Investigating the heterogeneity of "study twins"

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Meta-analyses are commonly performed based on random-effects models, while in certain cases one might also argue in favour of a common-effect model. One such case may be given by the example of two "study twins" that are performed according to a common (or at least very similar) protocol. Here we investigate the particular case of meta-analysis of a pair of studies, e.g. summarizing the results of two confirmatory clinical trials in phase III of a clinical development programme. Thereby, we focus on the question of to what extent homogeneity or heterogeneity may be discernible, and include an empirical investigation of published ("twin") pairs of studies. A pair of estimates from two studies only provides very little evidence on homogeneity or heterogeneity of effects, and ad-hoc decision criteria may often be misleading.

Key words: Meta-analysis; Random effects; Sparse data; Shrinkage.

1 Introduction

In drug licensing, evidence from several independent sources is often required to demonstrate efficacy and safety of novel treatments (The European Agency for the Evaluation of Medicinal Products (EMEA), 2001; Kennedy-Shaffer, 2017). Especially in health technology assessment (HTA), meta-analysis methods are commonly applied to combine and judge evidence from several sources, e.g. typically a small number of clinical trials conducted in the later development phases (Dias et al., 2013a; Bender et al., 2018).

The case of meta-analysis of only few studies, however, presents particular challenges. The assessment of heterogeneity (or homogeneity) of effect estimates turns out central in the evaluation of implications (Cochran, 1937; Veroniki et al., 2016; Friede et al., 2017a,b). In the case of k = 2 studies, Bender et al. (2018) proposed to assess plausibility of the homogeneity assumption based on contextual information, and if possible resort to a common-effect analysis. A common-effect analysis would effectively mean a relatively simple "pooling" of effect estimates, while *stratification* by study is usually still implemented (Gail, 2005). In a certain sense, however, homogeneity (or zero heterogeneity) may also be considered a "most optimistic" assumption (Röver et al., 2021), so it may not be a suitable "default" option.

As a prime example where homogeneity of treatment effects may often be assumed, "*twin studies*" are sometimes quoted, that is, when a common study protocol is implemented for a pair of otherwise independently conducted trials (Bender et al., 2018; Schulz et al., 2022). The reasoning here is that with similar study populations as well as treatment and outcome assessment procedures, one may expect the eventual quantitative outcome also to be consistent (Higgins et al., 2019, Sec. 10.10). This might be particularly true for relative effect measures.

The recent example of the RESPIRE trials highlights how even the suggestion of the potential presence of heterogeneity may generate considerable unease (Chotirmall and Chalmers, 2018). However, judging the presence or magnitude of heterogeneity among a pair of studies is very hard; heterogeneity would need to be substantial in order to become apparent, and often rather ad-hoc criteria are consulted, which may in fact not constitute very conclusive evidence. Given the commonly substantial uncertainty around the

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homogeneity assumtion, and the potential consequences of its violation, one might then prefer to anticipate the possibility of heterogeneity in the analysis.

Here we investigate the interface between a common-effect and a random-effects meta-analysis of a pair of "study twins", with a focus on the question to what extent one can actually judge whether heterogeneity is present or absent in a pair of estimates. We will also illustrate heterogeneity issues by considering an empirical sample of pairs of published study twins.

In the following, we will first introduce some context and terminology; we will then consider examples of *study twins* in detail. We will investigate to what extent heterogeneity can be recognized from only a pair of studies, and we will consult an empirical sample of study twins for commonly observed (empirical) heterogeneity. We will eventually return to the examples and close with some conclusions.

2 Meta-analysis of few studies

2.1 Study twins

Regulatory guidelines commonly require independent replication of experimental results before these are considered convincing (The European Agency for the Evaluation of Medicinal Products (EMEA), 2001; Kennedy-Shaffer, 2017). The degree to which it is possible to replicate the results of one study in another study is also referred to as "(*results*) reproducibility" (Goodman et al., 2016; Plesser, 2018). In order to try and generate consistent results in replicate studies, factors that might induce between-study heterogeneity (e.g., inclusion criteria, treatment regimens, outcome assessment, modeling assumptions, ...) are usually carefully controlled. Higgins et al. (2019, Sec. 10.10) in this context distinguish between *clinical* and *methodological diversity*, i.e., heterogeneity in study populations and design aspects, which may eventually be reflected in the *statistical heterogeneity*, i.e., the heterogeneity in the eventual quantitative study outcomes. In this spirit, Bender et al. (2018) characterized *twin studies* as a pair of trials "*where the same (or at least a very similar) study protocol is replicated in a second study*". For the present purpose, we define *study twins* as a study pair that is: (i) either jointly planned, or where one is planned as a replication of the other; and (ii) (essentially) identical especially with respect to inclusion criteria and treatment details.

2.2 Between-trial heterogeneity in treatment effects

Effect estimates from clinical trials are typically accompanied by measures of uncertainty, e.g., standard errors or confidence intervals. *Homogeneity* of different estimates then means that, despite numerical inequality, these refer to a common underlying "true" value. Quite commonly, however, there is additional variability present going beyond what could be attributed to mere measurement error; such excess variance is termed *heterogeneity*. Unless such heterogeneity can be attributed to certain trial-specific features (e.g., in a meta-regression), it is commonly accounted for by including extra variance components (random effects) into the analysis models (Cochran, 1937; Ades et al., 2005; Higgins et al., 2009).

