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Comparison of the Mantel-Haenszel and Peto Methods Used in Meta-Analysis: Methodological Study

Metaanalizde Kullanılan Mantel-Haenszel ve Peto Yöntemlerinin Karşılaştırılması: Metodolojik Çalışma

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ABSTRACT Objective: Meta-analysis methods aim to achieve a single common summary statistic for the parameter estimation by combining homogeneous statistics from different studies. In this study, the performances of two of the most preferred meta-analysis approach used for combining summary statistics calculated from binary data sets, the Mantel-Haenszel (MH) and Peto methods, are examined. **Material and Methods:** In the study, the performances of the MH and Peto methods, were examined by means of a simulation study. Hypothetical populations formed from 1,000,000 units with different disease-cause rates ($P(E^+\backslash P^+)$=0.50, 0.60, 0.70, 0.80, 0.90) were created. Both methods were applied by generating odds ratios with data obtained from samples taken from each hypothetical population having different disease-cause rates (P), in different sample sizes (n), and with different numbers of studies (k). To compare the performance of the methods, relative bias (RB) and relative mean squared error scales were used. **Results:** Considering that the studies taken for meta-analysis are both homogeneous and heterogeneous, the data obtained from the simulation study were analyzed and the results obtained from the analysis were presented through tables. Evaluation of the performance of the 2 methods according to RB and relative mean squared error criteria according to (n) and (k) are presented with graphics. **Conclusion:** For both the fixed effects model and the random effects model, the Peto method provides more coherent estimates for the population parameter than the MH method.

Keywords: Meta-analysis; odds ratio; Mantel-Haenszel method; Peto method; simulation

ÖZET Amaç: Metaanaliz yöntemleri, farklı çalışmalardan elde edilen homojen özet istatistikleri birleştirerek, parametre tahmini için tek bir ortak özet istatistik elde etmeyi amaçlar. Bu çalışmada, ikili değerler alan veri setlerinden hesaplanan özet istatistiklerinin birleştirilmesinde kullanılan ve en çok tercih edilen metaanaliz yaklaşımlarından 2'si olan Mantel-Haenszel (MH) ve Peto yöntemlerinin performansları incelenmiştir. **Gereç ve Yöntemler:** Çalışmada, MH ve Peto yöntemlerinin performansları simülasyon çalışması ile incelenmiştir. Farklı hastalık-etken oranlarına sahip ($P(E^+\backslash P^+)$=0,50, 0,60, 0,70, 0,80, 0,90) olan 1.000.000 birimden oluşan varsayımsal popülasyonlar oluşturulmuştur. Her iki yöntem, farklı hastalık-etken oranlarına (P) sahip her bir varsayımsal popülasyondan, farklı örneklem büyüklüklerinde (n) ve farklı sayıda çalışmadan (k) alınan örneklerden elde edilen verilerle göreceli olasılıklar oranları üretilerek uygulanmıştır. Yöntemlerin performanslarının karşılaştırılması amacıyla rölatif bias (RB) ve rölatif hata kareleri ortalaması ölçekleri kullanılmıştır. **Bulgular:** Meta-analiz için alınan çalışmaların hem homojen hem de heterojen olduğu dikkate alınarak gerçekleştirilen simülasyon çalışmasından elde edilen veriler analiz edilmiştir ve analizden elde edilen sonuçlar tablolar aracılığıyla sunulmuştur. İki yöntemin performansının RB ve rölatif hata kareleri ortalaması kriterlerine göre örneklem büyüklüğü (n) değerleri ve metaanaliz için alınan çalışma sayısı (k) referans alınarak değerlendirilmesi grafikler aracılığıyla sunulmuştur. **Sonuç:** Hem sabit etki modeli hem de rastgele etki modeli için Peto yöntemi, popülasyon parametresi için MH yönteminden daha tutarlı tahminler sağlamıştır.

Anahtar kelimeler: Meta-analiz; odds oranı; Mantel Haenszel yöntemi; Peto yöntemi; simülasyon

In scientific researches, it may not always be possible to conduct researches with high representativeness for the population or having a large sample size, due to cost or lack of time, experts or staff. For this reason, especially in researches conducted in the field of health, clinical trials and studies are undertaken on

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a limited number of units. In some cases, too, due to the fact that the number of units bearing the relevant characteristic is limited, it is considered necessary to conduct multicentre studies or expand them to different time frames. It is also sometimes necessary to work with small samples due to ethical reasons.[1] Consequently, despite the place and time differences, if these studies are combined by means of suitable approaches, more valid parameter estimations with regard to population will be made.[2,3] For these reasons, the need to develop suitable combination methods has arisen.

Meta-analysis methods aim to achieve a single common summary statistic for the parameter estimation by combining homogeneous statistics from different studies. By this means, effective, coherent, and unbiased parameter estimations are achieved by combining the results of researches undertaken in different places and at different times.[3-5] For this purpose, sub-methods and sub-techniques in the form of different parameter estimations such as mean, ratio, odds ratio (OR), or relative risk (RR), or for making parameter estimations according to different statistics such as test statistics or significance level, have been developed in the meta-analysis.

In health sciences, one of the data types commonly used is categorical data. Especially in cases where the relevant variable is binary, different-type summary statistics are calculated. Respectively, these are risk difference (RD), which is calculated from the difference between 2 probabilities; RR, obtained from the ratio of these 2 probabilities; OR, which is formed from the ratio between the probability of a property's presence and that of its absence; and the number needed to treat (NNT).[6-10]

In this study, the performances of 2 of the most preferred meta-analysis approach used for combining summary statistics calculated from binary data sets, the Mantel-Haenszel (MH) and Peto methods, are examined.[11-13] The 2 methods are compared by means of a simulation study of different rates, of incidence, of disease by cause, both for different numbers of studies and for different sample sizes, in homogeneous and non-homogeneous patterns.

