Methods

Indirect comparison meta-analysis

Four continuous outcomes were included in the review (SSs, MSs, SMSs and QoL scores). Each score y_{jk} can be assumed to have a normal likelihood with standard deviation sd_{jk}, sample size N_{jk} and, therefore, standard error $se_{jk} = \frac{sd_{jk}}{N_{jk}}$ for study j and arm k (*Equation 2*). Scores have been measured on different scales across studies. Therefore, these needed to be standardised before the inclusion in the meta-analysis by means of the pooled SD (SD_j)[263,264] (*Equation 3*). Standardised mean scores are represented by μ_{jk} in *Equation 3*, whereas SMDs δ_{jk}s are estimated via a linear regression model (*Equations 4a* and *4b*), where a random-effects parameter σ^2 can be estimated as an alternative to the fixed-effects model, where $\delta_{jk} = d_k - d_{bj}$ would replace *Equation 4b*, where d_k is the pooled SMD score between treatment k (2 = SCIT; 3 = SLIT) and placebo (i.e. $b_j = 1$ for every study j, the reference baseline intervention arm for every study included in the ICMA). Finally, the indirect comparison of SLIT vs SCIT can be estimated by subtracting the pooled SMD slope between SLIT and placebo and the pooled SMD slope between SCIT and placebo as in *Equation 5*. A positive value for d_{32} would indicate that the SLIT pooled score is higher than the SCIT pooled score (i.e. SCIT is a better treatment); similarly, a negative value for d_{32} would indicate that SLIT is a better treatment.

$$y_{jk} \sim dnorm\left(mean\_score_{jk}, se_{jk} = \frac{sd_{jk}}{N_{jk}}\right) \tag{2}$$

$$mean\_score_{jk} = \mu_{jk} * SD_j \tag{3}$$

$$\mu_{jk} = \begin{Bmatrix} base_j & Interventionb_j \\ base_j + \delta_{jk} & Interventionk \end{Bmatrix} \tag{4a}$$

$$\delta_{jk} \sim Normal\left(\left(d_k - d_{b_j}\right), \sigma^2\right) \tag{4b}$$

$$d_{32} = d_3 - d_2 \tag{5}$$

Indirect comparison meta-regression

Random-effects modelling is a first step to account for unexplained between-study variability or heterogeneity.[265] Heterogeneity can be further explored by means of meta-regression when covariates are available from the review. In this review a number of covariates were available. The linear regression model described in *Equations 4a* and *4b* would instead become as in *Equation 6a*, where each comparison d_k is substituted by a regression equation where α_k is the intercept, β_k is the slope and X_j is the covariate for study j (i.e. $d_k = \alpha_k + \beta_k * X_j$). The indirect comparison of SCIT compared with SLIT for a given level of the covariate $X_j = x$ is then described in Equation 6b.

$$\delta_{jk} \sim Normal\left(\left(a_k - b_{b_j}\right) + \left(\beta_k - \beta_{b_j}\right)\mathrm{X}_j, \sigma^2\right) \tag{6a}$$

$$d_{32,x} = \left(a_3 - a_2\right) + \left(\beta_3 - \beta_2\right)\chi \tag{6b}$$

In meta-regressions, α_k corresponds to $d_{k,x=0}$ (i.e. when the covariate value is zero). For example, the dichotomous covariate Age has been coded as 1 = Adult and 0 = Child; therefore, α_2 represents the SMD between treatment 2 and placebo for those studies that only recruited adults. Similarly, variables considered as continuous such as Year of Publication and Number of Symptoms have been centred to AD2005 and six symptoms, respectively. For example, α_2 when Year of publication is included in the model represents the SMD between SCIT and placebo as regressed for AD2005 by the model. Therefore, α_ks have not been explicitly reported in the tables to avoid duplication of reporting of results. For every score, the data sets were composed of a number of studies. The meta-regression models may require the cancellation of the entire record of the study where the covariate value is missing (e.g. it is not reported or it is unclear). In this case, the DIC and pD (the estimate of the effective number of parameters in the model) for the null model with the same number of studies is included in the meta-analysis.

Implementation

Parameter estimates were obtained via Bayesian modelling and Markov chain Monte Carlo (MCMC) modelling. The software for Bayesian modelling WinBUGS 1.4[139] was used to implement the models. There was no preconceived prior opinion on the values of the intervention and baseline parameters and therefore these were given non-informative prior distributions. Heterogeneity parameter was given a priori uniform distribution between 0 and 300 (on the between-study SD) and, for sensitivity analysis, a gamma prior with parameters both equal to 0.001 (on the between-study variance).[266]

Multiple chains were run by initialising every chain in different points of the space of parameters; convergence and the length of the burn-in period[267] were assessed by setting the burn-in period to zero and by looking at history plots (available by default in WinBUGS) for those chains simultaneously. The length of the chain after the burn-in period was determined so that the MC error was lower than 10^{-4}, where the MC error measures the proportion of variability that is consequent to sampling algorithm, i.e. the higher the number of iterations the lower the MC error.[268] Longer chains were also useful to adjust parameter estimates in case of autocorrelation in the MCMC chains.

The choice between random- and fixed-effects models and the significance of regression parameters when heterogeneity was explored by means of covariates was assessed by means of the DIC.[269] The DIC statistic is a compound measure of the model fit (the deviance) and the complexity of the model (pD). The lower the DIC, the better the fit; for choosing between two models, a minimum difference of 5 in the DIC is recommended.[139]

Results

Model checking

Convergence was achieved in the first 50 iterations for every model; model results did not appear to be sensitive to initial values. Autocorrelation in the MCMC chains was found, especially on the between-studies variance parameter (i.e. the maximum lag was >40 iterations). Therefore, long chains were run, with a burn-in period of 10,000 iterations, and a further 100,000 iterations were used to build posterior distributions. Model results were not sensitive to the choice of prior distribution for the heterogeneity parameter.

The following interpretation of SSs is given as an example.

Symptom scores

For every meta-analysis and meta-regression model, *Table 57* presents estimates of parameters and of the model fit statistic DIC for symptoms scores. Probabilistic analysis is given in *Table 58*, where for every model, and eventually for all (where possible) or some significant levels of the covariate, the probability of each treatment being the best treatment is given.

The fixed- and random-effects model for symptoms score included 59 studies. The DIC for the random-effects model (508) is meaningfully lower than the DIC for the fixed-effects model (542), although the difference in pD (+34) indicates that it is far more complex. The indirect comparison of SLIT with SCIT is in favour of SCIT, whereas the difference between scores is significantly positive {i.e. SCIT corresponds to lower SS [d_{32} 0.351 (0.127 to 0.586)]}. The probabilistic analysis also indicates SCIT as the best treatment when symptoms scores are considered, with a probability associated with SCIT being the best treatment nearly equal to 100%. For every meta-analysis and meta-regression model, probabilistic analyses indicate the probability of zero that placebo is the best treatment. The data present a substantial amount of unexplained heterogeneity [σ^2 0.089 (CrI 0.027 to 0.187)]. Meta-regression results are presented below separately for each covariate. For simplicity, as the fixed-effects model corresponds to a much worse fit to the data than the random-effects model, meta-regression will be fit on the random-effects model, and therefore the null model will refer to the random-effects model without covariate effects.