It is important to note that assuming treatment effect homogeneity does not necessarily lead to a "naïve" pooling of data. When the estimates to be combined themselves result as differences or contrasts (e.g., as an odds ratio comparing a treatment to a control group), then the "common-effect" analysis (e.g., referring to a common odds ratio among several experiments) will usually correspond to a *stratified* analysis allowing for differences e.g. between the individual studies' control groups (Gail, 2005; Deeks and Altman, 2001).

2.3 The normal-normal hierarchical model

In the following, we will consider the normal-normal hierarchical model (NNHM), a simple random-effects model that constitutes the basis of many meta-analyses, and where homogeneity and heterogeneity simply correspond to zero or positive values for the heterogeneity variance component (Fleiss, 1993; Ades et al., 2005; Higgins et al., 2009; Röver, 2020). Within the NNHM, estimates y_i and their associated standard

study	Ν	MD	95% Cl						
Glow 1	822	108.0	[79.0, 137.0]					-	
Glow 2	798	97.0	[64.6, 130.2]					-	
				0	25	50	75	100	125
			mean difference (MD)						

Figure 1 The GLOW 1/2 example data. The effect measure is the mean difference (MD) in *trough* FEV_1 *at week 12* compared to placebo (mL). Both studies show consistent results.

errors s_i (where i = 1, ..., k) are modeled as

$$y_i|\theta_i \sim \text{Normal}(\theta_i, s_i^2) \text{ and } \theta_i|\mu, \tau \sim \text{Normal}(\mu, \tau^2)$$
 (1)

leading to the marginal expression

$$y_i|\mu, \tau \sim \operatorname{Normal}(\mu, \tau^2 + s_i^2)$$
 (2)

(Fleiss, 1993; Ades et al., 2005; Higgins et al., 2009; Röver, 2020). Homogeneity ($\tau = 0$) leads to the special case of the *common-effect* model (with $\theta_i = \mu$), and in case of heterogeneity ($\tau > 0$), the estimates y_i relate to "study-specific" mean parameters θ_i that are not identical, but only similar across studies.

Assessment of heterogeneity is challenging in case of few studies (small k), since significance tests suffer from low power, and quantification is sensitive to the choice of estimator (Hardy and Thompson, 1998; Gavaghan et al., 2000; Ioannidis, 2008; Pereira et al., 2010; Veroniki et al., 2016). In a Bayesian context, the likelihood conveys little information on the heterogeneity, and the prior tends to remain influential for inference (Röver, 2020; Röver et al., 2021). In case of few studies only, frequentist meta-analysis procedures often suffer from problems originating from heterogeneity estimation. While for Bayesian methods this is no fundamental obstactle, prior specification may require particularly solid motivation (Friede et al., 2017a,b; Röver et al., 2021).

3 Two examples

3.1 The GLOW trials

The GLOW 1 and GLOW 2 studies are randomized controlled trials (RCTs) that investigated the use of glycopyrronium bromide ($50\mu g$ daily) in patients with moderate to severe chronic obstructive pulmonary disease (COPD) (D'Urzo et al., 2011; Kerwin et al., 2012). Both were phase III studies using the same set of inclusion criteria; only the GLOW 2 study was of a longer duration and included another additional treatment arm. A pooled analysis was also published subsequent to the individual studies' results (D'Urzo et al., 2013).

The primary endpoint related to the *forced expiratory volume in 1 second* (FEV_1). The *trough* FEV_1 is defined as the "mean of the values at 23 h 15 min and 23 h 45 min after dosing". The treatment effects (mean differences in *trough* FEV_1 *at week 12*, relative to placebo) are shown in Figure 1. A positive difference here indicates a benefit for the patient. With an average increase in volume by roughly 100 mL in both cases, the studies showed consistent results.

3.2 The RESPIRE trials

Recently, results of the RESPIRE 1 and RESPIRE 2 studies were published, which were two randomized controlled trials investigating ciprofloxacin for the treatment of non-cystic fibrosis bronchiectasis

endpoint	study	Ν	IRR	95% CI	
14-day	Respire 1	205	0.61	[0.43, 0.87]	
	Respire 2	264	0.83	[0.59, 1.17]	
28-day	Respire 1	211	0.98	[0.68, 1.41]	
	Respire 2	257	0.55	[0.38, 0.79]	
					0.50 0.70 1.0 1 incidence rate ratio (IRR)

Figure 2 The RESPIRE 1/2 example data. The treatment effect here is expressed in terms of incidence rate ratios (IRRs) for exacerbation events. Not only do the effect estimates differ between trials, but also the overall picture differs for the two (14-day and 28-day) endpoints.

(De Soyza et al., 2018; Aksamit et al., 2018). The two studies may be considered *twins*, yet the outcomes turned out somewhat discordant, triggering lively dissussions of the role of heterogeneity (Aksamit et al., 2018; Chotirmall and Chalmers, 2018).

The RESPIRE 1 and RESPIRE 2 studies included 416 and 521 patients, respectively. Each study had four treatment groups; two treatment regimens (14-day vs. 28-day on/off cycles for 48 weeks) were each compared to a corresponding control group. Figure 2 shows both studies' data on the primary endpoint *incidence rate ratio (IRR) of exacerbations* for the two regimens (14-day and 28-day).

In the 14-day dosing regimen, the CIs are overlapping and mutually covering the other study's estimate. In the 28-day regimen, CIs are also overlapping, but do not include each other's estimates. In both cases, there is one significant and one non-significant outcome; however, in the 14-day regimen, only RESPIRE 1 showed a significant effect, while in the 28-day regimen, RESPIRE 2 turned out significant.

