16b).
- Splitting of the 'Synthesis of results' item in the Results section into four sub-items recommending authors: briefly summarise the characteristics and risk of bias among studies contributing to the synthesis; present results of all statistical syntheses conducted; present results of any investigations of possible causes of heterogeneity among study results; and present results of any sensitivity analyses (see item #20a-20d).
- Addition of new items recommending authors report methods for and results of an assessment of certainty (or confidence) in the body of evidence for an outcome (see items #15 and #22).
- Addition of a new item recommending authors declare any competing interests (see item #26).
- Addition of a new item recommending authors indicate whether data, analytic code and other materials used in the review are publicly available and if so, where they can be found (see item #27).

PRISMA, 2020

Table 2 | PRISMA 2020 for Abstracts checklist*

Section and topic	Item #	Checklist item
Title		
Title	1	Identify the report as a systematic review.
Background		
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.
Methods		
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.
Synthesis of results	6	Specify the methods used to present and synthesise results.
Results		
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).
Discussion		
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).
Interpretation	10	Provide a general interpretation of the results and important implications.
Other		
Funding	11	Specify the primary source of funding for the review.
Registration	12	Provide the register name and registration number.

*This abstract checklist retains the same items as those included in the PRISMA for Abstracts statement published in 2013,[54] but has been revised to make the wording consistent with the PRISMA 2020 statement and includes a new item recommending authors specify the methods used to present and synthesise results (item #6).