Age of participants (59 records)

Age of participants did not improve model fit significantly, with a difference of –2 points in DIC (506) when compared with the null model. In fact, CrIs for regression coefficients included the no-effect value of zero [β_2 0.455 (CrI –0.434 to 1.358); β_3 0.186 (CrI –0.083 to 0.466)] and the between-study variance remained unchanged compared with the random-effect null model [σ^2 0.091 (CrI 0.028 to 0.192)]. The probabilistic analysis indicates that there is a high probability a posteriori that SCIT is the best treatment for adults (around 96%), reflecting a significantly positive estimates of the indirect comparison of SLIT vs SCIT via the estimated SMD score [$d_{32,\text{adult}}$ 0.328 (CrI 0.088 to 0.579)]. However, for studies that included only children this probability is almost even and the SMD indirectly estimated from the model was not significantly different from zero [$d_{32,\text{child}}$ 0.059 (CrI –0.837 to 0.966)]. This uncertainty can be explained by the fact that there is only one study comparing SCIT with placebo in children and indicates that more studies may be needed.

Year of publication (59 records)

Year of publication (time) can be considered a source of differences between studies that depend on time, for example a proxy for technological advancements that are not explicitly considered. For symptoms scores, year of publication improves the fit of the model to the data compared with the null model (i.e. six-point improvement in DIC: 502 compared with 508). In fact, the between-study variance seems to be slightly lower than for the null model [σ^2 0.067 (CrI 0.017 to 0.147)]. The effect of time affects mainly the comparison SCIT vs placebo [σ_2 0.056 (CrI 0.027 to 0.086], whereas there is a 50% posterior probability that time has a positive effect (or negative effect) for the comparison of SLIT with placebo [β_3 0.001 (CrI –0.024 to 0.025)], the posterior CrI is nearly symmetrical around the posterior mean. The indirect comparison of SLIT vs SCIT favours SCIT until 2005, then from 2006 seems to be more favourable to SLIT.

Tables of results

TABLE 57 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ^2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (*d*)-SSs

Symptom scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo:[a] direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT[a]: indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Fixed effects (no covariates)	59	d_k	–0.604 (–0.720 to –0.489)	–0.317 (–0.374 to –0.261)	0.287 (0.160 to 0.416)	542 (61)
Random effects (no covariates) **null model**	59	d_k	–0.713 (–0.921 to –0.521)	–0.362 (–0.484 to –0.248)	0.351 (0.127 to 0.586)	508 (95)
		σ^2	0.089 (0.027 to 0.187)			
Random effects (age of participants)	59	β_k	0.455 (–0.434 to 1.358)	0.186 (–0.083 to 0.466)	–	506 (96)
		$d_{k,child}$	–0.282 (–1.156 to 0.586)	–0.223 (–0.461 to 0.015)	0.059 (–0.837 to 0.966)	
		$d_{k,adult}$	–0.736 (–0.953 to –0.537)	–0.409 (–0.551 to –0.276)	0.328 (0.088 to 0.579)	
		σ^2	0.091 (0.028 to 0.192)			
Random effects (year of publication)	59	β_k	0.056 (0.027 to 0.086)	0.001 (–0.024 to 0.025)	–	502 (92)
		$d_{k,2000}$	–0.763 (–0.956 to –0.583)	–0.359 (–0.529 to –0.196)	0.404 (0.159 to 0.655)	
		$d_{k,2005}$	–0.485 (–0.699 to –0.273)	–0.356 (–0.468 to –0.252)	0.128 (–0.113 to 0.364)	
		$d_{k,2010}$	–0.206 (–0.519 to 0.113)	–0.353 (–0.517 to –0.20)	–0.148 (–0.510 to 0.20)	
		σ^2	0.067 (0.017 to 0.147)			
Random effects (no. of symptoms[b])	48	β_k	–0.090 (–0.209 to 0.024)	0.022 (–0.036 to 0.078)	–	449 (79) [529 (75)][c]
		$d_{k,3sym}$	–0.410 (–0.912 to 0.095)	–0.473 (–0.787 to –0.158)	–0.062 (–0.658 to 0.534)	
		$d_{k,6sym}$	–0.679 (–0.934 to –0.439)	–0.407 (–0.584 to –0.235)	0.273 (–0.024 to 0.578)	
		$d_{k,12sym}$	–1.217 (–1.884 to –0.592)	–0.275 (–0.547 to –0.020)	0.942 (0.268 to 1.653)	
		σ^2	0.096 (0.019 to 0.213)			

Symptom scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo:[a] direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT[a]: indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Random effects (duration[b])	57	β_{k1}	0.558 (–0.126 to 1.277)	–0.011 (–0.313 to 0.287)	–	477 (95) [481 (93)][c]
		β_{k2}	0.639 (0.141 to 1.173)	0.004 (–0.304 to 0.316)	–	
		$d_{k,<6months}$	–1.187 (–1.621 to –0.788)	–0.365 (–0.577 to –0.160)	0.822 (0.379 to 1.299)	
		$d_{k,6–12months}$	–0.629 (–1.205 to –0.066)	–0.376 (–0.599 to –0.164)	0.252 (–0.357 to 0.862)	
		$d_{k,>12months}$	–0.548 (–0.863 to –0.237)	–0.361 (–0.592 to –0.132)	0.187 (–0.199 to 0.577)	
		σ^2	0.112 (0.040 to 0.221)			
Random effects (MAC)[b]	42	β_{k1}	–0.095 (–0.595 to 0.408)	0.182 (–0.176 to 0.556)	–	309 (66) [310 (60)]*
		β_{k2}	–0.447 (–1.013 to 0.072)	0.151 (–0.219 to 0.541)	–	
		$d_{k,<5\mu g}$	–0.460 (–0.845 to –0.089)	–0.476 (–0.813 to –0.155)	–0.016 (–0.516 to 0.483)	
		$d_{k,5–6\mu g}$	–0.556 (–0.891 to –0.226)	–0.294 (–0.458 to –0.133)	0.262 (–0.108 to 0.634)	
		$d_{k,>20\mu g}$	–0.907 (–1.338 to –0.536)	–0.325 (–0.511 to –0.135)	0.582 (0.167 to 1.060)	
		σ^2	0.053 (0.005 to 0.13)			

continued

TABLE 57 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ^2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (*d*)-SSs (*continued*)