The evidence from the two studies appears somewhat puzzling: each indicates significance for one of the treatment regimens, while none of the two is consistently superior. This discordant pattern of estimates probably added to the controversy here. There also was a second co-primary survival (hazard ratio) endpoint, which similarly did not point to a clear-cut conclusion.

A lively discussion of results and of potential sources of heterogeneity followed (Aksamit et al., 2018; Chotirmall and Chalmers, 2018). While the two studies had identical inclusion and exclusion criteria, they had been conducted in different geographical regions, and differing COPD prevalences as well as (significantly) differing exacerbation rates at baseline were pointed out. Chotirmall and Chalmers (2018) note a *"failure of replicate trials to reproduce results"* here.

4 Evidence on heterogeneity from a pair of studies

In the case of a single pair of studies (k = 2), homogeneity or heterogeneity empirically only manifests itself in the difference between the two estimates (y_1 and y_2). The two corresponding 95% confidence intervals (CIs) are calculated as $y_i \pm z_{0.975}s_i$, where $z_{0.975} \approx 1.96$ is the 97.5% quantile of the standard normal distribution. When looking at such a pair of estimates along with their associated CIs, several features may suggest homogeneity:

- overlapping CIs,
- a non-significant test for homogeneity (e.g., Cochran's Q test),
- CIs mutually covering the other study's effect estimate,



Figure 3 Probabilities of overlapping CIs, a non-significant *Q*-test, CIs with mutually covered effect estimates, or a zero heterogeneity estimate for the special case of equal standard errors ($\sigma_2 = \sigma_1 = \sigma$). In this case, all these probabilities only depend on the ratio of $\frac{\tau}{\sigma}$ (and, with that, on I^2).

• a zero heterogeneity estimate ($\hat{\tau} = 0$).

In the case of two studies, the evidence to decide between homogeneity and heterogeneity commonly is very weak. Significance tests for homogeneity generally are known to have little power, especially for as few as k = 2 studies (Hardy and Thompson, 1998; Ioannidis, 2008; Pereira et al., 2010), and heterogeneity often tends to be underestimated (Kontopantelis et al., 2013). For some more details on Cochran's Q test, see also Appendix A.2.4.

For the simple case of two studies, the probabilities for the above four events may be computed numerically (see the appendix for details). Figure 3 illustrates these for the special case of equal standard errors ($\sigma_1 = \sigma_2 = \sigma$, so that the I^2 heterogeneity measure results as $I^2 = \frac{1}{1+(\frac{\sigma}{\tau})^2}$ and only depends on the relative magnitudes of τ and σ (Higgins and Thompson, 2002)). Note that all of these (CI overlap, a non-significant *Q*-test, mutually covered effect estimates, or a zero heterogeneity estimate) are often taken to be indicative of homogeneity. From the figure one can see that all of these are likely to occur even for substantial amounts of heterogeneity, i.e., the data may in that sense often falsely suggest homogeneity, or may at least "look homogeneous". The reverse is also not uncommon: under homogeneity, the data may also exhibit features suggestive of some heterogeneity with non-negligible probability. Consequently, homogeneity and heterogeneity are hard to distinguish based only on a pair of estimates.

5 An empirical investigation

Aim, search strategy and data extraction 5.1

To gain some insights into homogeneity or heterogeneity among published pairs of studies that one may consider to be "study twins", we performed a literature search to gather some examples. We devised a relatively simple search strategy in order to obtain a sizeable number of studies, taking advantage of the meanwhile common requirement for pre-registration of clinical trials, e.g., in the United States National Library of Medicine (NLM) registry ("clinicaltrials.gov") (DeAngelis et al., 2004). We focused on publications in the New England Journal of Medicine (NEJM) in the decade of 2010–2019. Due to the NEJM's policy of quoting clinicaltrials.gov identifiers in the abstract, we were able to single out studies referring to more than one identifier based on an exported list of abstracts. In order to select pairs of "study twins" among the abstracts in question, we then employed the following inclusion criteria:

- studies have been planned jointly
- studies are assigned to the same clinical phase
- differences like additional arms, differing follow-up times, or additional investigations are unproblematic as long as the primary endpoint is unaffected.

Exclusion criteria were:

- differences in the studies' inclusion criteria (age groups, diseases, severities, genotypes, ...)
- differing treatments, doses, or modes of administration (e.g., subcutaneous vs. intravenous).

We then focused on the primary endpoint; in case of several co-primaries, we picked the one reported first; in case no primary endpoint is explicitly specified, we picked the first endpoint quoted in the "results" section. From the qualifying studies, we eventually extracted the following information:

- publication reference (DOI),
- study names (or acronyms), NCT identifiers,
- · primary endpoint name and effect measure,
- whether primary endpoint analyses were pooled or reported separately,
- primary endpoint data (estimates and standard errors).

5.2 Search results

A PubMed search for articles published in the decade 2010–2019 in NEJM and quoting the term "clinicaltrials.gov" in the abstract yielded 1371 references. Out of these, 103 quoted more than one clinicaltrials.gov (NCT) identifier. 30 studies met the inclusion criteria, and 26 studies reported adequate data, i.e., eventually yielding 26 twin pairs of studies.

