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Meta-Analysis Of Results And Individual Patient Data In Epidemiologal Studies

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Epidemiological information can be aggregated by combining results through a meta-analysis technique, or by pooling and analyzing primary data. Common approaches to analyzing pooled studies through an example on the effect of occupational exposure to wood dust on sinonasal cancer are described. Results were combined applying a meta-analysis technique. Alternatively, primary data from all studies were pooled and re-analyzed using mixed effect models. The combination of individual information rather than results is desirable to facilitate interpretations of epidemiological findings, leading also to more precise estimations and more powerful statistical tests for study heterogeneity.

Key words: Pooled-analysis, meta-analysis, generalized linear mixed models, random effects, epidemiological methods

Introduction

The requirement of large samples of subjects is particularly important in studies of uncommon diseases, such as most types of cancer, and even in diseases with higher prevalence, such as asthma. Large multi-center studies, or combining information from multiple studies, are the best approaches for improving the information from, and overcoming lack of power in individual studies. Information from multiple epidemiological studies can be aggregated either by combining results, such as summary measures (for example, odds ratios), through a meta-analysis technique, or by pooling and analysing primary data.

The combination of results, usually called meta-analysis, involves the compilation of published results from different studies (Thacker, 1988). Another option is to pool individual information from each study and to conduct an analysis for the entire data set, this being defined as meta-analysis of individual patient data (Stewart & Parmar, 1993). Meta-analysis of individual patient data was originally applied to clinical trials, although in epidemiological studies this procedure is usually known as pooled-analysis (Checkoway, 1991).

Both, meta-analysis of results and meta-analysis of individual patients have advantages and limitations (Thacker, 1988; Friedenreich, 1993). Meta-analysis of results has a relatively low cost and the appropriate statistical techniques are straightforward to understand and implement. It does not require sharing of primary data, because it can be performed from reviews of internal reports in multi-center

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studies, or from reviews of published and unpublished results. In this situation, meta-analysis of results is sensitive to publication bias, since unpublished results are usually difficult to locate or obtain. This fact must be taken into account, treating results with caution (Vanderbroucke, 1988). Practices of data reporting also pose difficulties when examining specific diseases (Checkoway, 1991).

Meta-analysis of published results is limited to the information available, permitting usually only a meta-analysis of overall risks. The procedure has also been criticised since it can be conducted without full consideration of the underlying statistical assumptions and inferences required for this type of analysis (Oakes, 1990). Further, the use of a chi-square statistic for assessing heterogeneity in the original studies has been criticised due to its lack of power (Spector & Thompson, 1991).

An alternative to meta-analysis is to pool and then re-analyse individual data. Pooled analysis of epidemiological studies, defined as a combination of primary data from published and unpublished studies has become common recently. With such an approach, rare exposures can be more easily studied (Clayton, 1991), and confounding and possible interaction effects can be more accurately estimated.

Pooled analysis however, is more difficult to conduct since it is more labour and time-intensive. Common definitions for outcomes and other covariates must be used. Thus, important issues are how to accommodate differences in the populations and methods used in the original studies, and to assess their possible effect on the results. Friedenreich (1993) outlined guideline procedures on pooling of primary data for the integration of qualitative assessments of studies with quantitative estimates of the results. However, there are no clear guidelines on the statistical analysis of pooled data, especially if there is heterogeneity in the original studies.

The objective of this article is to describe and compare common statistical techniques for analysing pooled and multi-center studies. Discussed are the alternative methodologies of performing a meta-analysis of results, and of pooling and re-analysing primary data.