Symptom scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo:[a] direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT[a]: indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Random effects (allergen type[b])	60[d]	β_{k1}	–0.326 (–0.868 to 0.204)	0.053 (–0.423 to 0.538)	–	523 (100) [525 (95)][c]
		β_{k2}	0.196 (–0.291 to 0.699)	–0.108 (–0.438 to 0.223)	–	
		β_{k3}	0.437 (–0.468 to 1.371)	–1.092 (–2.119 to –0.067)	–	
		β_{k4}	0.276 (–196.40 to 197.30)	–	–	
		$d_{k,grass}$	–0.721 (–1.013 to –0.451)	–0.326 (–0.473 to –0.185)	0.396 (0.090 to 0.721)	
		$d_{k,Parietaria}$	–1.047 (–1.532 to –0.599)	–0.272 (–0.728 to 0.188)	0.775 (0.140 to 1.446)	
		$d_{k,tree}$	–0.526 (–0.941 to –0.121)	–0.433 (–0.735 to –0.138)	0.092 (–0.408 to 0.597)	
		$d_{k,Alternaria}$	–0.285 (–1.150 to 0.594)	–1.418 (–2.431 to –0.404)	–1.133 (–2.460 to 0.199)	
		$d_{k,ragweed}$	–0.445 (–197.20 to 196.60)	–0.435 (–0.867 to –0.007)	0.011 (–197.0 to 196.70)	
		σ^2	0.096 (0.030 to 0.20)			

sym, symptoms.

a The DIC (pD) of the null model when the same number of studies is included in the meta-analysis is reported within square brackets.

b A number of studies were missing for NoSym <ref> and for Duration <ref>.

c Differences d_k relative to the comparison of A vs B need to be interpreted as $Y_A - Y_B$, where Y_A and Y_B are the score for treatment A and B, respectively.

d For Drachenberg (2001, SLIT)[91] the data used were combined scores for allergen types (AT) TREE and GRASS. However, when the effect of different AT was explored via meta-regression, separate scores for the two allergen types were used. Therefore, the number of studies in the analysis is 60 instead of 59.

TABLE 58 Probabilistic analysis for SSs [probability (%) that treatment *k* is the best under different modelling assumptions]

Model (covariate included in the model)	Placebo	SCIT	SLIT
Fixed effect (59)	00.0	>99	00.0
Random effect (59)	00.0	99.9	00.1
Age group of participants (59)			
Child[a]	00.9	54.9	44.2
Adult	00.0	99.6	00.4
Year of publication (59)			
2000	00.0	99.9	00.1
2005	00.0	86.1	13.9
2010	00.0	20.3	79.7
No. of symptoms (48)			
3 symptoms	00.0	41.5	58.5
6 symptoms	00.0	96.5	03.5
12 symptoms	00.0	99.7	00.3
Duration			
Low	00.0	>99	00.0
Medium	00.0	80.1	19.9
High	00.0	83.4	16.6
MAC			
<5 µg	00.0	47.4	52.6
5–20 µg	00.0	92.0	08.0
>20 µg	00.0	99.7	00.3
Allergen type			
Grass	00.0	99.4	00.6
Parietaria	00.0	99.1	00.9
Tree	00.0	64.3	35.7
Alternaria	00.1	04.6	95.3
Ragweed	01.2	50.0	48.8

a Few studies on children compared SCIT vs placebo and SLIT vs placebo.

Figure 27 shows a plot of the results (based on SSs) when year of publication is included in the model. Dashed vertical lines highlight the period 2007–8 when, in theory, SLIT is more likely to be beneficial than SCIT.

Figure 28 shows a plot of the results (based on SSs) when number of symptoms is included in the model.

Figure 29 shows a plot of the results (based on MSs) when year of publication is included in the model.

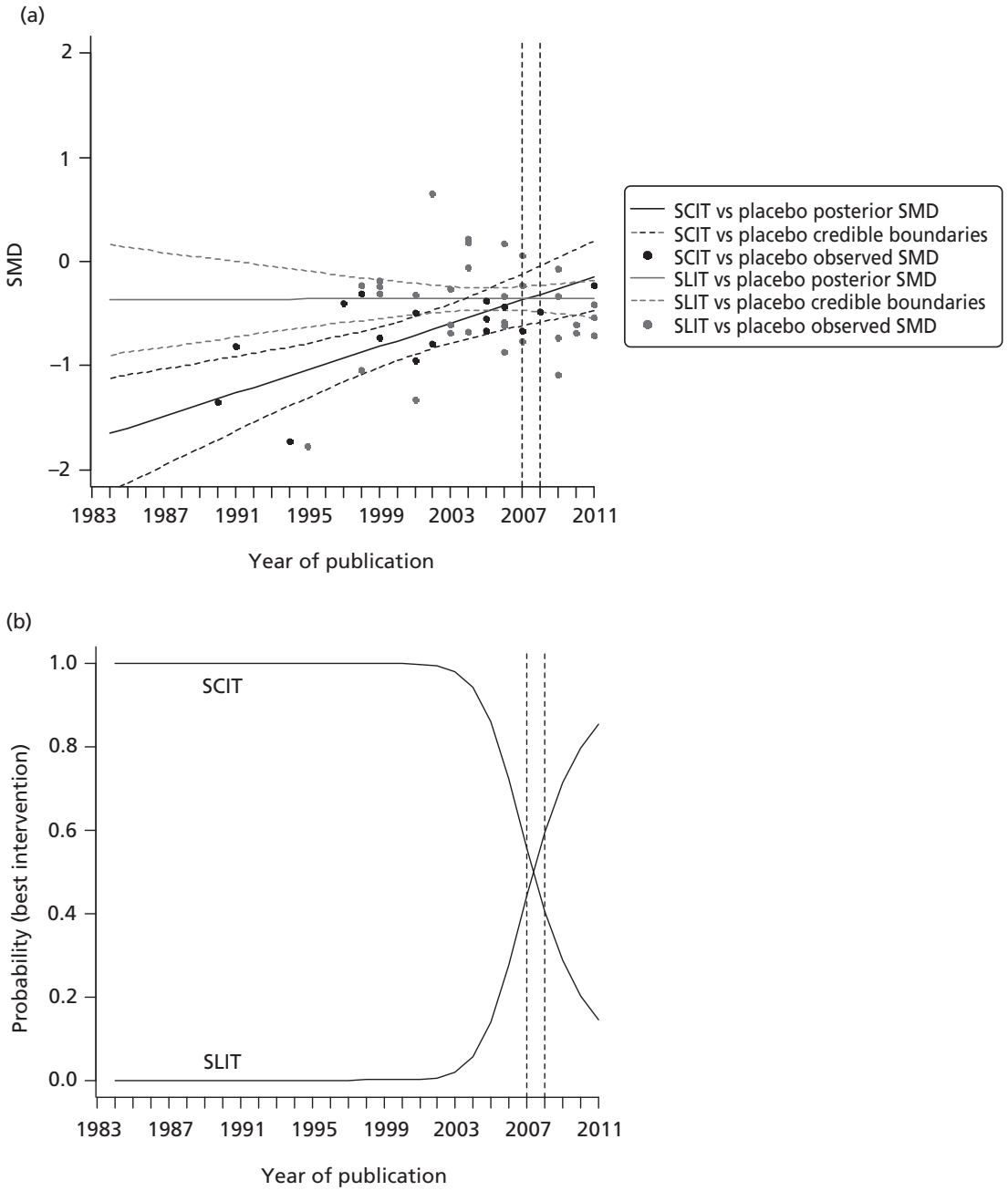

FIGURE 27 (a) Theoretical and observed SMDs (and credible boundaries) vs year of publication for the direct comparisons SCIT vs placebo and SLIT vs placebo, respectively. (b) Given the data included in the meta-regression, probability of SCIT and SLIT, respectively, being the best treatment vs year of publication.

