

Degree irregularity and rank probability bias in network meta-analysis

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— Supplementary Material —

S1. DEGREE IRREGULARITY AND PROBABILITY OF INTER-SPECIFIC ENCOUNTER (PIE)

In network meta-analysis (NMA) the probability of inter-specific encounter (PIE) index measures the probability that two randomly sampled treatment groups (trial arms) from the network are associated with two different treatments [2, 3]. The sampling is understood to occur *without* replacement. This diversity measure was originally introduced in ecology [1], and first applied in the context of NMA by Salanti et al. (2008) [2, 3].

The probability that the two sampled arms represent different treatments is given by

$$\text{PIE} = 1 - \sum_a \left(\frac{k_a}{k_{\text{tot}}} \right) \left(\frac{k_a - 1}{k_{\text{tot}} - 1} \right), \quad (\text{S1})$$

where k_{tot} is the total number of arms in the network,

$$k_{\text{tot}} = \sum_a k_a = N\bar{k}. \quad (\text{S2})$$

We recall that $\bar{k} = N^{-1} \sum_a k_a$ is the mean degree of a node in the weighted network, and N the total number of treatments.

In Equation (S1), k_a/\bar{k} is the probability that a randomly picked trial arm is of type a , and $(k_a - 1)/(\bar{k} - 1)$ is the probability that an arm sampled randomly from the remaining $\bar{k} - 1$ arms is also of type a . Using Equation (S2) and a modest amount of algebra one shows that PIE can be written in the more commonly used form

$$\text{PIE} = \frac{k_{\text{tot}}}{k_{\text{tot}} - 1} \left[1 - \sum_a \left(\frac{k_a}{k_{\text{tot}}} \right)^2 \right], \quad (\text{S3})$$

PIE is a probability and takes values between zero and one. PIE' is defined as PIE normalised with respect to the maximum value of PIE for a given number of studies,

$$\text{PIE}' = \frac{\text{PIE}}{\max(\text{PIE})}. \quad (\text{S4})$$

At fixed N PIE takes its maximum value when $k_a = \bar{k}$ for all treatments a . This means that the fraction of arms associated with any one treatment is $k_a/k_{\text{tot}} = 1/N$ for all a . In this case therefore

$$\max(\text{PIE}) = \frac{k_{\text{tot}}}{k_{\text{tot}} - 1} \left(1 - \frac{1}{N} \right). \quad (\text{S5})$$

In order to relate h^2 to PIE' we start from Equation (11) in the main paper. We have

$$\begin{aligned} h^2 &= \frac{1}{N} \sum_a^N (k_a - \bar{k})^2 \\ &= \frac{1}{N} \left(\sum_a k_a^2 - 2\bar{k} \sum_a k_a + N\bar{k}^2 \right) \\ &= \frac{1}{N} \left(\sum_a k_a^2 - N\bar{k}^2 \right). \end{aligned} \quad (\text{S6})$$

Therefore, using Equation (S2),

$$\frac{h^2}{\bar{k}^2} = \frac{1}{N\bar{k}^2} \sum_a k_a^2 - 1 \quad (\text{S7})$$

$$= \frac{N}{\bar{k}_{\text{tot}}^2} \sum_a k_a^2 - 1. \quad (\text{S8})$$

From the definitions of PIE and max(PIE) we have

$$\begin{aligned} \text{PIE}' &= \frac{1 - \sum_a \left(\frac{k_a}{\bar{k}_{\text{tot}}} \right)^2}{1 - \frac{1}{N}} \\ &= \frac{N - \frac{N}{\bar{k}_{\text{tot}}^2} \sum_a k_a^2}{N - 1} \\ &= \frac{N - \left(\frac{h^2}{\bar{k}^2} + 1 \right)}{N - 1}. \end{aligned} \quad (\text{S9})$$

Therefore

$$\text{PIE}' = 1 - \frac{1}{N-1} \frac{h^2}{\bar{k}^2}. \quad (\text{S10})$$

S2. MAXIMUM TOTAL BIAS

To compare the extent of total rank probability bias and total SUCRA bias, we express these measures as a proportion of the maximum bias that is possible to observe in each case. In this section we calculate the values of these maxima.