GENERAL INFORMATION

SUMMARY STATISTICS FOR BINARY DATA

Descriptive statistics that are frequently used in comparing the risk between 2 groups are known as RR, OR, RD, and NNT.[6-10]

In this study, the performances of the MH and Peto methods, frequently encountered in the field of health in the analysis of data obtained from case-control studies, and based upon the OR, a summary statistic that enables calculation of the degree of cause and effect relationship, are compared. For the calculation of summary statistics and an explanation of the methods, Table 1 is given.

TABLE 1: Contingency table used in the calculation of summary statistics for binary data.

		Exposure		Total
		E^+	E^-	
Group	Patient (P^+)	a_i	b_i	n_P (a_i+b_i=g_i)
	Healthy (P^-)	c_i	d_i	n_H (c_i+d_i=$\square_i$)
Total		(a_i+c_i=e_i)	(b_i+d_i=f_i)	n_i

CHOICE OF STATISTICAL MODEL USED IN COMBINING STUDIES

Choice of the statistical model is of importance in the meta-analysis, and analyses are carried out by selecting either the fixed effects model or the random effects model.[6,8,14-16]

FIXED EFFECTS MODEL

Each study taken up for meta-analysis is based on the assumption that it possesses a common effect size. That is since it is assumed that all factors influencing effect size are the same in all studies taken up for meta-analysis, it is accepted that actual effect size is constant for all studies. The actual effect size is shown by θ and is equal to the mean of actual effect sizes for all studies.[14-16]

Generally, the observed effect size belonging to each study (Y_i) is the total of the actual effect size belonging to each study (μ) and the sampling error for that study (ε_i) (equation (1)).[14,15]

$$Y_i = \mu + \varepsilon_i \qquad (1)$$

RANDOM EFFECTS MODEL

When decisions are made in the meta-analysis, while it is assumed that the effect sizes of all studies are similar, the actual effect size is not exactly the same in all studies.

When the random effects model is used in the meta-analysis, observed effect size (Y_i) and real effect size (θ_i) show normal distribution ($N(\theta_i, \sigma^2)$ shows normal distribution here with $N(\mu, \tau^2)$ in θ_i).[14-16]

In the random effects model, the observed effect size for each study (Y_i) is the sum of the variance $\left((\theta - \mu) = \xi_i\right)$ between real effect size (θ_i) and population mean (μ), and the variance between the real and observed effect sizes in the study $\left((Y_i - \theta) = \varepsilon_i\right)$ (equation (2)).[14,15]

$$Y_i = \mu + \xi_i + \varepsilon_i \qquad (2)$$

In both effect models, each study is weighted with the inverse of its variance. However, differently from the fixed effects model, the study variance in the random effects model is equal to the sum of the within-study variance and the between-study variance (τ^2).

In the meta-analysis, the fixed effects model is used for homogeneous studies resulting from homogeneity tests, whereas for heterogeneous studies, the random effects model is used.[14,15]

METHODS USED FOR COMBINING SUMMARY STATISTICS OF BINARY DATA

MANTEL HAENSZEL METHOD

In the form of two-by-two data sets, the MH method is commonly used to combine research findings. This method is mostly used for the combining of ORs.[11] In the calculation of the OR from the 2x2 tables, if one or more of the cells in the table contains a value of zero, the typical approach is to add the value 0.5 (or some other value) to all of four cells. The combined OR for the MH technique may be calculated using the information in Table 1.

$$OR_{MH} = \frac{\sum_{i=1}^{k} OR_i \times W_i}{\sum_{i=1}^{k} W_i} \qquad (3)$$

Here, OR_i shows each study summary statistic, k shows the number of studies and W_i shows the weight of each study. In equation (3),

$$Var_i = \frac{n_i}{b_i \times c_i} \qquad (4)$$

and is calculated in this way:

$$W_i = \frac{1}{Var_i} \qquad (5)$$

The variance in the combined OR with the MH method is obtained as shown in equation (6).[14,17]

$$VarOR_{MH} = \left[\sum_{i=1}^{k}\left[\frac{1}{(a_i)^{-1} + (b_i)^{-1} + (c_i)^{-1} + (d_i)^{-1}}\right]\right]^{-1} \quad (6)$$

PETO METHOD

The Peto method is a different form of the MH method. An alternative method is used to combine data when the summary statistic is the OR. It is similar to the MH method and easier to evaluate as well.[12] The combined OR for the Peto method can also be calculated using the information presented in Table 1, the following process is given:[14,17]

i. The expected number of cases in the patient group for each study is as shown in equation (7).

$$E_i = \frac{(e_i \times g_i)}{n_i} \quad (7)$$

ii. The difference between the observed number of cases (O_i) and the expected number of cases (E_i) in the patient group for each study is $Difference_i = O_i - E_i$.

iii. The variance is the difference between the observed and expected number of cases for each study is estimated with equation (8).

$$Var_i = \frac{(E_i \times f_i \times \square_i)}{n_i(n_i - 1)} \quad (8)$$

iv. The sum of the observed and expected difference values is $Total = \sum_{i=1}^{k}(O_i - E_i)$.

v. The variance totals are as shown in equation (9).

$$Var_{Tot} = \sum_{i=1}^{k} Var_i \quad (9)$$

vi. The natural logarithm of the combined OR obtained total difference values by dividing total variance is estimated with equation (10).

$$ln\ OR_{Peto} = \frac{\sum_{i=1}^{k}(O_i - E_i)}{\sum_{i=1}^{k} Var_i} \quad (10)$$

vii. The combined OR obtained by taking the exponential value of $lnOR_{Peto}$ is estimated with $OR_{Peto} = e^{lnOR_{Peto}}$.