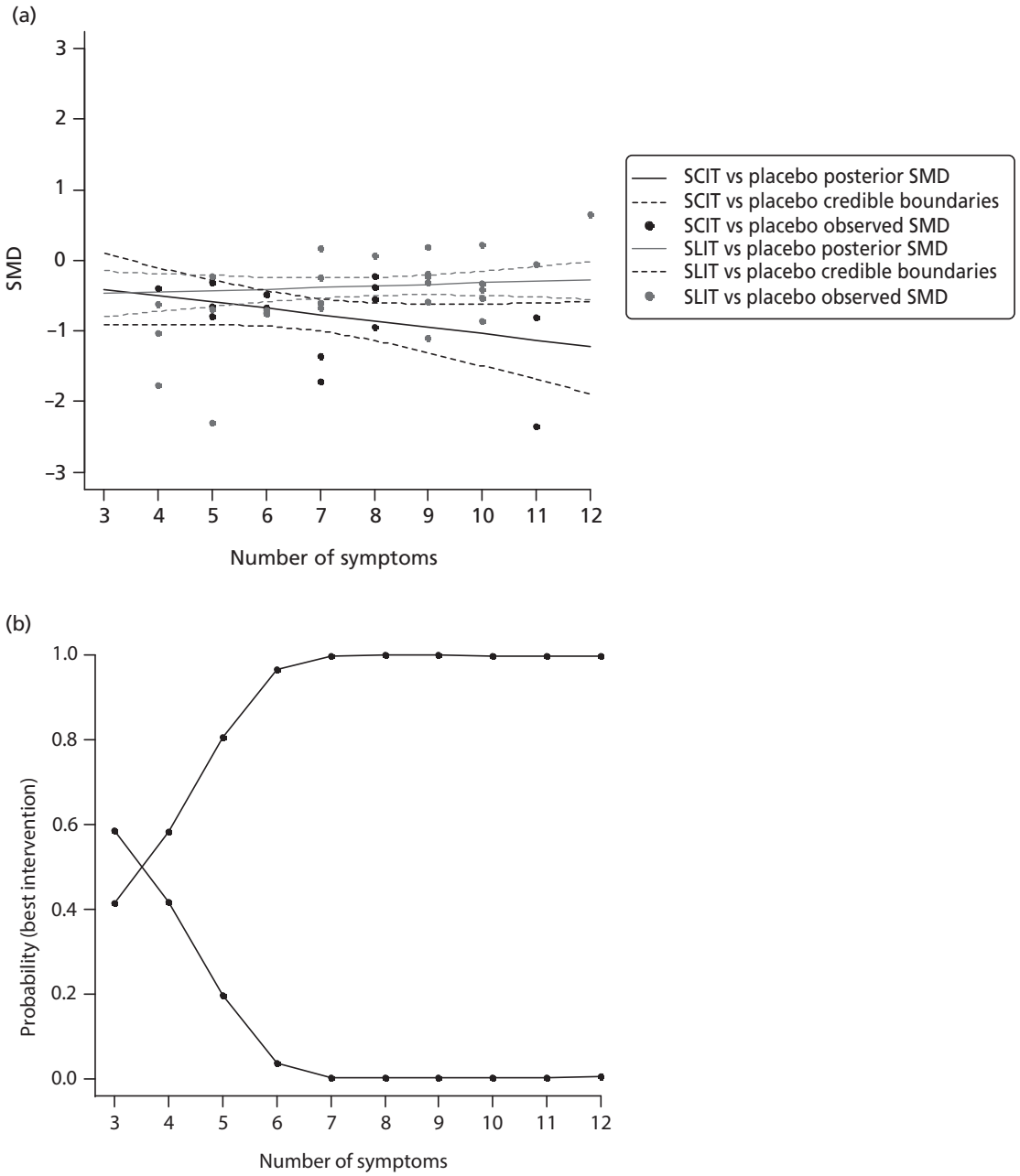

FIGURE 28 (a) Theoretical and observed SMDs (and credible boundaries) vs number of symptoms for the direct comparisons SCIT vs placebo and SLIT vs placebo, respectively. (b) Given the data included in the meta-regression, probability of SCIT and SLIT, respectively, being the best treatment vs number of symptoms.