Methodology

Fixed effects model

The meta-analysis technique is a straightforward process of weighting results under a simplistic assumption, that the true effect (θ) is the same for each centre, or study, that is an assumption of homogeneity ($\theta_i=\theta$ for all i). Most meta-analyses use fixed effects estimates. The weighted average $\hat{\theta}=\Sigma(w_i\hat{\theta}_i)/\Sigma w_i$ is an unbiased estimate of θ, where the weight $w_i=1/v_i$ is determined by variance (v_i) of the effect estimate, which depends on the effect size and the size of the study. This weighted average has the smallest estimated variance $\hat{v}=1/\Sigma w_i$ among the weighted averages of $\hat{\theta}_i$ (Cox, 1982).

There are different versions of this estimator, differing either in the scale of the effect (log or untransformed odds ratio) or in the approximation of the variance used. The Mantel-Haenszel (Mantel & Haenszel, 1959) method weights the untransformed odds ratios approximately proportional to their sample sizes. In Woolf's method (Woolf, 1955), the log odds ratio are weighted inversely according to their estimated variances from a 2x2 table or asymptotically from a logistic regression. Finally, Peto's method (Peto et al., 1977) uses the observed minus expected values over their variances as an approximation to the log odds ratio. Among these, Woolf's method is the most frequently used. Although Peto's method has been recommended to analyse experimental studies other authors suggest using Woolf's method for any type of study (Greenland, 1987).

Testing heterogeneity

An overall test of heterogeneity of the original studies is provided by calculating $Q=\Sigma w_i(\hat{\theta}_i-\hat{\theta})^2$ following a χ^2_{k-1} distribution under the homogeneity assumption, where k is the number of studies to pool. The lack of power of this test has been well established (Spector & Thompson, 1991), and the absence of formal statistical significance need not imply true homogeneity. Graphically, heterogeneity can also be assessed in first instance from a Forrest plot (Light et al., 1994), although other methods

have been developed to complement this test and also to detect sources of heterogeneity. Among these, the Galbraith plot (Galbraith, 1988) has been more frequently recommended (Thompson, 1993) than others, such as the l'Abbé plot (l'Abbé et al., 1987) or the odd man-out procedure (Walker et al., 1988), which will not be discussed further.

Random effects model

An alternative method suggested by DerSimonian and Laird (1986) considers that the heterogeneity between studies is unexplained. This is known as a random effects model where, $\hat{\theta}_i \sim N(\theta_i, v_i)$, and $\theta_i \sim N(\theta, \sigma^2)$. Here the θ_i effects have some dispersion around the overall estimate θ, indicated by the between-study variance σ^2. An estimate $\hat{\sigma}^2$ of σ^2 must therefore be derived from the results. Then, the inverse variance weights become $w_i^* = 1/(v_i + \sigma^2)$, where v_i is the variance within the i^{th} original study and σ^2 and is the variance between studies. The combined estimate of the effect is defined by $\hat{\theta} = \Sigma(w_i^* \hat{\theta}_i)/\Sigma w_i^*$ with variance $\hat{v} = 1/\Sigma w_i^*$.

Among the standard packages, Stata, S-Plus and SAS have available macros to perform meta-analysis, which can be downloaded from http://www.prw.le.ac.uk/epidemio/personal/ajs22/meta/. However, meta-analysis formulae could be easily programmed in other standard packages or even in a simple spreadsheet.

Pooled analysis of primary data

Fixed-effects model and testing heterogeneity

The analysis of pooled data does not present any difficulty if a fixed effect model is considered, that is assuming that all the effects are fixed for study. For example, if the outcome variable is dichotomous (i.e., case-control status) standard logistic regression can be used. Test for heterogeneity by comparing the model that includes the interaction between study and the exposure of interest and the previous model without the interaction, using the likelihood ratio test. From the statistical point of view, the most important question is to consider or not the presence of heterogeneity. If statistical heterogeneity is presented mixed effects models must be used (Breslow & Clayton, 1993).