MATERIAL AND METHODS

In the study, the performance of the MH and Peto methods, which are the most frequently preferred methods used for combining the summary statistics of binary data, were examined by means of a simulation study. For this purpose, hypothetical populations formed from 1,000,000 units with different disease-cause rates ($P(E^+\backslash P^+)$=0.50, 0.60, 0.70, 0.80, 0.90) were created. MH and Peto methods were applied by generating OR using data obtained from samples taken from each hypothetical population having different disease-cause rates (P), in different sample sizes (n), and with different numbers of studies (k). The homogeneity of the studies to be combined was tested according to Cochran's Q test at a significance level of α=0.10. The study was carried out for both homogeneous and heterogeneous cases.[18] To compare the performance of the methods, relative bias (RB) and relative mean squared error (RMSE) criteria were used.[19] These criteria, arranged in a way to suit the OR summary statistic, are shown in equations (11) and (12):

$$RB = \sum_{i=1}^{n} \frac{\left(\frac{\widehat{OR}_i}{OR} - 1\right)}{n} \quad (11)$$

and

$$RMSE = \sum_{i=1}^{n} \frac{\left(\frac{\widehat{OR}_i}{OR} - 1\right)^2}{n} \qquad (12)$$

RB can take either positive or negative values. If RB is negative, this estimated value shows that it is below the population value (underestimate), whereas, the estimated value shows that it is above the population value (overestimate) when it is positive. Therefore, approaching low values according to absolute value for this criterion signifies that the estimates are good and that they approach population value.

The RMSE criterion, however, takes values between 0 and ∞. In other words, the estimates can be expressed as the amount of general deviation from the population parameter. In this criterion, it is stated that as the value decreases, the estimated value approaches population value.

SIMULATION SCENARIOS

In the simulation study, hypothetical populations, N_H=1,000,000, having $P(E^+\backslash P^-)$=0.5 probability of cause (E^+) for the healthy group (P^-), and N_P=1,000,000, for each patient group and having $P(E^+\backslash P^+)$=0.5, 0.6, 0.7, 0.8, 0.9 probabilities of cause (E^+) for the patient group (P^+), were generated from the binomial distribution. From each hypothetical population generated, k=4, 6, 8, 10, 25 and 50 random samples were taken in small and large sample sizes (n_P=n_H=4, 8, 12, 16, 25, 50 and 100). In the simulation study, the repeat number was taken as 1,000. The simulation study was carried out by using the R-project v4.0.3 program. For the meta-analysis, the "metabin" function in the R-project program was used.[20]

By combining the OR values calculated from the homogeneous and heterogeneous random samples taken from the created hypothetical populations by means of the MH and Peto methods, the combined OR values (OR_{MH} and OR_{Peto}) were obtained. For the homogeneous studies, the fixed effects model was used, and the RB and RMSE values were calculated by using the obtained OR_{MH} and OR_{Peto} values and the related population OR values.

Similarly, for the heterogeneous studies, the random effects model was used, and the RB and RMSE values were calculated by using the obtained OR_{MH} and OR_{Peto} values and the related population OR values. To ensure heterogeneity, each study was analyzed by sampling from different populations.

RESULTS

The data obtained from the simulation study, which was carried out by considering that the studies taken up for meta-analysis were both homogeneous and heterogeneous, were analyzed and the results obtained from the analysis are shown in Table 2 and Table 3.

For the fixed effects model, the RB and RMSE values, calculated with the OR values of the hypothetical populations according to different disease-cause rates, for evaluating the performance of the MH and Peto methods, are presented in Table 2.

For the random effects model, the combined ORs, combined by the MH and Peto methods for OR values calculated as $OR_{0.6}$=1.502, $OR_{0.7}$=2.344 $OR_{0.8}$=4.000, $OR_{0.9}$=9.036 from hypothetical populations with disease-cause rates of $P(E^+\backslash P^+)$=0.60, 0.70, 0.80, 0.90, were calculated as OR_{MH}=3.359, OR_{Peto}=3.057. The RB and RMSE values, calculated according to the combined ORs, are presented in Table 3.

The graphs aiming to evaluate the performance of the 2 methods according to the RB and RMSE criteria, with reference to sample size (n) values and the number of studies (k) taken up for meta-analysis, are presented in 2 different figures (Figure 1, Figure 2, Figure 3, Figure 4).

TABLE 2: Simulation results for fixed effect model.