A. Maximum total rank probability bias

The sets of true and estimated rank probability biases, $P_a(r)$ and $\hat{P}_a(r)$, each form doubly stochastic matrices. We call these matrices \mathbf{P} and $\hat{\mathbf{P}}$ such that their elements are $P_{ij} = P_{T_i}(j)$ and $\hat{P}_{ij} = \hat{P}_{T_i}(j)$. The properties of a doubly stochastic matrices are

$$\sum_{i=1}^N P_{ij} = 1, \quad \sum_{j=1}^N P_{ij} = 1, \quad P_{ij} \geq 0. \quad (\text{S11})$$

That is to say, all matrix elements are positive, and all elements in any row of \mathbf{P} sum to one, and similarly, the sum of elements in any column is one. Analogous relations hold for $\hat{\mathbf{P}}$.

The total rank probability bias can be written as

$$|\Delta P|_{\text{tot}} = \sum_{i=1}^N \sum_{j=1}^N |P_{ij} - \hat{P}_{ij}|. \quad (\text{S12})$$

We can work out the maximum of this quantity by using the triangle inequality

$$|P_{ij} - \hat{P}_{ij}| \leq P_{ij} + \hat{P}_{ij}. \quad (\text{S13})$$

Therefore

$$\begin{aligned} |\Delta P|_{\text{tot}} &\leq \sum_{i=1}^N \sum_{j=1}^N (P_{ij} + \hat{P}_{ij}) \\ &= \underbrace{\sum_{i=1}^N \sum_{j=1}^N P_{ij}}_{=1} + \underbrace{\sum_{i=1}^N \sum_{j=1}^N \hat{P}_{ij}}_{=1} \\ &= N + N = 2N. \end{aligned} \quad (\text{S14})$$

This bound is tight, for example it is saturated if \mathbf{P} is the identity matrix, and $\hat{\mathbf{P}}$ a permutation matrix mapping no number onto itself.

For $N = 4$ treatments one has

$$\max(|\Delta P|_{\text{tot}}) = 8. \quad (\text{S15})$$

B. Maximum total SUCRA bias

To work out the maximum value of total SUCRA bias we first write it in terms of the $\{\Delta P_a(r)\}$,

$$|\Delta \text{SUCRA}|_{\text{tot}} = \sum_a |\Delta \text{SUCRA}_a| = \sum_a \left| \frac{\sum_r r \hat{P}_a(r) - \sum_r r P_a(r)}{N-1} \right|, \quad (\text{S16})$$

Therefore we have

$$|\Delta \text{SUCRA}|_{\text{tot}} = \frac{1}{N-1} \sum_a \left| \sum_r r \Delta P_a(r) \right|. \quad (\text{S17})$$

Again using the doubly stochastic matrices \mathbf{P} and $\hat{\mathbf{P}}$ to represent the true and estimated rank probabilities, we can write

$$|\Delta \text{SUCRA}|_{\text{tot}} = \frac{1}{N-1} \sum_{i=1}^N \left| \sum_{j=1}^N j(P_{ij} - \hat{P}_{ij}) \right|. \quad (\text{S18})$$

The minimum possible value of $\sum_{j=1}^N j P_{ij}$ is 1 and the maximum is N . Similarly, $\sum_{j=1}^N j \hat{P}_{ij}$ takes values between 1 and N . Therefore for a fixed value of i

$$\left| \sum_{j=1}^N j(P_{ij} - \hat{P}_{ij}) \right| \leq N-1. \quad (\text{S19})$$

However, due to the doubly stochastic nature of \mathbf{P} and $\hat{\mathbf{P}}$, equality can hold in this relation for only two values of i , namely one in which $\sum_{j=1}^N j P_{ij} = 1$ and $\sum_{j=1}^N j \hat{P}_{ij} = N-1$, and the other for which the reverse holds.

The next largest value that $\left| \sum_{j=1}^N j(P_{ij} - \hat{P}_{ij}) \right|$ can take is $N-3$ (for $\sum_{j=1}^N j P_{ij} = N-1$ and $\sum_{j=1}^N j \hat{P}_{ij} = 2$ or vice versa). Following this pattern, the maximum values of $\left| \sum_{j=1}^N j(P_{ij} - \hat{P}_{ij}) \right|$ are $N-1, N-3, N-5, N-7, \dots, N-7, N-5, N-3, N-1$. For even $N = 2k$ this gives

$$\begin{aligned} \max \left(\sum_{i=1}^N \left| \sum_{j=1}^N j(P_{ij} - \hat{P}_{ij}) \right| \right) &= 2 \sum_{l=0}^{k-1} (2k-1-2l) \\ &= 2 \left[k(2k-1) - 2 \underbrace{\sum_{l=0}^{k-1} l}_{=(k-1)k/2} \right] \\ &= 2k^2 = \frac{N^2}{2}. \end{aligned} \quad (\text{S20})$$