Mixed-effects model

Mixed effects model differs from conventional fixed effects model in that, as well as modelling location parameters, they also model the underlying covariance structure of the data. The simplest way to model covariance is by specifying random effects in the model. Briefly, a Normal Mixed Model is defined as $y = X\alpha + Z\beta + e$, where X is a design matrix for fixed effects and Z is a design matrix for random effects, then $\beta \sim N(0, G)$, $V(e) = R$ and $V(y) = ZGZ' + R$, where G is a diagonal matrix of variance parameters, R is the residual variance matrix, and e is the residual error.

However, when the dependent variable is non-linear, define a Generalised Linear Mixed Model as follows: $y = \mu + e$, $g(\mu) = X\alpha + Z\beta$, with $\beta \sim N(0, G)$, $V(e) = R$ and $V(y) \approx BZGZ'B + R$, where the new parameter μ are the expected values, g is the link function, and B is the diagonal matrix of variance terms. An extended notation about mixed models can be found in Brown and Prescott (1999).

There are no clear rules to define if the variables included in the model should be defined as fixed or random effects. Pooled analyses in epidemiology are usually carried out because insufficient subjects are available for the study at any one centre. Thus, there will be extra variability in the risk factor estimates, which can usually be due to differences between studies (for example different investigators, types of patients, etc.) This extra variability can be taken into account by including study and interaction between study and risk factor in the model. When study and interaction between study and risk factor are taken as random, allowance is made for variability in the magnitude of risk factor estimates between studies.

The choice will depend on whether risk factor estimates are related to the set of studies used in the pooled analysis. Thus, local risk factor estimates for the sampled set of individual studies will be obtained fitting the study and interaction between study and risk factor variables. To obtain a global risk factor estimate the study and interaction between study and risk factor should be fitted as random. When this is done the standard error of the risk factor

estimate is increased to reflect the heterogeneity across studies. Taking study as a random effect can increase the accuracy of risk factor estimates since information from the study error stratum is used in addition to that from the residual stratum (Brown & Prescott, 1999).

In a pooled analysis of epidemiological studies there are other factors that differ at the study level that can help to explain differences in results between studies. These may be sensible to be included as random effects in a mixed model and reduce the variability of the interaction between study and risk factor, leading to more precise estimates.

Mixed effects for linear models are available in standard packages: SAS (GLM and MIXED procedures), Stata (xtreg) and S-Plus (lsfit). To fit a mixed effects model for non-linear data, specific macros for Stata (gllamm) and SAS (GLIMMIX) have been recently developed. However, mixed-effects models can also be fitted in other specialised software such as MLnWin.

Analysis of 8 case-control studies on sinonasal cancer

The aim of the investigation was to reanalyse data available from eight previously published case-control studies focused on the differential effect that occupations exposed to wood dust have on the major histological types of sinonasal cancer. The reanalysis was done within each individual study, and pooling them after that to obtain a summary measure of the exposure effect. This research formed part of a wider project on occupational cancer in Europe by the International Agency for Research on Cancer.

Primary data from 8 case-control studies from Germany, Netherlands, France, Sweden, and four studies in Italy (Vigevano, Brescia, Biella, Siena) were available. These studies examined the association of occupational wood dust exposures and sinonasal cancer, taking into account histological types. A detailed description of the process for selection of the

Table 1. Description of eight published case-control studies on the association between occupational wood dust exposures and sinonasal cancer.

	Sex		Age		
	Male	Female	< 55	55-65	> 65
Study	n (%)	n (%)	n (%)	n (%)	n (%)
Germany	59 (59.6)	40 (40.0)	25 (25.3)	23 (23.2)	51 (51.5)
Netherlands	286 (100.0)	0 (0.0)	87 (30.4)	87 (30.4)	112 (39.2)
France	487 (79.1)	129 (20.9)	216 (35.1)	191 (31.0)	209 (33.9)
Sweden	585 (100.0)	0 (0.0)	190 (32.5)	129 (22.0)	266 (45.5)
Italy					
Siena	238 (71.9)	93 (28.1)	83 (25.1)	79 (23.9)	169 (51.0)
Biella	110 (83.9)	21 (16.3)	32 (24.4)	48 (36.7)	51 (38.9)
Brescia	93 (68.4)	43 (31.6)	41 (30.1)	21 (15.4)	74 (54.4)
Vigevano	31 (77.5)	9 (22.5)	10 (21)	11 (27.5)	19 (47.5)
TOTAL	1889 (84.9)	335 (15.1)	684 (30.8)	589 (26.5)	951 (42.8)

Table 1 continued.