k	$n_P=n_H$	$P(E^+\|H^-)=0.5$ vs $P(E^+\|H^+)=0.5$ Population OR=1.0024				$P(E^+\|H^-)=0.5$ vs $P(E^+\|H^+)=0.7$ Population OR=2.3362				$P(E^+\|H^-)=0.5$ vs $P(E^+\|H^+)=0.9$ Population OR=9.0080			
		RB_{MH}	RB_{Peto}	$RMSE_{MH}$	$RMSE_{Peto}$	RB_{MH}	RB_{Peto}	$RMSE_{MH}$	$RMSE_{Peto}$	RB_{MH}	RB_{Peto}	$RMSE_{MH}$	$RMSE_{Peto}$
4	4	0.4620	0.3339	1.9012	1.0305	-0.0741	-0.2028	0.5593	0.2980	-0.6590	-0.7208	0.4840	0.5394
	8	0.3299	0.2729	1.3959	0.9930	0.3095	0.1202	1.2743	0.5460	-0.3382	-0.5002	0.2892	0.3022
	12	0.1871	0.1644	0.6706	0.5450	0.2672	0.1293	0.9153	0.4280	-0.1319	-0.3853	0.2996	0.2108
	16	0.1458	0.1330	0.4453	0.3789	0.2231	0.1166	0.6735	0.3361	-0.0032	-0.3252	0.3318	0.1639
	25	0.0695	0.0657	0.2084	0.1950	0.1033	0.0477	0.2497	0.1693	0.1403	-0.2621	0.4461	0.1236
	50	0.0503	0.0491	0.1004	0.0974	0.0720	0.0361	0.1303	0.0960	0.1223	-0.2419	0.2417	0.0906
	100	0.0221	0.0218	0.0447	0.0441	0.0226	0.0002	0.0489	0.0404	0.0809	-0.2398	0.1132	0.0750
6	4	0.3757	0.2706	1.5778	0.8983	-0.1114	-0.2227	0.4666	0.2710	-0.6604	-0.7214	0.4838	0.5396
	8	0.2463	0.2008	1.1065	0.7713	0.2409	0.0734	1.1103	0.4844	-0.3408	-0.5040	0.3029	0.3095
	12	0.2052	0.1785	0.7949	0.6042	0.2452	0.1165	0.8116	0.4148	-0.1175	-0.3821	0.3150	0.2101
	16	0.1640	0.1511	0.4312	0.3785	0.2396	0.1276	0.7196	0.3646	0.0162	-0.3189	0.3996	0.1687
	25	0.0950	0.0904	0.2345	0.2184	0.1264	0.0663	0.2831	0.1891	0.1431	-0.2618	0.4706	0.1230
	50	0.0550	0.0538	0.0949	0.0922	0.0755	0.0401	0.1197	0.0910	0.1374	-0.2358	0.2533	0.0862
	100	0.0120	0.0118	0.0403	0.0398	0.0188	-0.0033	0.0489	0.0409	0.1030	-0.2302	0.1334	0.0711
8	4	0.4205	0.3002	1.8422	0.9936	-0.1094	-0.2284	0.5349	0.2957	-0.6643	-0.7241	0.4890	0.5436
	8	0.3445	0.2798	1.5157	1.0040	0.2561	0.0816	1.2330	0.5300	-0.3327	-0.4986	0.3017	0.3054
	12	0.1753	0.1540	0.6147	0.4916	0.2808	0.1368	0.9707	0.4706	-0.1218	-0.3844	0.3454	0.2147
	16	0.1422	0.1308	0.3981	0.3524	0.2175	0.1160	0.5935	0.3358	0.0277	-0.3164	0.4016	0.1651
	25	0.1083	0.1030	0.2357	0.2194	0.1013	0.0447	0.2641	0.1787	0.1532	-0.2557	0.4525	0.1183
	50	0.0526	0.0513	0.0970	0.0940	0.0391	0.0070	0.1074	0.0835	0.1621	-0.2315	0.3357	0.0874
	100	0.0219	0.0216	0.0479	0.0472	0.0263	0.0036	0.0484	0.0398	0.0869	-0.2379	0.1246	0.0759
10	4	0.3522	0.2435	1.7423	0.9433	-0.0729	-0.1995	0.5239	0.2842	-0.6515	-0.7160	0.4770	0.5332
	8	0.3097	0.2577	1.2167	0.8630	0.3566	0.1532	1.4628	0.5973	-0.3526	-0.5123	0.3353	0.3202
	12	0.2052	0.1783	0.7839	0.6174	0.2361	0.1014	0.9680	0.4230	-0.1029	-0.3716	0.2984	0.2026
	16	0.1269	0.1162	0.3730	0.3279	0.2076	0.1037	0.6552	0.3450	0.0172	-0.3210	0.3795	0.1675
	25	0.0862	0.0817	0.2182	0.2037	0.1415	0.0730	0.3730	0.2242	0.1671	-0.2508	0.4674	0.1191
	50	0.0229	0.0222	0.0827	0.0805	0.0515	0.0182	0.1136	0.0867	0.1602	-0.2298	0.2934	0.0850
	100	0.0140	0.0137	0.0448	0.0442	0.0283	0.0053	0.0508	0.0414	0.0642	-0.2462	0.1106	0.0775
25	4	0.3769	0.2752	1.4529	0.8533	-0.0585	-0.1917	0.5701	0.2977	-0.6619	-0.7220	0.4852	0.5402
	8	0.3222	0.2543	1.7309	1.0833	0.3296	0.1327	1.4232	0.5756	-0.3181	-0.4920	0.3260	0.3025
	12	0.1958	0.1697	0.7461	0.5628	0.2538	0.1171	0.9030	0.4474	-0.1174	-0.3773	0.2898	0.2023
	16	0.1402	0.1260	0.4953	0.4143	0.1887	0.0878	0.6359	0.3256	0.0275	-0.3114	0.3476	0.1592
	25	0.1162	0.1095	0.2871	0.2600	0.1320	0.0643	0.3949	0.2155	0.1671	-0.2525	0.4408	0.1177
	50	0.0237	0.0228	0.0867	0.0841	0.0519	0.0188	0.1103	0.0845	0.1378	-0.2388	0.2846	0.0909
	100	0.0268	0.0265	0.0472	0.0465	0.0297	0.0068	0.0490	0.0403	0.0770	-0.2393	0.1104	0.0742
50	4	0.3659	0.2578	1.7016	0.9357	-0.0680	-0.1988	0.5634	0.3017	-0.6527	-0.7182	0.4811	0.5371
	8	0.2880	0.2329	1.3762	0.9162	0.2242	0.0687	0.9566	0.4605	-0.3231	-0.4977	0.3317	0.3080
	12	0.1550	0.1355	0.6111	0.5004	0.2820	0.1452	0.8458	0.4247	-0.1163	-0.3802	0.3224	0.2105
	16	0.1784	0.1635	0.4904	0.4233	0.2154	0.1089	0.6728	0.3561	0.0205	-0.3175	0.3902	0.1658
	25	0.0808	0.0766	0.2062	0.1923	0.1271	0.0678	0.2653	0.1820	0.1324	-0.2628	0.4115	0.1210
	50	0.0595	0.0582	0.0995	0.0966	0.0523	0.0192	0.1151	0.0883	0.1463	-0.2364	0.2839	0.0892
	100	0.0157	0.0154	0.0427	0.0421	0.0275	0.0048	0.0494	0.0400	0.0717	-0.2420	0.1036	0.0750

OR: Odds ratio; RB: Relative bias; RMSE: Relative mean squared error.