Figure 4 illustrates three example cases that were selected based on their associated Cochran's Q statistic values (smallest, largest, and a moderate one); the ones shown here then correspond to Q = 0.0076(p = 0.93), Q = 0.54 (p = 0.46) and Q = 5.6 (p = 0.017), respectively. In all three cases, the two studies' CIs overlap; in the third case, the CIs however do not include the other study's estimate. Also, only in the third case heterogeneity is significant (p = 0.017 for Cochran's Q test), and the heterogeneity estimate is positive ($\hat{\tau} = 0.093$). The complete data are available in the online supplement.

study	Ν	LRR	95% CI			
OPERA I	821	-0.62	[-0.91, -0.32]	-		
OPERA II	835	-0.63	[-0.92, -0.35]			
				I	I	I
				-1	–0.5 log rate ratio (Ll	C RR)

Hauser et al. (2017)



study	Ν	MD	95% Cl				
KODIAC-04	428	15.0	[6.0, 24.0]			8	
KODIAC-05	464	10.3	[1.7, 18.9]				
					1		
				0	10	20	
				mean difference (MD)			

Feagan *et al.* (2016)

study	Ν	RD	95% CI				
UNITI-1	496	0.123	[0.045, 0.201]				
UNITI-2	418	0.268	[0.177, 0.359]				
				0	0.1 risk diff	0.2 erence (0.3 (RD)

Figure 4 Three examplary forest plots corresponding to "small", "moderate" and "large" values for Cochran's *Q* statistic within the data set (Hauser et al., 2017; Chey et al., 2014; Feagan et al., 2016).

				event			
	$\frac{\tau}{\sigma}$	I^2	overlap	nonsig. Q	mutual	$\hat{\tau} = 0$	
empirical frequency			100.0	84.6	80.8	65.4	
	0.0	0%	99.4	95.0	83.4	68.3	
theoretical probability	0.5	20%	99.1	93.5	80.9	65.4	
(assuming $\sigma_1 = \sigma_2$)	1.0	50%	97.6	89.0	74.2	58.6	
	2.0	80%	89.0	74.2	57.6	43.6	

Table 1 The empirically observed frequencies in comparison to the theoretically expected probabilities (in percent) for selected heterogeneity values τ/σ (see also Figure 3).

5.3 Descriptive analysis

Table 1 shows the empirically observed frequencies of CI overlap, a non-significant Q-test, mutual effect coverage of CIs, or a zero heterogeneity estimate for the empirical data. Under homogeneity ($\tau = 0$) and equal standard errors ($\sigma_1 = \sigma_2$), the corresponding probabilities would be at 99.4%, 95.0%, 83.4%, and



Table 2 Frequencies of concordant and discordant effect estimates and significances among the 26 pairsof study twins.

Figure 5 Empirical cumulative distribution function (CDF) of the *Q*-test's *p*-values (left panel). The empirical distribution is close to a uniform distribution, which is indicated by the dashed line. The right panel shows the corresponding empirical distribution of test statistic (*Q*) values, which under the null hypothesis of homogeneity follow a χ_1^2 -distribution (bright blue line).

68.3%, respectively (see also Figure 3). Event probabilities are also shown for a selection of heterogeneity values $\tau/\sigma > 0$ (and assuming equal standard errors $\sigma_2 = \sigma_1 = \sigma$). In order to match probabilities to the observed frequencies above, it would require heterogeneity values τ/σ of 1.3, 0.51 and 0.50, respectively.

The study pairs were usually of roughly equal size and precision. The larger study had a median of a 1.04-fold sample size compared to the smaller study, and the largest ratio was at 2.78. The associated standard errors were also very similar: the larger standard error was a median of a 1.07 times greater than the smaller standard error; the maximum ratio was at a factor of 1.50.

Table 2 shows frequencies of combinations of effect estimates. In the majority of cases, both estimates were significant and were pointing in the same direction (where "significant" here means that $|\frac{y_i}{\sigma_i}| > 1.96$). In only two cases, effect estimates were of opposing signs, and then both were also not significant. Yusuf et al. (1984) also termed such cases of differing treatment effects with differing or equal signs as *qualitative and quantitative interactions*, respectively.

Figure 5 (left panel) shows the empirical distribution of the *p*-values of Cochran's *Q*-test for heterogeneity. In case of homogeneity, these should follow a uniform distribution, as indicated by the dashed line. A Kolmogorow-Smirnow-test for a uniform distribution of *p*-values yields p = 0.71, i.e., no indication of non-uniformity. We may also investigate whether the lower tail of the distribution of *p*-values suggests non-uniformity; the minimum of *n* uniformly distributed *p*-values follows a Beta(1, n)-distribution. The smallest *p*-value in the sample is at $p_{(1)} = 0.0177$, which is at the 37%-quantile of the corresponding (Beta(1, 26)) distribution; it is hence also in no way "unusually small" under the hypothesis of homogeneity.

The right panel of Figure 5 shows a similar picture, but at the scale of the Q-test statistics (where large Q-values correspond to small p-values). Under the null hypothesis of homogeneity, these are χ_1^2 -distributed, as indicated by the bright blue line, and again the empirical distribution appears to match well. At the Q scale, it is also possible to derive the distribution under certain alternatives (see the Appendix for details); two cases (with equal $\sigma_1 = \sigma_2 = \sigma$) are shown in the same plot.