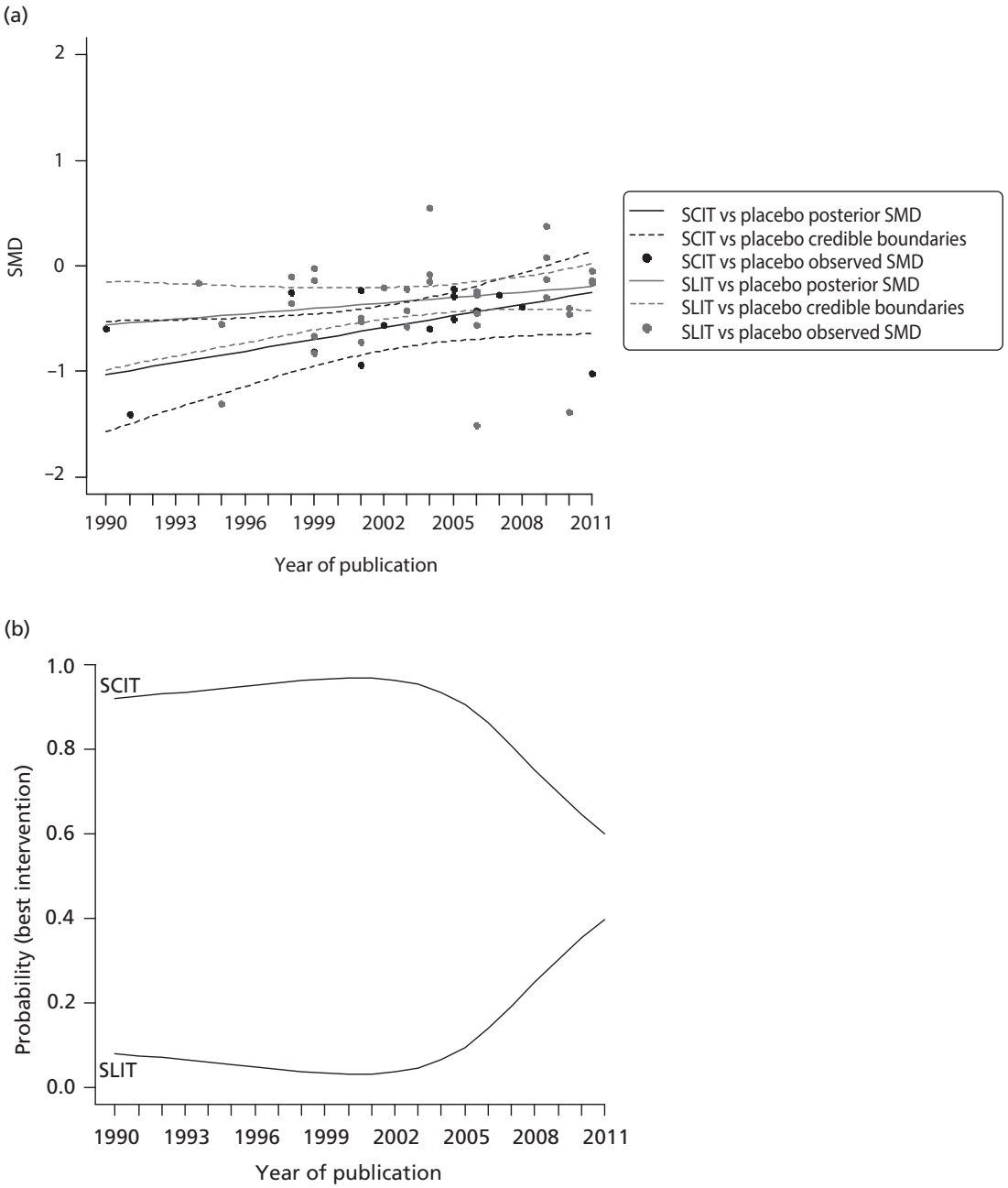

FIGURE 29 (a) Theoretical and observed SMDs (and credible boundaries) vs year of publication for the direct comparisons SCIT vs placebo and SLIT vs placebo, respectively. (b) Given the data included in the meta-regression, probability of SCIT and SLIT, respectively, being the best treatment vs year of publication.

TABLE 59 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (*d*)-MSs

Medication scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo[a]: direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT:[a] indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Fixed effects (no covariates)	51	d_k	–0.469 (–0.592 to –0.347)	–0.220 (–0.283 to –0.158)	0.249 (0.111 to 0.386)	459 (53)
Random effect (no covariates) **null model**	51	d_k	–0.579 (–0.808 to –0.370)	–0.306 (–0.449 to –0.177)	0.273 (0.027 to 0.529)	423 (83)
		σ^2	0.099 (0.030 to 0.211)			
Random effect (age of participants)	51	β_k	0.017 (–0.085 to 0.125)	–0.002 (–0.064 to 0.063)	–	429 (79)
		$d_{k,child}$	–0.051 (–0.087 to –0.019)	–0.041 (–0.069 to –0.017)	0.009 (–0.031 to 0.050)	
		$d_{k,adult}$	–0.034 (–0.133 to 0.065)	–0.043 (–0.101 to 0.015)	–0.009 (–0.124 to 0.106)	
		σ^2	0.002 (0.001 to 0.005)			
Random effects (year of publication)	51	β_k	0.037 (–0.001 to 0.076)	0.017 (–0.010 to 0.044)	–	422 (82)
		$d_{k,2000}$	–0.661 (–0.899 to –0.437)	–0.388 (–0.576 to –0.208)	0.273 (–0.016 to 0.571)	
		$d_{k,2005}$	–0.476 (–0.715 to –0.247)	–0.302 (–0.439 to –0.176)	0.174 (–0.091 to 0.439)	
		$d_{k,2010}$	–0.291 (–0.650 to 0.067)	–0.217 (–0.416 to –0.029)	0.074 (–0.335 to 0.477)	
		σ^2	0.091 (0.027 to 0.196)			
Random effects (duration[b])	48	β_{k1}	–0.111 (–0.894 to 0.671)	0.075 (–0.261 to 0.405)	–	375 (81) [376 (77)][c]
		β_{k2}	–0.287 (–0.977 to 0.379)	0.219 (–0.142 to 0.589)	–	
		$d_{k,6months}$	–0.395 (–0.994 to 0.202)	–0.389 (–0.620 to –0.170)	0.006 (–0.634 to 0.643)	
		$d_{k,6–12months}$	–0.506 (–1.013 to –0.007)	–0.314 (–0.573 to –0.073)	0.192 (–0.376 to 0.750)	
		$d_{k,>12months}$	–0.682 (–1.010 to –0.375)	–0.170 (–0.461 to 0.114)	0.511 (0.094 to 0.950)	
		σ^2	0.120 (0.039 to 0.255)			

continued

TABLE 59 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (*d*)-MSs (*continued*)

Medication scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo[a]: direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT:[a] indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Random effects (MAC)	37	β_{k1}	–0.135 (–0.670 to 0.397)	0.434 (0.074 to 0.806)	–	243 (57) [243 (53)][c]
		β_{k2}	–0.231 (–0.853 to 0.371)	0.352 (–0.035 to 0.740)	–	
		$d_{k,<5\mu g}$	–0.317 (–0.765 to 0.121)	–0.603 (–0.943 to –0.274)	–0.286 (–0.849 to 0.266)	
		$d_{k,5–6\mu g}$	–0.452 (–0.754 to –0.153)	–0.169 (–0.319 to –0.016)	0.283 (–0.049 to 0.622)	
		$d_{k,>20\mu g}$	–0.549 (–0.981 to –0.139)	–0.251 (–0.461 to –0.054)	0.298 (–0.164 to 0.765)	
		σ^2	0.042 (0.006 to 0.108)			
Random effects (allergen type)	52[d]	β_{k1}	0.276 (–0.317 to 0.915)	–0.297 (–0.776 to 0.184)	–	440 (87) [438 (83)][c]
		β_{k2}	0.351 (–0.142 to 0.879)	–0.199 (–0.540 to 0.143)	–	
		β_{k3}	–0.114 (–1.061 to 0.855)	–1.226 (–2.203 to –0.246)	–	
		β_{k4}	0.125 (–0.896 to 1.152)	–0.129 (–0.586 to 0.337)	–	
		$d_{k,grass}$	–0.715 (–1.052 to –0.416)	–0.211 (–0.383 to –0.050)	0.504 (0.169 to 0.873)	
		$d_{k,Parietaria}$	–0.440 (–0.967 to 0.092)	–0.508 (–0.958 to –0.058)	–0.068 (–0.761 to 0.619)	
		$d_{k,tree}$	–0.365 (–0.771 to 0.041)	–0.410 (–0.712 to –0.114)	–0.045 (–0.550 to 0.453)	
		$d_{k,Alternaria}$	–0.829 (–1.734 to 0.067)	–1.437 (–2.399 to –0.472)	–0.608 (–1.933 to 0.710)	
		$d_{k,ragweed}$	–0.591 (–1.575 to 0.381)	–0.340 (–0.771 to 0.095)	0.251 (–0.809 to 1.325)	
		σ^2	0.094 (0.024 to 0.209)			

a Differences d_k relative to the comparison of A vs B, need to be interpreted as $Y_A - Y_B$, where Y_A and Y_B are the score for treatment A and B, respectively.

b A number of studies were missing for NoSym <ref> and for Duration <ref>.

c The DIC (pD) of the null model when the same number of studies is included in the meta-analysis is reported within square brackets

d For Drachenberg (2001, SLIT)[91] the data used were combined scores for allergen types (AT) TREE and GRASS. However, when the effect of different AT was explored via meta-regression, separate scores for the two allergen types were used. Therefore, the number of studies in the analysis is 60 instead of 59.