For $N = 4$ treatments we have

$$\max(|\Delta \text{SUCRA}|_{\text{tot}}) = \frac{1}{N-1} \frac{N^2}{2} = \frac{8}{3}. \quad (\text{S21})$$

Technically, the above argument only produces a lower bound on the maximum value of $|\Delta \text{SUCRA}|_{\text{tot}}$. However, we have tested the relation in Equation (S20) numerically using large samples of randomly generated doubly stochastic matrices. We have found no instances in which the maximum value indicated was higher than the bound in Equation (S20).

S3. WITHIN NETWORK PLOTS: THE EFFECT OF THE NUMBER OF STUDIES PER TREATMENT FOR EQUALLY EFFECTIVE TREATMENTS

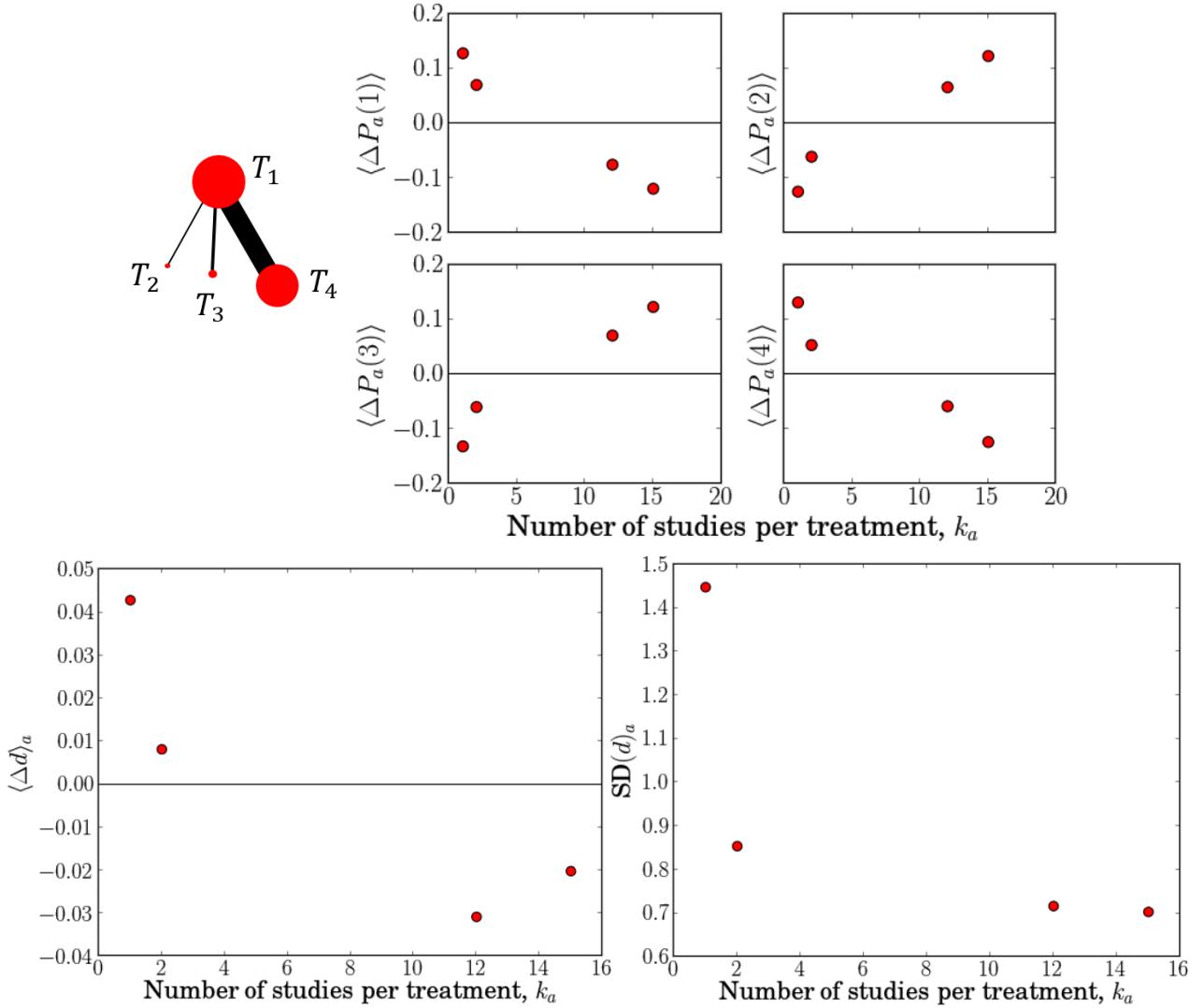


FIG. S1. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a star network with $K = (1, 2, 12, 0, 0, 0)$.

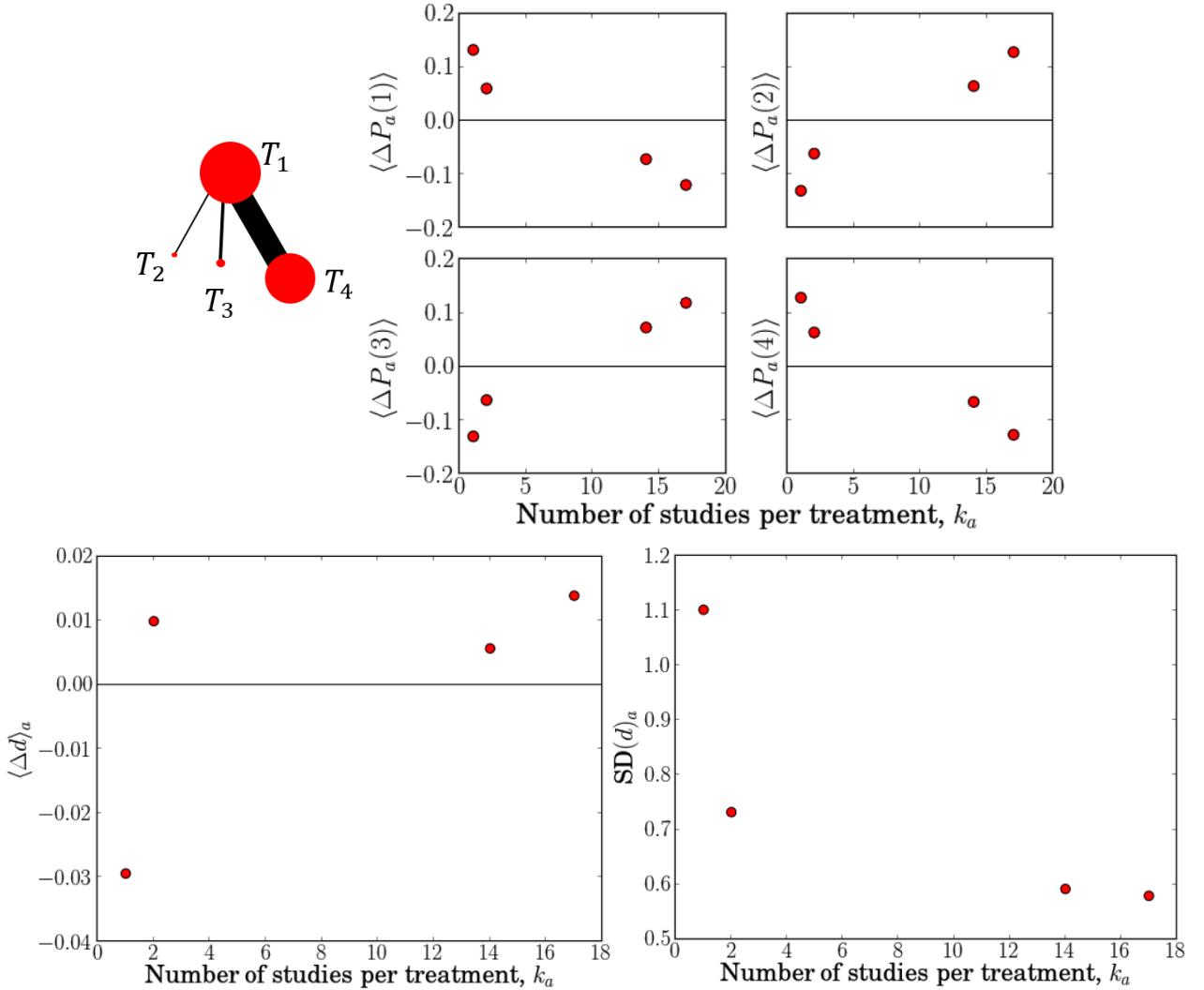


FIG. S2. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a star network with $\mathbf{K} = (1, 2, 14, 0, 0, 0)$.