TABLE 3: Simulation results for random effect model.

k	$n_P=n_H$	Combined population OR values: $OR_{MH}=3.359$, $OR_{Peto}=3.057$			
		RB_{MH}	RB_{Peto}	$RMSE_{MH}$	$RMSE_{Peto}$
4	4	0.4620	0.3339	1.9012	1.0305
	8	0.3299	0.2729	1.3959	0.9930
	12	0.1871	0.1644	0.6706	0.5450
	16	0.1458	0.1330	0.4453	0.3789
	25	0.0695	0.0657	0.2084	0.1950
	50	0.0503	0.0491	0.1004	0.0974
	100	0.0221	0.0218	0.0447	0.0441
6	4	0.3757	0.2706	1.5778	0.8983
	8	0.2463	0.2008	1.1065	0.7713
	12	0.2052	0.1785	0.7949	0.6042
	16	0.1640	0.1511	0.4312	0.3785
	25	0.0950	0.0904	0.2345	0.2184
	50	0.0550	0.0538	0.0949	0.0922
	100	0.0120	0.0118	0.0403	0.0398
8	4	0.4205	0.3002	1.8422	0.9936
	8	0.3445	0.2798	1.5157	1.0040
	12	0.1753	0.1540	0.6147	0.4916
	16	0.1422	0.1308	0.3981	0.3524
	25	0.1083	0.1030	0.2357	0.2194
	50	0.0526	0.0513	0.0970	0.0940
	100	0.0219	0.0216	0.0479	0.0472
10	4	0.3522	0.2435	1.7423	0.9433
	8	0.3097	0.2577	1.2167	0.8630
	12	0.2052	0.1783	0.7839	0.6174
	16	0.1269	0.1162	0.3730	0.3279
	25	0.0862	0.0817	0.2182	0.2037
	50	0.0229	0.0222	0.0827	0.0805
	100	0.0140	0.0137	0.0448	0.0442
25	4	0.3769	0.2752	1.4529	0.8533
	8	0.3222	0.2543	1.7309	1.0833
	12	0.1958	0.1697	0.7461	0.5628
	16	0.1402	0.1260	0.4953	0.4143
	25	0.1162	0.1095	0.2871	0.2600
	50	0.0237	0.0228	0.0867	0.0841
	100	0.0268	0.0265	0.0472	0.0465
50	4	0.3659	0.2578	1.7016	0.9357
	8	0.2880	0.2329	1.3762	0.9162
	12	0.1550	0.1355	0.6111	0.5004
	16	0.1784	0.1635	0.4904	0.4233
	25	0.0808	0.0766	0.2062	0.1923
	50	0.0595	0.0582	0.0995	0.0966
	100	0.0157	0.0154	0.0427	0.0421

OR: Odds ratio; RB: Relative bias; RMSE: Relative mean squared error.

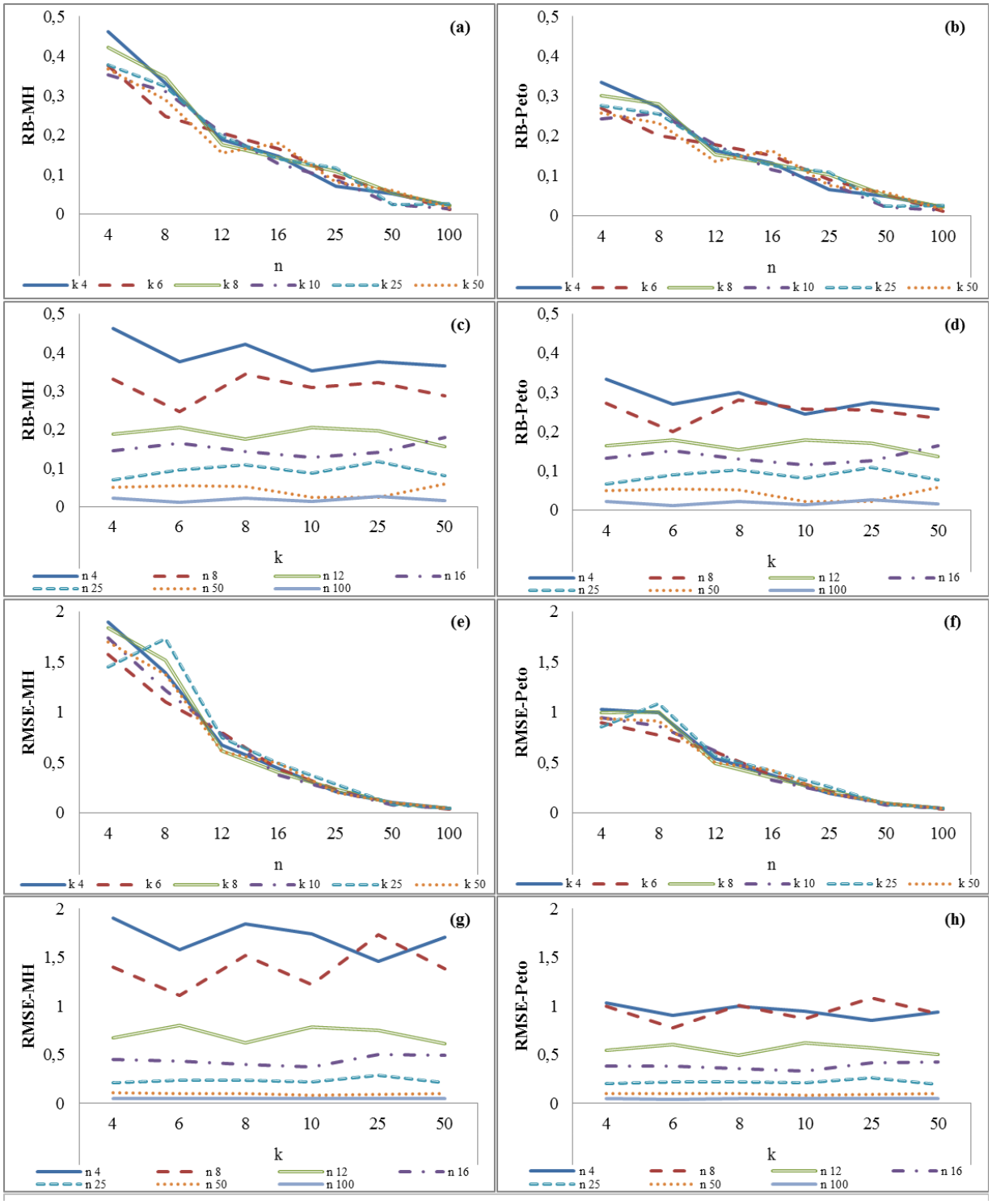

FIGURE 1: Graph of relative bias [for MH (a, c) and for Peto method (b, d)] and RMSE [for MH (e, g) and for Peto method (f, h)] values with reference to sample size (n) and to number of studies (k) for $P(E^{+}\backslash H^{-})=0.5$ and $P(E^{+}\backslash H^{+})=0.5$.