TABLE 60 Probabilistic analysis for MSs [probability (%) that treatment *k* is the best under different modelling assumptions]

	Placebo	SCIT	SLIT
Fixed effect (51)	00.0	>99	00.0
Random effect (51)	00.0	98.4	01.6
Age group of participants (51)			
Child	00.0	68.1	31.9
Adult	01.8	43.1	55.1
Year of publication (51)			
2000	00.0	96.9	03.1
2005	00.0	90.6	09.4
2010	00.1	64.6	35.3
Duration (48)			
Low	00.0	50.9	49.1
Medium	00.0	75.6	24.3
High	00.0	99.1	00.9
MAC (37)			
<5 µg	00.0	15.1	84.9
5–20 µg	00.0	95.3	04.7
>20 µg	00.0	90.4	09.6
Allergen type (52)			
Grass	00.0	99.8	00.2
Parietaria	00.1	42.1	57.9
Tree	00.0	43.0	57.0
Alternaria	00.0	18.0	82.0
Ragweed	00.8	67.8	31.4

TABLE 61 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ^2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (*d*) –SMS

Medication scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo:[a] direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo[a]: direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT[a]: indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Fixed effects (no covariates)	15	d_k	–0.414 (–0.499 to –0.328)	–0.389 (–196.20 to 193.70)	0.024 (–195.80 to 194.10)	94 (16)
Random effects (no covariates) **null model**	15	d_k	–0.440 (–0.579 to –0.326)	–0.127 (–196.20 to 196.70)	0.313 (–195.80 to 197.10)	95 (20)
		σ^2	0.017 (0.0 to 0.086)			
Random effects (age of participants)	15	β_k	0.206 (–0.155 to 0.604)	–0.012 (–195.50 to 195.10)	–	95 (20)
		$d_{k,child}$	–0.258 (–0.616 to 0.097)	–0.170 (–277.60 to 274.30)	0.089 (–277.30 to 274.70)	
		$d_{k,adult}$	–0.464 (–0.616 to –0.346)	–0.157 (–196.90 to 196.20)	0.307 (–196.40 to 196.70)	
		σ^2	0.019 (0.0 to 0.097)			
Random effects (year of publication)	15	β_k	0.010 (–0.011 to 0.032)	0.337 (–195.60 to 196.40)	–	96 (21)
		$d_{k,2000}$	–0.513 (–0.716 to –0.331)	–1.606 (–1005.0 to 994.80)	–1.093 (–1004.0 to 995.30)	
		$d_{k,2005}$	–0.461 (–0.605 to –0.338)	0.079 (–196.30 to 195.80)	0.540 (–195.80 to 196.20)	
		$d_{k,2010}$	–0.409 (–0.566 to –0.276)	1.764 (–998.50 to 1003.0)	2.173 (–998.10 to 1003.0)	
		σ^2	0.020 (0.0 to 0.101)			
Random effects (duration[b])	12	β_{k1}	–0.016 (–0.544 to 0.387)	–0.109 (–195.40 to 195.40)	–	97 (18) [95 (17)]
		β_{k2}	–0.106 (–0.427 to 0.253)	0.092 (–196.0 to 195.10)	–	
		$d_{k,<6months}$	–0.387 (–0.668 to –0.160)	0.288 (–196.10 to 197.70)	0.676 (–195.70 to 198.10)	
		$d_{k,6–12months}$	–0.404 (–0.915 to –0.079)	0.180 (–275.0 to 279.10)	0.583 (–274.60 to 279.40)	
		$d_{k,>12months}$	–0.494 (–0.736 to –0.272)	0.380 (–276.60 to 278.70)	0.874 (–276.10 to 279.20)	
		σ^2	0.037 (0.0 to 0.210)			

Medication scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo:[a] direct comparisons (k = '2'), posterior mean (95% CrI)**	**SLIT vs placebo[a]: direct comparisons (k = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT[a]: indirect comparison (k = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Random effects (MAC)	10	β_{k1}	0.169 (–0.257 to 0.668)	–0.189 (–196.60 to 194.90)	–	75 (16) [75 (15)]
		β_{k2}	–0.244 (–0.855 to 0.403)	0.094 (–195.0 to 196.40)	–	
		$d_{k,<5\mu g}$	–0.508 (–0.911 to –0.180)	–0.004 (–197.40 to 197.90)	0.505 (–196.90 to 198.40)	
		$d_{k,5-6\mu g}$	–0.340 (–0.638 to –0.061)	–0.192 (–278.30 to 277.40)	0.148 (–278.0 to 277.80)	
		$d_{k,>20\mu g}$	–0.753 (–1.285 to –0.251)	0.091 (–277.10 to 280.20)	0.843 (–276.50 to 280.90)	
		σ^2	0.061 (0.0 to 0.338)			
Random effects (AT)	15	β_{k1}	–0.586 (–1.075 to –0.109)	0.359 (–194.90 to 197.30)	–	93 (22)
		β_{k2}	0.028 (–0.321 to 0.371)	0.039 (–196.40 to 198.10)	–	
		β_{k3}	–0.847 (–1.655 to –0.040)	–0.129 (–195.70 to 195.70)	–	
		β_{k4}	–0.149 (–0.679 to 0.374)	0.418 (–195.10 to 194.60)	–	
		$d_{k,grass}$	–0.387 (–0.512 to –0.269)	0.236 (–195.30 to 195.40)	0.623 (–194.90 to 195.70)	
		$d_{k,Parietaria}$	–0.973 (–1.447 to –0.509)	0.595 (–276.60 to 276.20)	1.568 (–275.70 to 277.10)	
		$d_{k,tree}$	–0.359 (–0.688 to –0.042)	0.274 (–278.10 to 277.80)	0.633 (–277.90 to 278.20)	
		$d_{k,Alternaria}$	–1.234 (–2.035 to –0.439)	0.107 (–275.90 to 277.50)	1.341 (–274.70 to 278.70)	
		$d_{k,ragweed}$	–0.536 (–1.059 to –0.028)	0.654 (–279.10 to 277.90)	1.189 (–278.60 to 278.40)	
		σ^2	0.011 (0.0 to 0.059)			

a Differences d_k relative to the comparison of A vs B, need to be interpreted as $Y_A - Y_B$, where Y_A and Y_B are the score for treatment A and B, respectively.

b A number of studies were missing for NoSym <ref> and for Duration <ref>.