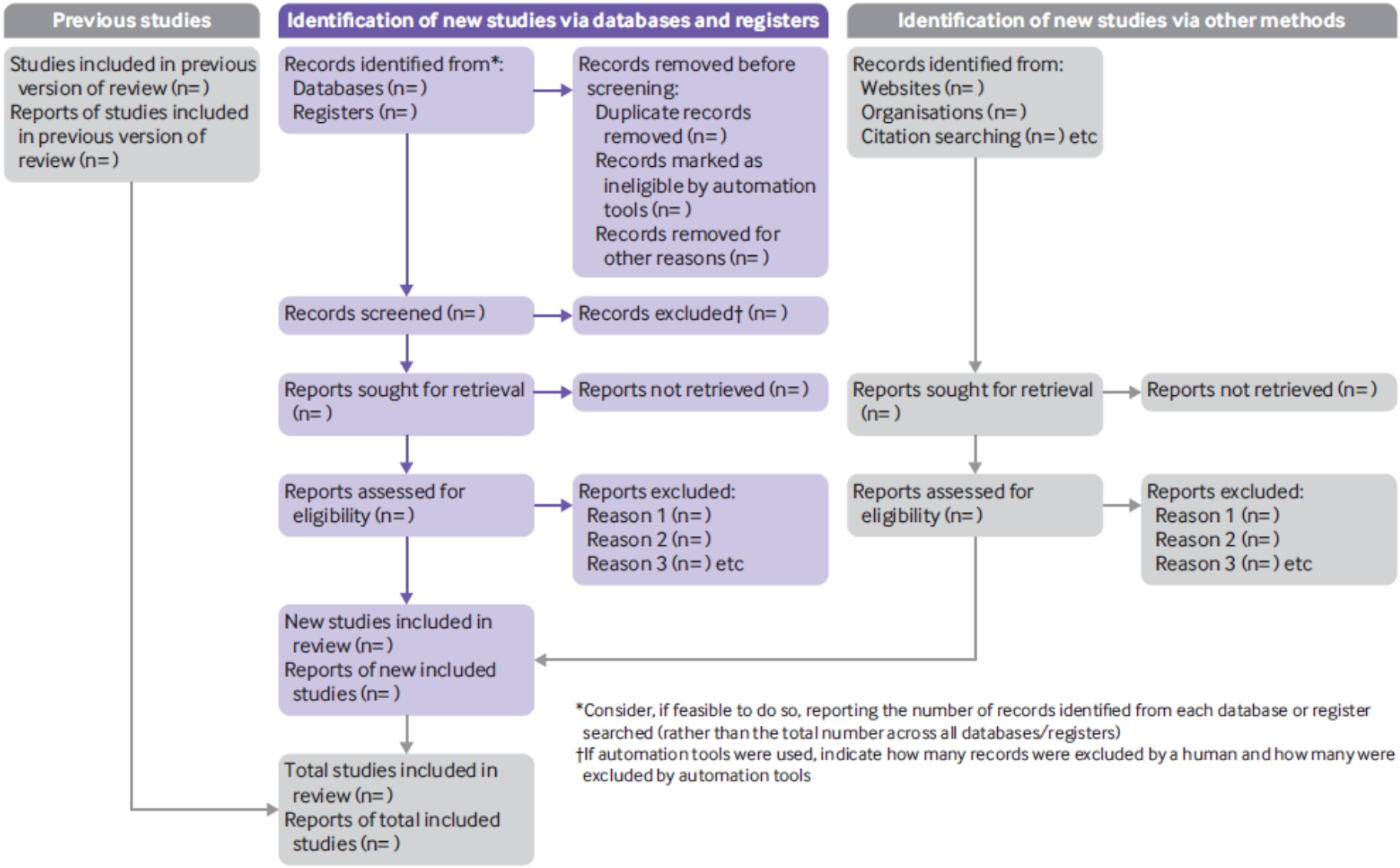

Fig 1 | PRISMA 2020 flow diagram template for systematic reviews. The new design is adapted from flow diagrams proposed by Boers,[55] Mayo-Wilson et al.[56] and Stovold et al.[57] The boxes in grey should only be completed if applicable; otherwise they should be removed from the flow diagram. Note that a "report" could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report or any other document providing relevant information.

Μετα-Μετα-Επιδημιολογία

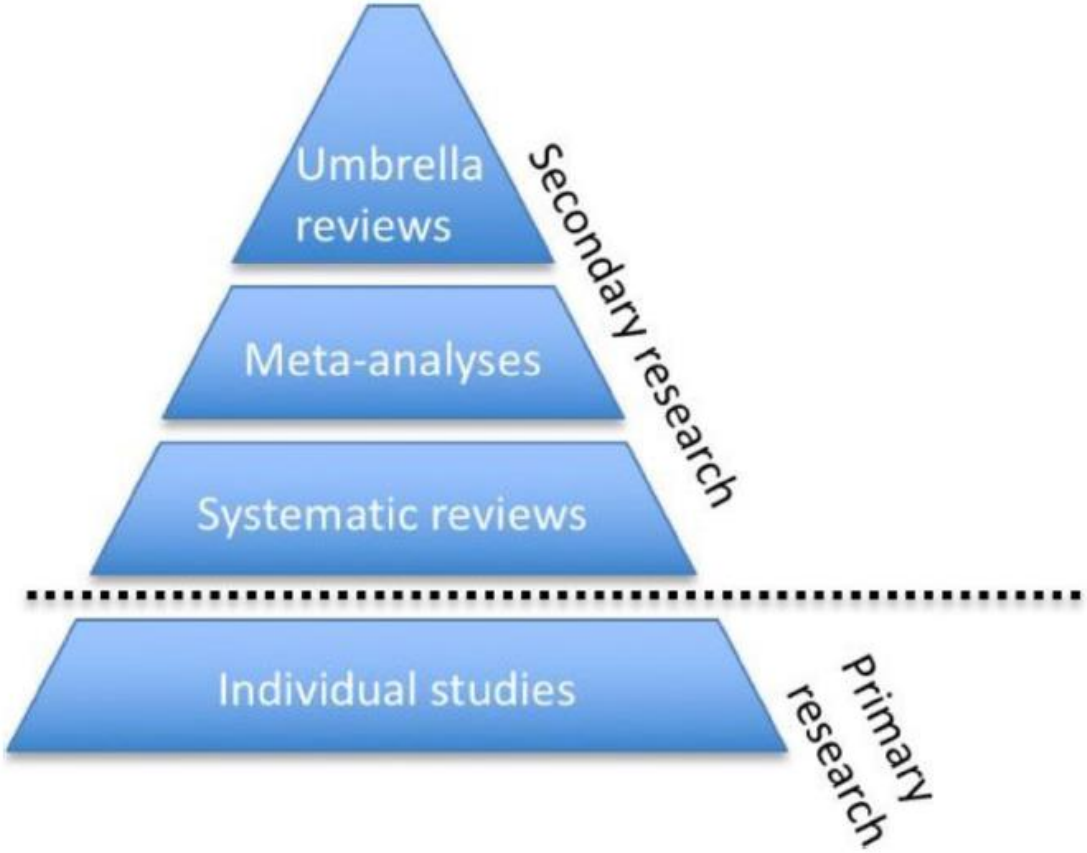

Figure 1 Hierarchy of evidence synthesis methods.

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

Ποια η θέση της Μετα-ανάλυσης;

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