Smoking status			Controls	Cases
non n (%)	ex n (%)	Current n (%)	(exposed/ non-exposed)	(exposed/ non-exposed)
46 (46.5)	11 (11.1)	42 (42.4)	1/53	2/43
16 (5.6)	108 (37.8)	91 (27.6)	35/160	25/66
234 (38.0)	237 (38.5)	145 (23.5)	46/363	99/108
215 (36.6)	136 (23.2)	234 (40.0)	272/269	20/24
113 (34.1)	127 (38.4)	91 (27.5)	26/228	16/62
38 (29.0)	45 (34.3)	48 (36.6)	7/98	7/19
64 (47.1)	35 (25.7)	37 (27.2)	7/95	3/31
12 (30.0)	11 (27.5)	17 (42.5)	4/23	0/13
738 (33.2)	710 (31.9)	776 (34.9)	398/1288	176/366

studies and classification of exposures can be found elsewhere (Mannetje et al., 1999). The pooled data set includes cases includes 538 cases and 1,686 controls. The cases also includes 238 squamous cell carcinomas, 155 adenocarcinomas, 79 other histologies, and 59 unknown histology. However, the studies differed in the methods for recruitment and interview of the subjects. Table 1 presents a description of the studies by sex, age, smoking status and occupational wood dust exposures to sinonasal cancer.

Results

Meta-analysis of results

Initially the odds ratio was obtained (OR) by each study using logistic regression adjusted by age, sex and smoking status. Results for each study are showed in a Forrest plot (Figure 1). Note that the logistic regression model for the study from Vigevano (Italy) did not converge because no cases were exposed. However, a crude odds ratio for Vigevano using a Mantel-Haenzsel estimate or thorough an exact-method could be obtained, but that estimate may be seriously biased since it would be unadjusted by the potential confounding variables considered in the logistic regression models. Results are presented for 7 of the studies. The Forrest plot gives a first indication that there is heterogeneity between studies.

Thus, as a first approach to obtain a summary measure of the exposure effect, combined the results of each study applying a meta-analysis technique, weighting by the inverse of variance (OR=2.93, 95% CI: 2.24 to 3.83). The Forrest plot gives an initial indication that there is heterogeneity between studies. Heterogeneity of effects between studies was tested using the Q-statistic (Table 2), which confirms that there is a considerable amount heterogeneity between studies (χ^2=45.357, df=6, p<0.001). Finally, a random effects model was applied using DerSimonian and Laird's method (OR=2.43, 95% CI: 1.06 to 5.59). Analyses were done using Stata, release 7.0, statistical software.

Pooled analysis of individual data

Primary data from all studies were pooled and first analysed using a fixed effects model (Table 2). Thus, standard logistic regression was applied adjusting again by sex, age and smoking status, providing different risk estimates with a narrowness confidence interval than meta-analysis (OR=3.05, 95% CI: 2.36 to 3.95). This difference is mainly due to the fact that in the pooled-analysis the data from Vigevano study are included, while in the meta-analysis they were not, because no risk estimates can be estimated for this study.

Figure 1. Results from eight published case-control studies on the association between occupational wood dust exposures and sinonasal cancer. Odds ratios for each study are adjusted by sex, age, and smoking status.