RMSE: RMSE: Relative mean squared error; MH: Mantel-Haenszel.

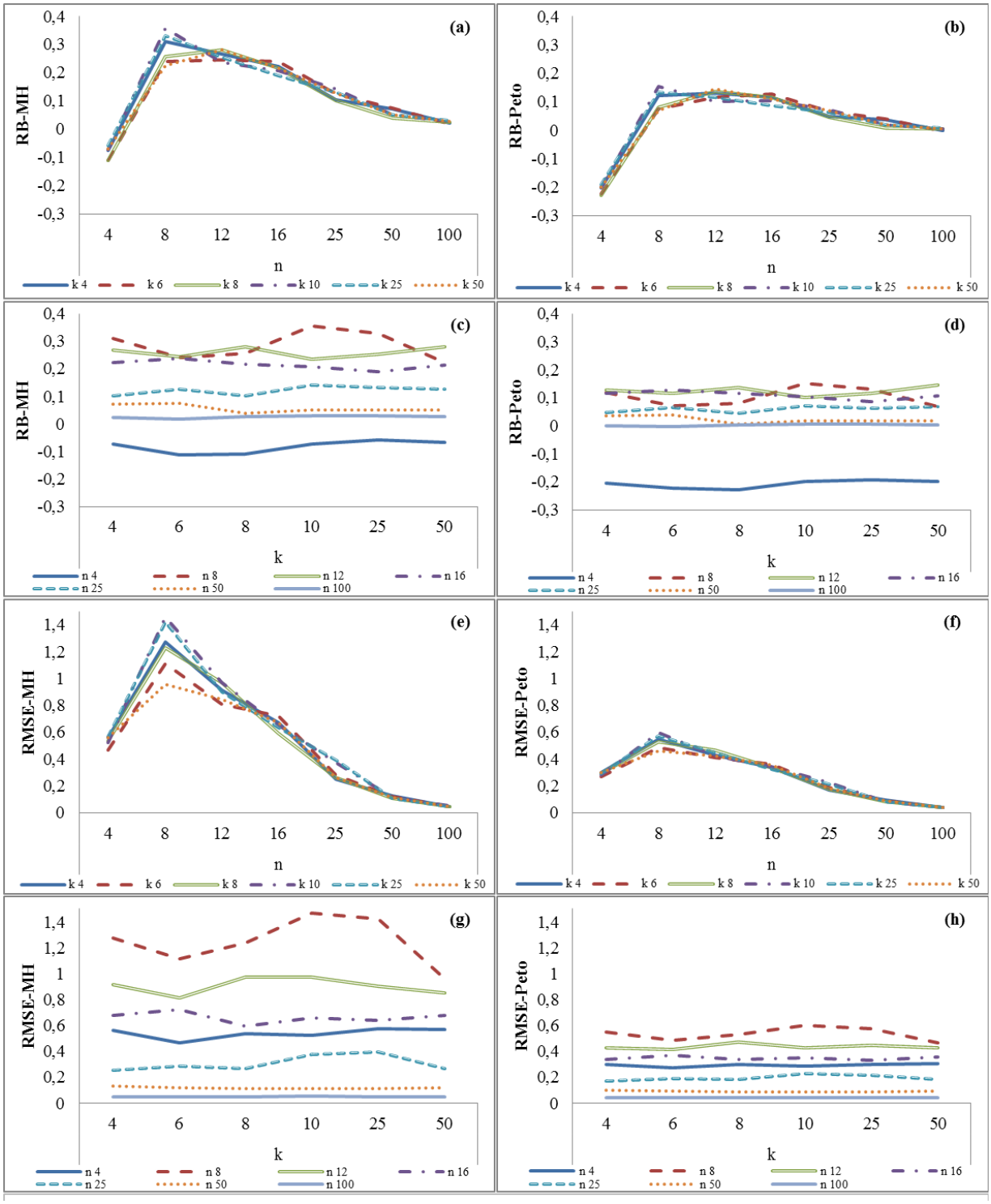

FIGURE 2: Graph of relative bias [for MH (a, c) and for Peto method (b, d)] and RMSE [for MH (e, g) and for Peto method (f, h)] values with reference to sample size (n) and to number of studies (k) for $P(E^{+}\backslash H^{-})=0.5$ and $P(E^{+}\backslash H^{+})=0.7$.

RMSE: RMSE: Relative mean squared error; MH: Mantel-Haenszel.