5.4 Estimating heterogeneity

5.4.1 Joint meta-analysis

Heterogeneity values or their estimates (τ or $\hat{\tau}$) for different meta-analyses are only comparable when the treatment effects are on the same or a similar scale (Röver et al., 2021). Among our sample of 26 study twins, the largest group with a common effect measure are 8 study pairs with log-OR as effect measure and 5 more studies with log-HR, log-rate-ratio or log-risk-ratio; these may be considered to relate to a common (logarithmic) scale. In the following, we will investigate these 13 twin pairs more closely by fitting variations of the NNHM to the data set.

5.4.2 Common heterogeneity parameter

One way to quantify the heterogeneity (in particular in view of the possibility of homogeneity, i.e., $\tau = 0$ for all 13 meta-analyses) is to fit a model with a single, *common* heterogeneity parameter. Technically this may be implemented using a meta-regression approach, where pairs of (twin) studies are identified by a common indicator variable. Such a model may be fitted using either a frequentist or Bayesian approach, e.g., using the metafor or bayesmeta R packages (Viechtbauer, 2010; Röver and Friede, 2023).

A frequentist meta-analysis yields a (Paule-Mandel) point estimate of $\hat{\tau} = 0.0078$ and a 95% confidence interval [0.00, 0.16]. A (Cochran's Q) test for Heterogeneity turns out not significant (p = 0.42). A Bayesian analysis (for both an improper uniform or a half-Normal(0.5) prior) yields a posterior median of 0.046 along with a 95% credible interval [0.00, 0.13]. When using proper, weakly informative priors (Normal(0, 2.82) for the overall mean effect and half-Normal(0.5) for the heterogeneity) (Günhan et al., 2020; Röver et al., 2021)), a Bayes factor of 4 in favour of $\tau = 0$ (homogeneity) may be computed (Kass and Raftery, 1995; Gelman et al., 2014). Both analyses hence agree on inferring a very small amount of heterogeneity (mostly below $\tau = 0.1$), and consistency with homogeneity ($\tau = 0$).

5.4.3 Random heterogeneity parameters

Instead of a single common heterogeneity parameter, we may also use a random-effects model for the heterogeneity and infer a *distribution* of heterogeneity parameters. Such an approach was proposed by Rhodes et al. (2015) and Turner et al. (2015); here we are utilizing the implementation described by Röver et al. (2023). Using a half-normal distribution for the heterogeneity parameters, for the above 13 studies we yield a (predictive) distribution with a median of 0.035 and an upper 95% quantile of 0.22 for the heterogeneity τ^* . Again, the analysis points to a very small amount of heterogeneity, when considering the (logarithmic) effect scale investigated here (Röver et al., 2021).

Table 3 Estimated heterogeneity based on the GLOW 1/2 data from Figure 1 and several random-effects methods. Frequentist estimates are identical for the most common methods, and frequentist CIs are based on the Q-profile method (Viechtbauer, 2007). The a-priori expected heterogeneity for the half-normal HN(10) prior it is 6.7 [0.0, 19.6], for the HN(20) prior is 13.5 [0.0, 39.2], and for the HN(50) prior is 33.7 [0.0, 98.0].

method	$\hat{ au}$	95% CI
frequentist (DL/REML/PM)	0.0	[0.0, 247.7]
Bayes (HN(10))	6.1	[0.0, 18.1]
Bayes (HN(20))	10.5	[0.0, 33.4]
Bayes (HN(50))	19.4	[0.0, 73.9]

Table 4 Effect estimates (mean difference) based on the GLOW 1/2 data from Figure 1 and on the common-effect (fixed effect, FE) and several random-effects (RE) methods. The Hartung-Knapp-Sidik-Jonkman (HKSJ) and modified Knapp-Hartung (mKH) methods are based on adjusted standard errors and Student-*t* quantiles, the Bayesian estimates are based on half-normal (HN) heterogeneity priors of differing scales.

method	MD	95% CI
FE	103.2	[81.4, 124.9]
RE	103.2	[81.4, 124.9]
HKSJ	103.2	[33.8, 172.5]
mKH	103.2	[-37.7, 244.0]
Bayes (HN(10))	103.1	[77.7, 128.3]
Bayes (HN(20))	103.0	[70.6, 135.1]
Bayes (HN(50))	102.9	[45.7, 159.5]

6 Reconsidering the two examples

6.1 The GLOW trials

Heterogeneity estimates for the GLOW 1/2 data (see Section 3.1) are shown in Table 3 based on several analysis methods. Cochran's Q-test for homogeneity yields a p-value of 0.62 here (i.e., no indication of heterogeneity), and the frequentist point estimate of heterogeneity is also at $\hat{\tau} = 0$. Note that for k = 2 studies, the most common heterogeneity estimators, like DerSimonian-Laird (DL), restricted maximum likelihood (REML) or Paule-Mandel (PM), all coincide (Rukhin, 2012; Friede et al., 2017b). A Bayesian analysis of the data requires specification of a (proper, informative) heterogeneity prior that is suitable in the context of the present endpoint (the FEV₁ mean difference). The FEV₁ itself is of the order of 1.3–1.4 L at inclusion, with standard deviations of 0.5 L among patients (D'Urzo et al., 2011; Kerwin et al., 2012). Considering the GLOW trials' standard errors and sample sizes, the *unit information standard deviation (UISD)* (for the FEV₁ pre/post *difference*) amounts to $\sigma_u = 446$ mL for the example data (Röver et al., 2021). In a related review investigating a different bronchidilator (Tioptropium) in a similar context, Karner et al. (2014) observed a heterogeneity of $\tau \approx 20$ mL among a set of 22 (most likely more heterogeneous) included studies. Table 3 hence lists Bayesian estimates based on half-normal priors with scale parameters of 10, 20 and 50 mL.