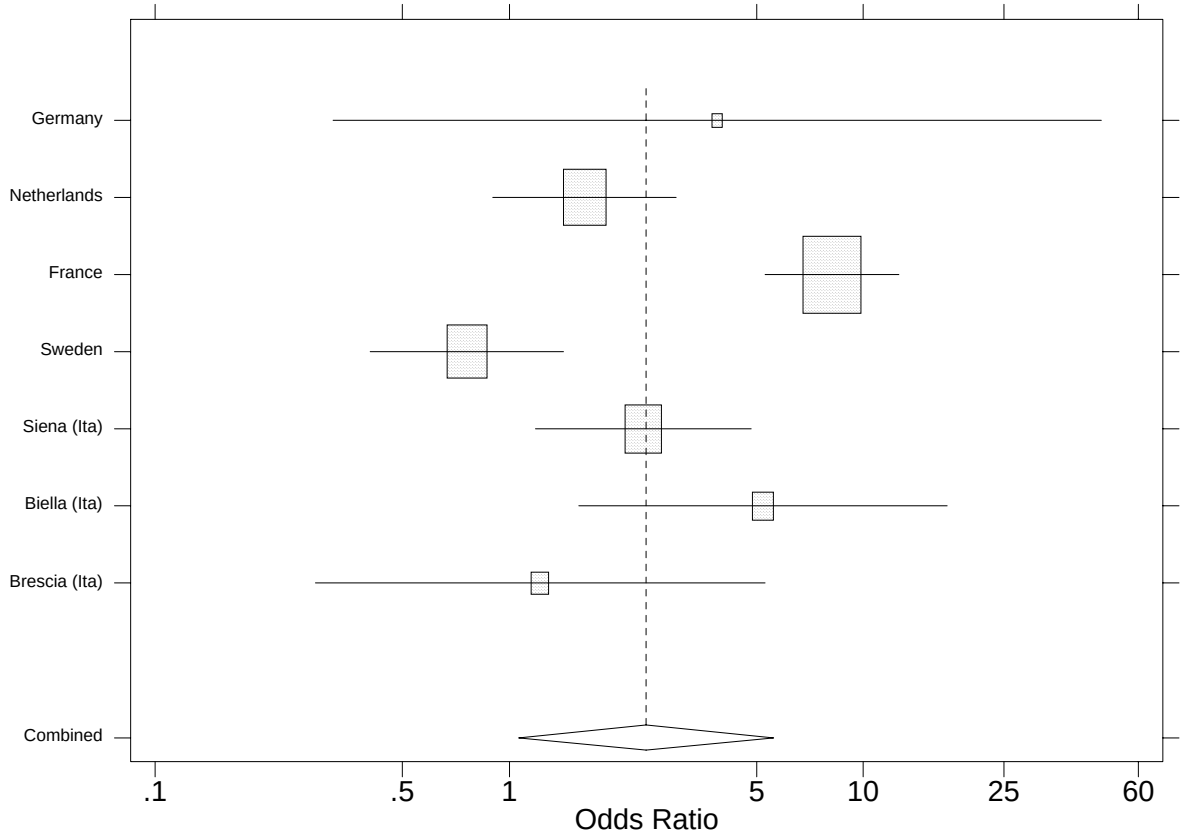

Table 2. Results from eight published case-control studies on the association between occupational wood dust exposures and sinonasal cancer, analysed combining results (meta-analysis using fixed and random effects model), and combining individual patient data (pooled analysis using a fixed effects model).

	Occupational dust wood esposure			Test for heterogeneity		
Model	β (se)	OR	(95% CI)	$\chi 2$	df	p-value
Meta-analysis						
Fixed effects	1.074 (0.136)	2.93	(2.24, 3.83)	45.357	6	<0.001
Random effects	0.891 (0.424)	2.43	(1.06, 5.59)			
Fixed effects pooled analysis						
Including all studies	1.116 (0.132)	3.05	(2.36, 3.95)	51.317	7	<0.001
Excluding Vigevano study	1.079 (0.131)	2.94	(2.28, 3.80)	44.374	6	<0.001

Table 3. Sensitivity analysis for mixed-effects models to combine individual patient data (pooled analysis) of eight published case-control studies on the association between occupational wood dust exposures and sinonasal cancer.