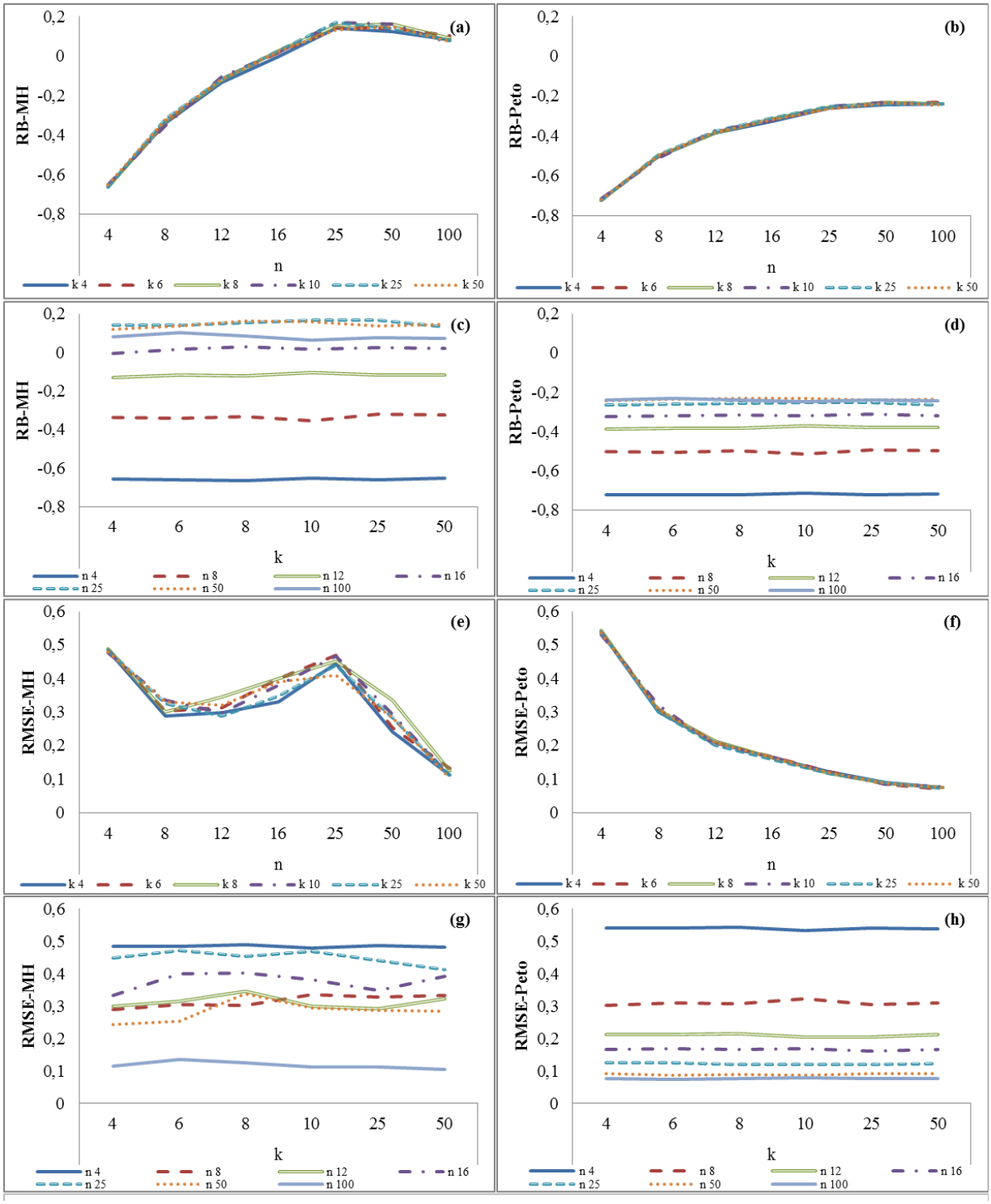

FIGURE 3: Graph of relative bias [for MH (a, c) and for Peto method (b, d)] and RMSE [for MH (e, g) and for Peto method (f, h)] values with reference to sample size (n) and to number of studies (k) for $P(E^{+}\backslash H^{-})=0.5$ and $(E^{+}\backslash H^{+})=0.9$.

RMSE: RMSE: Relative mean squared error; MH: Mantel-Haenszel.