TABLE 62 Probabilistic analysis for SMSs [probability (%) that treatment *k* is the best under different modelling assumptions]

Model (covariate included in the model)	Placebo	SCIT	SLIT
Fixed effect (15)	00.0	50.2	49.8
Random effect (15)	00.0	50.2	49.8
Age group of participants (15)			
Child	02.9	47.1	50.0
Adult	00.0	50.2	49.8
Year of publication (15)			
2000	00.0	49.8	50.2
2005	00.0	50.4	49.7
2010	00.0	50.3	49.7
Duration (12)			
Low	00.1	50.2	49.7
Medium	00.5	49.8	49.8
High	00.0	50.4	49.6
MAC (10)			
<5 µg	00.2	50.0	49.9
5–20 µg	00.7	49.2	50.0
>20 µg	00.2	49.8	50.0
Allergen type (15)			
Grass	00.0	50.3	49.7
Parietaria	00.0	50.4	49.6
Tree	00.7	49.5	49.8
Alternaria	00.1	50.3	49.7
Ragweed	01.0	49.5	49.5

TABLE 63 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ^2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (d)-QoL

QoL scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo[a]: direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT:[a] indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Fixed effects (no covariates)	15	d_k	–0.532 (–0.658 to –0.405)	–0.146 (–0.236 to –0.056)	0.386 (0.231 to 0.541)	43 (17)
Random effects (no covariates) **null model**	15	d_k	–0.580 (–0.892 to –0.280)	–0.197 (–0.498 to 0.089)	0.383 (–0.042 to 0.804)	–6 (27)
		σ^2	0.132 (0.041 to 0.342)			
Random effects (age of participants)	15	β_k	0.119 (–196.0 to 196.40)	–0.122 (–0.996 to 0.779)	–	–6 (27)
		$d_{k,child}$	–0.465 (–196.50 to 195.90)	–0.304 (–1.117 to 0.518)	0.161 (–196.0 to 196.40)	
		$d_{k,adult}$	–0.584 (–0.911 to –0.270)	–0.182 (–0.530 to 0.147)	0.402 (–0.062 to 0.864)	
		σ^2	0.149 (0.043 to 0.402)			
Random effects (year of publication)	15	β_k	–0.014 (–0.218 to 0.188)	0.039 (–0.170 to 0.267)	–	–5 (28)
		$d_{k,2000}$	–0.510 (–1.620 to 0.602)	–0.582 (–2.834 to 1.481)	–0.072 (–2.585 to 2.256)	
		$d_{k,2005}$	–0.581 (–0.926 to –0.247)	–0.387 (–1.525 to 0.659)	0.194 (–0.986 to 1.30)	
		$d_{k,2010}$	–0.651 (–1.691 to 0.364)	–0.193 (–0.532 to 0.137)	0.459 (–0.620 to 1.554)	
		σ^2	0.168 (0.048 to 0.467)			
Random effects (duration)	15	β_{k1}	0.462 (–1.082 to 2.002)	–0.085 (–1.087 to 0.975)	–	–4 (28)
		β_{k2}	0.571 (–0.745 to 1.869)	–0.260 (–1.048 to 0.576)	–	
		$d_{k,<6months}$	–1.096 (–2.327 to 0.146)	–0.113 (–0.616 to 0.343)	0.983 (–0.363 to 2.288)	
		$d_{k,6–12months}$	–0.634 (–1.562 to 0.297)	–0.198 (–1.113 to 0.719)	0.436 (–0.872 to 1.742)	
		$d_{k,>12months}$	–0.525 (–0.936 to –0.120)	–0.373 (–1.027 to 0.280)	0.152 (–0.617 to 0.925)	
		σ^2	0.197 (0.045 to 0.612)			

continued

TABLE 63 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ^2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (d)-QoL (*continued*)

QoL scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo[a]: direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT:[a] indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Random effects (MAC)	10	β_{k1}	–0.062 (–1.441 to 1.261)	–36.910 (–135.70 to 60.710)	–	1 (23) [–3 (18)]
		β_{k2}	–0.068 (–1.418 to 1.279)	–36.570 (–135.30 to 61.020)	–	
		$d_{k,<5\mu g}$	–0.587 (–1.767 to 0.593)	36.640 (–60.920 to 135.40)	37.220 (–60.470 to 136.0)	
		$d_{k,5–6\mu g}$	–0.649 (–1.354 to –0.007)	–0.274 (–0.889 to 0.332)	0.375 (–0.508 to 1.315)	
		$d_{k,>20\mu g}$	–0.655 (–1.303 to –0.008)	0.063 (–0.820 to 0.782)	0.718 (–0.393 to 1.670)	
		σ^2	0.260 (0.015 to 1.0)			
Random effects (allergen type)	15	β_{k1}	–0.159 (–0.899 to 0.585)	0.104 (–195.30 to 194.80)[b]	–	–5 (28)
		β_{k2}	0.393 (–195.20 to 196.20)[b]	–0.816 (–1.849 to 0.223)	–	
		β_{k3}	0.460 (–196.20 to 195.10)[b]	–0.157 (–195.20 to 194.0)[b]	–	
		β_{k4}	–0.629 (–1.853 to 0.591)	–0.030 (–195.50 to 197.20)[b]	–	
		β_{k5}	–0.304 (–1.319 to 0.723)	–0.017 (–195.80 to 195.90)[b]		
		$d_{k,grass}$	–0.461 (–0.891 to –0.037)	–0.127 (–0.445 to 0.196)	0.334 (–0.197 to 0.868)	
		$d_{k,Parietaria}$	–0.620 (–1.224 to –0.009)	–0.022 (–195.40 to 194.80)	0.597 (–194.80 to 195.30)	
		$d_{k,tree}$	–0.068 (–195.80 to 195.80)	–0.943 (–1.926 to 0.046)	–0.875 (–196.70 to 194.80)	
		$d_{k,Alternaria}$	–0.001 (–196.70 to 194.70)	–0.284 (–195.30 to 193.80)	–0.283 (–275.80 to 277.0)	
		$d_{k,ragweed}$	–1.090 (–2.237 to 0.050)	–0.157 (–195.60 to 197.10)	0.933 (–194.70 to 198.0)	
		$d_{k,Salsola\ kali}$	–0.765 (–1.696 to 0.164)	–0.143 (–195.90 to 195.80)	0.622 (–195.10 to 196.60)	
		σ^2	0.143 (0.038 to 0.420)			

a Differences d_k relative to the comparison of A vs B, need to be interpreted as $Y_A - Y_B$, where Y_A and Y_B are the score for treatment A and B, respectively..

b Such a wide CrI is due to the fact that there is no study reporting such covariate that can inform that parameter.