Variables defined as random effects	Deviance	Occupational wood dust exposure β (se)	OR	(95% CI)	Variance components
Study	2210.94	1.052 (0.133)	2.86	(2.21, 3.72)	0.6592
Study×wood dust exposure	2162.64	0.718 (0.369)	2.05	(0.99, 4.23)	0.3781
Study	2163.07	0.662 (0.361)	1.94	(0.96, 3.93)	0.3498
Study×wood dust exposure					0.3703
Study	2166.49	0.661 (0.356)	1.94	(0.96, 3.89)	0.3568
Study×wood dust exposure					0.3761
Sex					0.0375
Age					0.0076
Smoking status					0.0039

Pooled analysis, excluding the Vigevano study, gives a result from a fixed effects model much closer (OR=2.94, 95% CI: 2.28 to 3.80) to those from a meta-analysis. Heterogeneity was assessed using the likelihood ratio test (χ^2=51.317, df=7, p<0.001).

For the mixed-effects model the analyses were performed using the SAS macro GLIMMIX which implements the Penalised Quasi Likelihood (PQL) approach. Firstly, three different models are fit, defining study, the interaction between study and occupational dust exposure, and both study and its interaction with occupational dust exposure to be the random effects (with an unstructured covariance matrix), respectively.

Also introduced are the covariates sex, age and smoking status, as fixed effects (Table 3). In the first model, where only the variable study is defined as a random effect, occupational dust exposure is closer to the previous result using a fixed effect approach (OR=2.86, 95% CI: 2.21 to 3.72), although it increases the accuracy of the exposure estimate. However, when the interaction between study and occupational dust exposure are included as random effects the standard error of the exposure estimate is increased coming to lose the statistical significance (OR=2.05, 95% CI: 0.99 to 4.23), due to it is reflecting the heterogeneity across studies. Finally, when both study and its interaction with occupational dust exposure are included as random effects, although the standard error of the exposure estimate is again increase, results are more accurate than previous model (OR=1.94, 95% CI: 0.96 to 3.93).

However, as seen from Table 1, the effects of the covariates factors varied across studies. For this reason, it was decided to include these factors also as random effects, as a sensitivity analysis (Table 3). In this situation, occupational dust estimate do not change, although this model provides slightly more accurate result (OR=1.94, 95% CI: 0.96 to 3.89) due to inclusion of covariates sex, age and smoking status as a random effects. This fact is reflected in the variance components, being lower than those for previous models.

Conclusion

It is important to consider the differences between pooled studies using individual patient data and classical meta-analyses of results. The key point in a pooled study is to integrate accommodate in the populations and methods

used in the original studies, and to assess their possible effect on the results. Friedenreich (1993) reported useful guidelines for pooling of primary data.

The principal advantage of having individual patient data is that adjustments can be made for different covariates. However, the assumptions that are made in fitting the pooled analysis of individual patient data need to specified and discussed. In our analysis, the confounding effects of sex, age and smoking status must be assumed to be the same across the original studies. However, if the effects of the confounding factors varied across studies, then it may be sensible to include these as random effects.

The main difference between a fixed and a random effect will depend on the intention of the analysis. If local estimates need to be provided, then a fixed effects model must be fitted. Moreover, if the aim of the analysis is to report a global estimate, then always define the study and its interaction with the risk factor as random effects. Thus random effects are sources of variation in a model due to individuals or groups over above the individual error term (Campbell, 2001). For these reasons, one should consider that combining individual patient data from different sources is complex, and in practice, various assumptions need to be made. Various models with a variety of combinations of fixed and random effects should be fitted to assess the sensitivity of the chosen model.