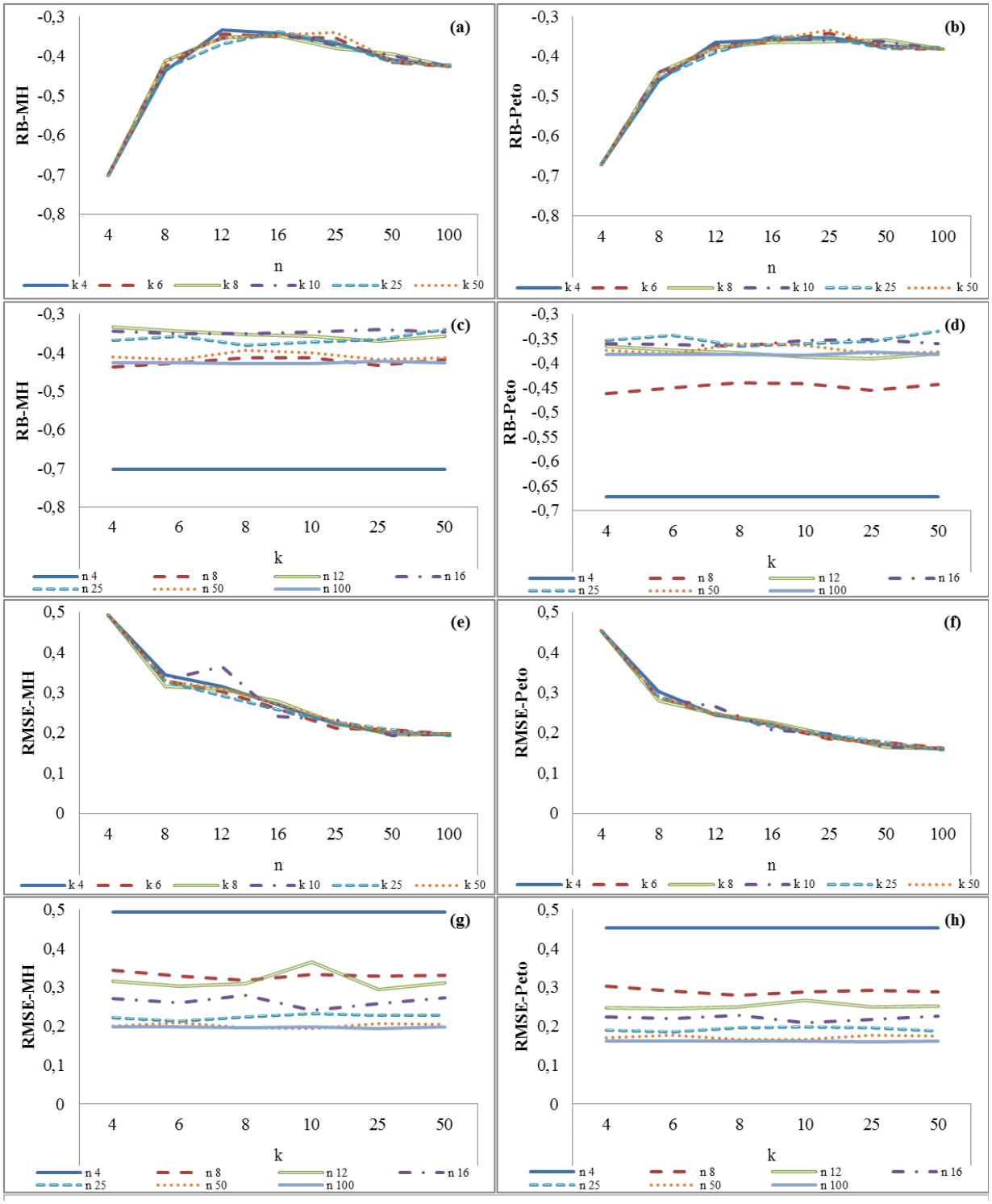

FIGURE 4: Graph of relative bias [for MH (a, c) and for Peto method (b, d)] and RMSE [for MH (e, g) and for Peto method (f, h)] values with reference to sample size (n) and to number of studies (k) for values combined according to probabilities of P ($E^+\backslash H^-$)=0.5 and P ($E^+\backslash H^+$)=0.6, 0.7, 0.8 and 0.9.

RMSE: RMSE: Relative mean squared error; MH: Mantel-Haenszel.

DISCUSSION

Meta-analysis allows for the estimation of population parameters with summary statistics calculated by combining results of researches made at different places and times. In health sciences, categorical data are one of the widely-used types of data. In cases where the relevant variable is binary, the RD, which is calculated from the difference between 2 probabilities; the RR, obtained from the ratio of these 2 probabilities; the OR, which is formed from the ratio between the probability of a property's presence and that of its absence; and the NNT are the most common statistical measures calculated. In this study, the performances of the MH and Peto methods, which are the most frequently preferred meta-analysis methods used for combining the summary statistics calculated in binary data, were evaluated for different disease-cause rates, and according to different sample sizes and the number of studies to be combined. For the combining of homogeneous studies, the fixed effects model was used, while for the combining of heterogeneous studies, the random effects model was used. In the literature review, no study similar to ours was encountered.

In cases where the disease-cause rate is equal ($P(H^+\backslash E^+)=0.50$), when the studies to be combined are in small sample sizes, both methods produce over-estimates, with the MH method at a higher level. When the evaluation is carried out with regard to the amount of general deviation from the population parameter, however, it is observed that the Peto method shows less deviation for small samples. Yet as large sample size levels are approached, it is observed that both methods show a similar level of general deviation from the population parameter.

In cases where the disease-cause rate is at a medium level ($P(H^+\backslash E^+)=0.70$), when the studies to be combined are in very small (n=4) sample sizes, both methods produce under-estimates, with the Peto method at a slightly higher level. With an increase in sample size, over-estimates occur for both methods. With regard to the overestimates produced by both methods, it is remarkable that higher estimates occur for the MH method, even when approaching large sample sizes. When the evaluation is carried out with regard to the amount of general deviation from the population parameter, however, it is observed that the Peto method shows less deviation for small samples. Yet as large sample size levels are approached, it is observed that both methods show a similar level of general deviation from the population parameter.

In cases where the disease-cause rate is at a high level ($P(H^+\backslash E^+)=0.90$), it is observed that although both the MH and Peto methods are not greatly affected by the number of studies to be combined for analysis, they are affected by the sample size of the studies to be combined. In cases where the studies to be combined have small sample sizes, both methods produce under-estimates in relation to the population parameter. As the sample size is increased, whereas the MH method begins to produce estimates close to the population parameter, it produces over-estimates for large sample sizes. For the Peto method, however, whilst proximity to the population parameter can be seen in estimates as sample size increases, these estimates occur as under-estimates. When the evaluation is carried out with regard to the amount of general deviation from the population parameter, however, while a similar amount of deviation is observed for small samples, it is observed that together with the increase in sample size there is a tendency for deviation from the population parameter to decrease. In addition, it is observed that in relation to variation in sample size for the MH method, there is a great deal of fluctuation in the value of general deviation from the population parameter.

When the disease-cause rate is heterogenized, it is observed that whilst the MH and Peto methods are not greatly affected by the number of studies to be combined for analysis, they are affected by the sample size of the studies to be combined. Also, both methods produce under-estimates in relation to the population parameter. As the number of samples is increased, it is seen that although the methods show a certain tendency for proximity to the population parameter, for large samples they still produce under-estimates. When the evaluation is carried out with regard to the amount of general deviation from the population parameter, however, while a similar amount of deviation can be observed in both methods for small samples, it is observed that together with the increase in sample size there is a tendency for deviation from the population parameter to decrease.

It can be seen that in our study, carried out for different disease-cause rates, whilst it is observed that neither MH nor Peto methods show a significant effect from the number of studies to be combined, they are significantly affected by the sample size of the studies to be combined. Furthermore, for large samples, both methods produce similar results that are close to the population parameter. It is observed in the study that for the MH method, a larger number of over-estimates occur and that with regard to general deviation, a greater amount of deviation from the population parameter is shown. Also, with regard to variation as sample size increases, Peto possesses a more regular and coherent variation characteristic.

CONCLUSION

For both the fixed effect model and the random effects model, the Peto method provides more coherent estimates for the population parameter than the MH method.

Informing

Due to the presence of the name of the journal editor's among the authors, the assessment process of the study was conducted by the guest editor.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** İlker Ercan, Mehmet Onur Kaya; **Design:** İlker Ercan, Mehmet Onur Kaya; **Control/Supervision:** İlker Ercan, Mehmet Onur Kaya; **Data Collection and/or Processing:** Mehmet Onur Kaya; **Analysis and/or Interpretation:** İlker Ercan, Mehmet Onur Kaya; **Literature Review:** Mehmet Onur Kaya; **Writing the Article:** İlker Ercan, Mehmet Onur Kaya; **Critical Review:** İlker Ercan, Mehmet Onur Kaya, Gökhan Ocakoğlu.*

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