Table 4 shows several estimates of the mean effect along with 95% CIs. Due to the heterogeneity being estimated as zero, the fixed-effect (FE) and random-effects (RE) estimates are identical. The Hartung-Knapp-Sidik-Jonkman (HKSJ) interval is wider, and the modified Knapp-Hartung (mKH) interval renders the overall effect not significant. The different Bayesian analyses yield wider intervals than FE, but all of

Table 5 Estimated heterogeneity based on the RESPIRE 1/2 data from Figure 2 and several randomeffects methods. Frequentist estimates are identical for several methods, and frequentist CIs are based on the *Q*-profile method (Viechtbauer, 2007). The a-priori expected heterogeneity for the half-normal HN(0.25) prior is 0.17 [0.00, 0.49], and for the HN(0.50) prior it is 0.34 [0.00, 0.98].

regimen	method	$\hat{ au}$	95% CI
14-day	frequentist (DL/REML/PM)	0.13	[0.00, 6.98]
	Bayes (HN(0.25))	0.15	[0.00, 0.49]
	Bayes (HN(0.50))	0.25	[0.00, 0.80]
28-day	frequentist (DL/REML/PM)	0.36	[0.00, 13.1]
	Bayes (HN(0.25))	0.23	[0.00, 0.51]
	Bayes (HN(0.50))	0.37	[0.00, 0.92]

them remain shorter than the HKSJ interval. D'Urzo et al. (2013) later quoted a pooled estimate of 103.0 [81.0, 125.0] based an analysis of the pooled data (stratified by study), which roughly matches the FE estimate.

6.2 The RESPIRE trials

Point estimates and significance tests for heterogeneity among the logarithmic incidence rate ratios (IRRs) in the RESPIRE example data (see Section 3.2) yield $\hat{\tau} = 0.13$ (p = 0.22) for the 14-day regimen, and $\hat{\tau} = 0.36$ (p = 0.028) at 28 days. The Q-test outcome is significant at the 5% level only for the 28-day regimen. A Bayesian meta-analysis again requires a proper, informative prior. For the present endpoint on a logarithmic scale, a half-normal prior with scale 0.50 is a reasonable choice; given the relatively small expected heterogeneity among a pair of study twins, a smaller scale (e.g., 0.25) may also be considered appropriate (Röver et al., 2021). The corresponding frequentist and Bayesian heterogeneity estimates are shown in Table 5.

The heterogeneity estimates are not extremely large; values up to 0.5 are commonly regarded as "reasonable" (Spiegelhalter et al., 2004; Röver et al., 2021), however, in this particular case of a twin pair of studies, the outcomes might be expected to be rather homogeneous. A heterogeneity value of $\tau = 0.36$ would imply that study-specific IRRs vary around a common mean value by factors roughly within 0.49 and 2.0 (with 95% probability) (Röver et al., 2021). When considering the Bayesian estimates and 95% intervals, it becomes clear that the posteriors differ little from the assumed priors, i.e., the data provide rather little evidence on the amount of heterogeneity actually present.

We may also compare the observed (estimated) heterogeneity magnitude to what was observed in the NEJM sample when we consider the subgroup of study pairs that also investigated endpoints on a logarithmic scale. Among the 13 "logarithmic" endpoints in NEJM sample (log-OR, log-RR, log-IRR or log-HR endpoints), 8 heterogeneity estimates turned out as zero; we have mean $\hat{\tau}$ of 0.052 and a maximum of 0.27; so the RESPIRE studies' estimate of $\hat{\tau} = 0.36$ is indeed at the upper end of the observed range in this (albeit small) sample.

Table 6 shows effect estimates from common-effect as well as several random-effects analyses of the RESPIRE 1/2 data. The analysis methods used were a common-effect (or fixed-effect (FE)) analysis, a random-effects (RE) analysis utilizing a plug-in estimate for the heterogeneity variance and confidence intervals based on a normal approximation, Hartung-Knapp-Sidik-Jonkman (HKSJ) and modified Knapp-Hartung (mKH) intervals based on a Student-*t* approximation (Röver et al., 2015), and a Bayesian analysis utilizing a half-Normal prior with scale 0.50 or 0.25 for the heterogeneity standard deviation (Röver, 2020; Röver et al., 2021). Whether the evidence on the treatment effect is deemed conclusive (IRR < 0), in this case depends on the model assumptions implemented.

regimen	method	IRR	95% CI
14-day	FE	0.718	[0.561, 0.919]
	RE	0.716	[0.529, 0.970]
	HKSJ	0.716	[0.100, 5.110]
	mKH	0.716	[0.100, 5.110]
	Bayes (HN(0.50))	0.715	[0.373, 1.362]
	Bayes (HN(0.25))	0.716	[0.474, 1.079]
28-day	FE	0.732	[0.566, 0.949]
	RE	0.733	[0.416, 1.294]
	HKSJ	0.733	[0.019, 29.02]
	mKH	0.733	[0.019, 29.02]
	Bayes (HN(0.50))	0.733	[0.337, 1.599]
	Bayes (HN(0.25))	0.733	[0.448, 1.120]

 Table 6
 RESPIRE 1/2 effect estimates (incidence rate ratios) based on the data from Figure 2 and on the common-effect (fixed effect, FE) and several random-effects (RE) methods.