It is usually desirable to work with individual information rather than combined results to facilitate interpretations of epidemiological findings (Blettner et al. 1999), although others (Steinberg et al., 1997) suggested that meta-analysis of results is adequate under certain circumstances. The obvious advantages in a pooled-analysis pertain to increases in the study size, both of the overall and the reference populations used in the analysis. This leads to more precise estimations and more powerful statistical tests for heterogeneity. Furthermore, there may be studies that are difficult or impossible to incorporate into a meta-analysis because of zero counts, as was the case with the study in Vigevano presented in the example for instance, which can be included in the pooled analysis. Their absence from the meta-analysis produces bias that the pooled analysis does not suffer from. However meta-analysis of results is much less costly (Steinberg et al., 1997).

The accuracy with which variance components are estimated is dependent on the number of studies included in the analysis. Problem arise when only few studies are available, which means that there will be considerable uncertainty in the estimate of the between study variance. Also mixed effects models, rather than classical fixed effects models, make more assumptions.

In consequence, there could be problems of bias or lack of convergence of the model fitting process for complex models, such as fitting fixed effects within a random effect, modelling repeated measurements, or dealing with small to moderate samples (Breslow & Lin, 1995; Kuk, 1995). Nevertheless potential solutions such as bootstrapping or full Bayesian analysis are available (Brown & Prescott, 1999), but these methods require very large amount of computer power and time. The main difference between a Bayesian analysis and a maximum likelihood method (as PQL approach used in our analysis) is that techniques are used to evaluate the likelihood surface, rather than estimate the parameters that maximise it.

In absence of heterogeneity, both meta-analysis and pooled analysis produce close results, in terms of estimates and variances. This is done because the meta-analysis estimate is a weighted mean of the means by each centre, and the pooled analysis estimate from a regression model is also a weighted mean. So, both methods are estimating the same quantity. In a meta-analysis technique, a random effects model will produce same estimates as a fixed effects model, and in a pooled analysis fixed and mixed effects models will produce similar results.

Whenever heterogeneity is assessed one approach is to look for possible sources of it. Meta-analyses should incorporate a careful investigation of potential sources of heterogeneity (Thompson, 1994), because statistical tests for heterogeneity may fail to detect moderate degrees of it. Graphical techniques, like Galbraith plots, are useful in searching for sources of heterogeneity. Statistical heterogeneity may be caused by

known clinical differences between populations or by methodological characteristics between studies. Interpretation of possible sources of heterogeneity requires caution because analyses are post-hoc (Spector & Thompson, 1991).

Frequently, heterogeneity is related to unknown causes. Then the formal approach should be to fit a random effects model -in a meta-analysis-, or a mixed effects model -in a pooled analysis-. The choice between these fixed and random, or mixed, effects rarely affect the conclusions obtained (Spector & Thompson, 1991). The greater is the amount of heterogeneity, the greater will be differences between estimates from fixed and random/mixed effects models. However, variances from random, or mixed, effects model will always be higher than those from fixed effects model, because in the former models both variances, between and within studies, are taken into account. Independently of whether fixed or random/mixed effects models are used, estimates from pooled analyses are more precise than those from meta-analyses.

When dealing with pooled or multi-centre studies, results for have to be evaluated for the researcher. Then, if an individual analysis for each centre, or study, is done, a meta-analysis can quickly and easily be performed. This result should be compared, as a sensitivity analysis, with the result from the model using individual data, due to conflicting results possibly being found.

For example, Harrison and Waterbor (1999) found disagreeing results in the relationship between dietary fat and breast cancer if primary study results were heterogeneous. In that way, it was seen in the study that if the two methods (meta-analysis and pooled analysis) produce marked different results then a possible source of divergence, such as absence of exposed cases, should be considered in further analysis. This implies that meta-analysis techniques are still useful; according to Spector and Thompson (1991), “Meta-analysis is here to stay. Epidemiologists, statisticians, and clinicians should all be aware the uses and limitations of the technique”.

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