TABLE 64 Probabilistic analysis for QoL scores [probability (%) that treatment *k* is the best under different modelling assumptions]

Model (covariate included in the model)	Placebo	SCIT	SLIT
Fixed effect (15)	00.0	>99	00.0
Random effect (15)	00.0	96.4	03.6
Age group of participants (15)			
Child	10.5	50.0	39.5
Adult	00.0	95.9	04.1
Year of publication (15)			
2000	05.0	45.0	49.9
2005	00.0	64.5	35.5
2010	01.2	81.0	17.8
Duration (15)			
Low	01.3	92.6	06.1
Medium	02.6	76.1	21.3
High	00.2	66.8	33.0
MAC (10)			
<5 µg	10.9	68.3	20.9
5–20 µg	00.6	83.3	16.2
>20 µg	01.2	91.3	07.5
Allergen type (15)			
Grass	00.5	90.2	09.3
Parietaria	01.2	49.1	49.8
Tree	01.5	49.7	48.8
Alternaria	25.0	37.4	37.6
Ragweed	01.5	48.9	49.6
Salsola kali	02.5	47.8	49.7

TABLE 65 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ^2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (d)-RQLQ scores

RQLQ scores						
Covariate (no studies)	***n***	**Parameter**	**SCIT vs placebo**	**SLIT vs placebo**	**SLIT vs SCIT (indirect comparison)**	**DIC (pD)**
Fixed effects	12	d_k	–0.740 (–0.920 to –0.560)	0.071 (–0.010 to 0.151)	0.811 (0.614 to 1.007)	49 (14)
Random effects	12	d_k	–0.764 (–1.116 to –0.425)	–0.247 (–0.729 to 0.156)	0.517 (–0.071 to 1.045)	–2 (26)
		σ^2	0.155 (0.033 to 0.494)			
Age of participants	12	β_k	–0.023 (–195.20 to 195.40)	–0.047 (–196.70 to 195.80)	–	–2 (21)
		$d_{k,child}$	–0.788 (–196.10 to 194.60)	–0.294 (–197.10 to 195.60)	0.493 (–276.90 to 278.70)	
		$d_{k,adult}$	–0.765 (–1.115 to –0.421)	–0.248 (–0.734 to 0.159)	0.517 (–0.085 to 1.051)	
		σ^2	0.158 (0.033 to 0.506)			
Year of publication	12	β_k	–0.034 (–0.280 to 0.216)	0.133 (–0.169 to 0.475)	–	–1 (22)
		$d_{k,2000}$	–0.588 (–1.962 to 0.763)	–1.526 (–4.797 to 1.357)	–0.939 (–4.488 to 2.230)	
		$d_{k,2005}$	–0.758 (–1.162 to –0.370)	–0.860 (–2.466 to 0.558)	–0.102 (–1.748 to 1.365)	
		$d_{k,2010}$	–0.928 (–2.154 to 0.306)	–0.193 (–0.756 to 0.338)	0.735 (–0.634 to 2.074)	
		σ^2	0.221 (0.044 to 0.734)			
Duration	12	β_{k1}	0.202 (–1.426 to 1.853)	–0.212 (–195.10 to 194.80)	–	1 (22)
		β_{k2}	0.393 (–0.986 to 1.763)	–0.182 (–1.092 to 1.039)	–	
		$d_{k,<6months}$	–1.094 (–2.395 to 0.206)	–0.144 (–1.107 to 0.518)	0.950 (–0.686 to 2.364)	
		$d_{k,6–12months}$	–0.892 (–1.909 to 0.138)	–0.355 (–195.20 to 194.60)	0.536 (–194.30 to 195.20)	
		$d_{k,>12months}$	–0.70 (–1.170 to –0.251)	–0.326 (–1.034 to 0.388)	0.374 (–0.454 to 1.228)	
		σ^2	0.226 (0.006 to 0.946)			

RQLQ scores						
Covariate (no studies)	***n***	**Parameter**	**SCIT vs placebo**	**SLIT vs placebo**	**SLIT vs SCIT (indirect comparison)**	**DIC (pD)**
MAC	10	β_{k1}	–0.309 (–138.70 to 137.60)	0.008 (–138.50 to 139.60)	–	4 (19) [1 (17)]
		β_{k2}	–0.230 (–196.80 to 195.50)	0.411 (–195.60 to 197.40)	–	
		$d_{k,<5\mu g}$	–0.546 (–138.40 to 137.90)	–0.171 (–139.80 to 138.30)	0.375 (–195.10 to 196.20)	
		$d_{k,5–6\mu g}$	–0.855 (–1.237 to –0.475)	–0.162 (–0.782 to 0.303)	0.692 (–0.046 to 1.281)	
		$d_{k,>20\mu g}$	–0.775 (–239.60 to 240.10)	0.240 (–238.80 to 240.70)	1.015 (–337.90 to 341.10)	
		σ^2				
Allergen type	12	β_{k1}	–0.121 (–0.987 to 0.780)	0.710 (–195.20 to 196.10)		–1 (22)
		β_{k2}	–0.128 (–195.90 to 195.90)	–1.222 (–2.588 to 0.152)		
		β_{k3}	0.014 (–194.60 to 195.0)	0.439 (–196.60 to 196.40)		
		β_{k4}	–0.416 (–1.741 to 0.937)	–0.140 (–195.50 to 194.70)		
		β_{k5}	–0.117 (–1.276 to 1.059)	–0.253 (–196.50 to 194.30)		
		$d_{k,grass}$	–0.685 (–1.213 to –0.171)	–0.109 (–0.637 to 0.411)	0.576 (–0.154 to 1.316)	
		$d_{k,Parietaria}$	–0.806 (–1.511 to –0.081)	0.602 (–195.40 to 195.90)	1.407 (–194.60 to 196.60)	
		$d_{k,tree}$	–0.813 (–196.60 to 195.20)	–1.330 (–2.597 to –0.062)	–0.518 (–196.60 to 195.30)	
		$d_{k,Alternaria}$	–0.671 (–195.50 to 194.40)	0.330 (–196.70 to 196.40)	1.001 (–276.20 to 276.10)	
		$d_{k,ragweed}$	–1.101 (–2.327 to 0.144)	–0.249 (–195.70 to 194.70)	0.852 (–194.50 to 195.50)	
		$d_{k,Salsola\ kali}$	–0.802 (–1.858 to 0.251)	–0.361 (–196.60 to 194.30)	0.440 (–195.70 to 195.20)	
		σ^2	0.196 (0.032 to 0.771)			

TABLE 66 Probabilistic analysis for RQLQ scores [probability (%) that treatment *k* is the best under different modelling assumptions]

Model (covariate included in the model)	Placebo	SCIT	SLIT
Fixed effects (12)	00.0	>99	00.0
Random effects (12)	00.0	96.2	03.8
Age group of participants (12)			
Child	24.7	37.8	37.5
Adult	00.0	96.0	04.0
Year of publication (12)			
2000	02.8	26.9	70.3
2005	00.0	46.3	53.7
2010	01.5	86.8	11.8
Duration (12)			
Low	01.5	88.9	09.6
Medium	01.9	48.3	49.8
High	00.1	85.8	14.0
MAC (10)			
<5 µg	24.9	37.7	37.4
5–20 µg	00.0	97.0	03.0
>20 µg	24.8	37.7	37.5
Allergen type (12)			
Grass	00.3	94.7	04.9
Parietaria	00.9	49.6	49.5
Tree	01.0	49.7	49.3
Alternaria	24.8	37.9	37.3
Ragweed	01.9	48.4	49.7
Salsola kali	03.0	47.3	49.8