7 Discussion

The present investigations showed that in general a single pair of effect estimates provides only very little evidence on the heterogeneity between studies. Even if studies are in fact homogeneous, they are not unlikely to suggest heterogeneity, or, conversely, even under substantial heterogeneity, the data may still appear homogeneous. Ad-hoc criteria employed to judge heterogeneity will often be misleading. When considering a larger number of published pairs of "study twins", overall these appear rather homogeneous, but it remains unclear whether this might be due to the fact that clinical and methodological homogeneity (similarity in study designs and protocols) in fact does lead to statistical homogeneity (consistent effect estimates), or whether this observation may be due to selection effects. Apparent heterogeneity might have triggered decisions precluding a joint analysis or its publication in a high-ranking journal such as the NEJM.

In the presence of (known or potential) effect modifiers, a certain amount of heterogeneity should be anticipated (Higgins, 2008); use of meta-regression to adjust for factors that may not be controlled by the study design then might help reconciling cases like the RESPIRE example of (apparent) clinical and statistical heterogeneity despite methodological homogeneity. However, the danger of overfitting based on a very small number of studies needs to be considered (Hartung et al., 2008). Careful reporting of studies' relevant characteristics may then help interpreting heterogeneous study results, and may facilitate valuable insights. On the other hand, efforts to ensure methodological homogeneity (standardization of protocols etc.) and measures of clinical homogeneity (patient characteristics) would need to be transparently and convincingly documented in order to possibly justify assuming little or no heterogeneity in a meta-analysis.

Heterogeneous results clearly do occur in practice (Kontopantelis et al., 2013; Rhodes et al., 2015; Turner et al., 2015). While heterogeneity may be perceived as a threat to external validity (Dias et al., 2013b), Ioannidis et al. (2006) in fact warn that "extreme homogeneity" may also raise suspicion, and Higgins (2008) questions the external validity of a meta-analysis when studies have been "sieved" for homogeneity. Efforts to ensure methodological and clinical homogeneity may on the one hand promote homogeneous and concordant outcomes, but might to some extent also counteract external validity or generalizability. This also points to the related question of whether the conduct of several (potentially heterogeneous) trials might sometimes be preferrable to a single, larger trial (Shrier et al., 2007), but, besides obvious budget constraints, this will also depend on whether the actual research question is of a confirmatory or exploratory nature (Tukey, 1980). With meta-analyses of study twins, the common-effect model

is often a sensible option. Sensitivity analyses might include Bayesian random-effect meta-analyses with prior distributions for the heterogeneity placing substantial probability at small levels of heterogeneity.

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Conflicts of interest

The authors have declared no conflict of interest.

A Appendix

A.1 The difference in estimates

In the special case of only k = 2 studies, the homogeneity or heterogeneity of studies only manifests itself in the (absolute) *difference* between the two estimates involved, $|y_2 - y_1|$. According to the model assumptions, the estimates' difference follows a normal distribution:

$$(y_2 - y_1) \sim \text{Normal}(0, \sigma_1^2 + \sigma_2^2 + 2\tau^2).$$
 (3)

The implications for the absolute difference may then be investigated by noting that

$$\frac{(y_2 - y_1)^2}{\sigma_1^2 + \sigma_2^2 + 2\tau^2} \sim \chi_1^2,\tag{4}$$

i.e., the squared (and scaled) difference follows a χ^2 distribution with one degree of freedom. Probabilities of exceeding certain thresholds may hence be computed via

$$P((y_2 - y_1)^2 \le c^2 | \sigma_1, \sigma_2, \tau) = F_{\chi_1^2} \left(\frac{c^2}{\sigma_1^2 + \sigma_2^2 + 2\tau^2} \right),$$
(5)

where $F_{\chi_1^2}(\cdot)$ denotes the χ_1^2 distribution's cumulative distribution function (CDF). In the special case of equal standard errors ($\sigma_2 = \sigma_1 = \sigma$), the expression simplifies further. In the following subsections, we will consider several thresholds for the difference in estimates that may often be taken as an indication of statistical homogeneity or heterogeneity.

A.2 Relevant thresholds for the difference

A.2.1 Overlapping CIs

Two studies exhibit overlapping 95% CIs whenever

$$|y_2 - y_1| \le z_{0.975}(\sigma_1 + \sigma_2),\tag{6}$$

where $z_{0.975} \approx 1.96$ is the 97.5% quantile of the standard normal distribution.

A.2.2 Mutual estimate coverage

A somewhat more strict condition is that each of the two CIs contains the other effect estimate. This happens whenever

$$|y_2 - y_1| \le z_{0.975} \min\{\sigma_1, \sigma_2\}.$$
⁽⁷⁾

A.2.3 A zero heterogeneity estimate

Frequentist heterogeneity estimates frequently turn out as zero (Friede et al., 2017a). In the case of only k = 2 studies, this happens for the more common estimators (at least for the DerSimonian-Laird, maximum-likelihood, restricted maximum-likelihood and Paule-Mandel estimators) whenever

$$(y_2 - y_1)^2 \le \sigma_1^2 + \sigma_2^2 \tag{8}$$

(Rukhin, 2012; Friede et al., 2017b).

A.2.4 A non-significant Q test

Cochran's Q test is a statistical test for the null hypothesis of *homogeneity* ($\tau = 0$). The test statistic is

$$Q = \sum_{i=1}^{k} \frac{(y_i - \hat{\mu})^2}{\sigma_i^2}, \quad \text{where} \quad \hat{\mu} = \frac{\sum_{i=1}^{k} \frac{y_i}{\sigma_i^2}}{\sum_{i=1}^{k} \frac{1}{\sigma_i^2}}.$$
(9)

The null hypothesis is rejected if $Q > \chi^2_{(k-1);(1-\alpha)}$, where α is the type-I error allowed for (Cochran, 1954; Fleiss, 1993). For the case of only two studies (k = 2), we have

$$Q = \frac{(y_2 - y_1)^2}{\sigma_1^2 + \sigma_2^2},\tag{10}$$

so that the Q test rejects if

$$(y_2 - y_1)^2 > \chi^2_{1;(1-\alpha)}(\sigma_1^2 + \sigma_2^2), \tag{11}$$

where in the common case of $\alpha = 5\%$, we have $\chi^2_{1;0.95} = (z_{0.975})^2 = 3.84$.

A.3 Probabilities of threshold exceedance

Based on the considerations from the previous subsections, we can derive probabilities for certain events that may commonly be taken as indicative of ("statistical") homogeneity. Table 7 lists thresholds for the difference in estimates $(|y_2 - y_1|)$ as well as the expressions to compute the probability of remaining below that threshold. For the case of equal standard errors ($\sigma_2 = \sigma_1 = \sigma$), these expressions simplify. In that case, there is also a one-to-one correspondence of τ to the popular I^2 heterogeneity measure proposed by Higgins and Thompson (2002), which results as $I^2 = \frac{\tau^2}{\tau^2 + \sigma^2}$ (so that $\frac{\sigma^2}{\sigma^2 + \tau^2} = (1 - I^2)$).

A.4 Distribution of Q under alternatives $(H_1, \tau > 0)$

Figure 5 in Section 5.3 showed the CDF of the Q-test statistic; the computation of this distribution is given in the following. Since for k = 2 the test statistic simplifies to the expression in (10), and the distribution of the difference in estimates is known to follow a (scaled) χ^2 -distribution (4), the Q-statistic's distribution under an alternative simply follows a scaled χ^2 -distribution. For example, the cumulative distribution function F_{τ} under an alternative ($\tau > 0$) is given by

$$F_{\tau}(x) = F_{\chi_1^2} \left(x \frac{\sigma_1^2 + \sigma_2^2}{\sigma_1^1 + \sigma_2^2 + 2\tau^2} \right).$$
(12)

Note that for the case of identical standard errors ($\sigma_2 = \sigma_1 = \sigma$), the factor again simplifies to

$$\frac{\sigma_1^2 + \sigma_2^2}{\sigma_1^1 + \sigma_2^2 + 2\tau^2} = \frac{2\sigma^2}{2\sigma^2 + 2\tau^2} = \frac{\sigma^2}{\sigma^2 + \tau^2} = 1 - I^2.$$
(13)

Table 7 Probabilities for events that may be seen as an indication of homogeneity. Each of the events is present whenever the (absolute) difference in estimates $|y_2 - y_1|$ is below a certain threshold. Event probabilities may then be computed based on the CDF of a χ^2 -distribution with 1 degree of freedom $(F_{\chi_1^2})$. $z_{0.975} \approx 1.96$ here denotes the 97.5%-quantile of a standard normal distribution, and α is the significance level of the Q-test.

	threshold	probab	ility
event	for $ y_2 - y_1 $	general case	special case
		$\sigma_2 eq \sigma_1$	$\sigma_2 = \sigma_1 = \sigma$
CI overlap	$z_{0.975}\left(\sigma_1+\sigma_2\right)$	$F_{\chi_1^2} \left(\frac{z_{0.975}^2 (\sigma_1 + \sigma_2)^2}{\sigma_1^2 + \sigma_2^2 + 2\tau^2} \right)$	$F_{\chi_1^2}\left(2z_{0.975}^2 \frac{\sigma^2}{\sigma^2 + \tau^2}\right)$
non-sig. Q-test	$z_{(1-\alpha/2)}\sqrt{\sigma_1^2+\sigma_2^2}$	$F_{\chi_1^2} \left(\frac{z_{(1-\alpha/2)}^2 (\sigma_1^2 + \sigma_2^2)}{\sigma_1^2 + \sigma_2^2 + 2\tau^2} \right)$	$F_{\chi_1^2}\left(z_{(1-\alpha/2)}^2 \frac{\sigma^2}{\sigma^2 + \tau^2}\right)$
mutual coverage	$z_{0.975} \min\{\sigma_1, \sigma_2\}$	$F_{\chi_1^2}\left(\frac{z_{0.975}^2(\min\{\sigma_1,\sigma_2\})^2}{\sigma_1^2 + \sigma_2^2 + 2\tau^2}\right)$	$F_{\chi_1^2}\left(\frac{z_{0.975}^2}{2}\frac{\sigma^2}{\sigma^2+\tau^2}\right)$
$\hat{\tau} = 0$	$\sqrt{\sigma_1^2+\sigma_2^2}$	$F_{\chi_1^2} \left(\frac{\sigma_1^2 + \sigma_2^2}{\sigma_1^2 + \sigma_2^2 + 2\tau^2} \right)$	$F_{\chi_1^2}\left(\frac{\sigma^2}{\sigma^2+\tau^2}\right)$

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