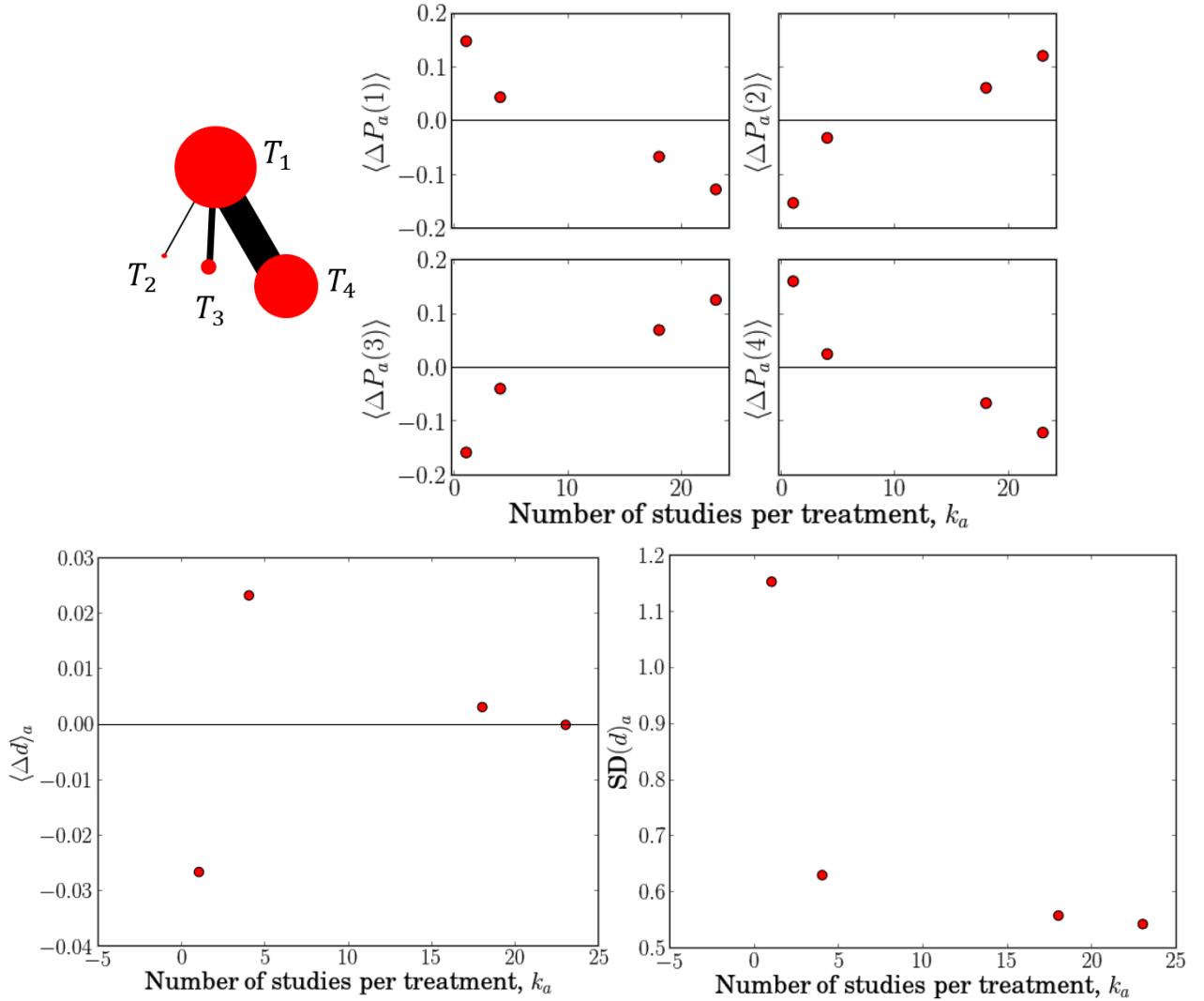


FIG. S3. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a star network with $\mathbf{K} = (1, 4, 18, 0, 0, 0)$.

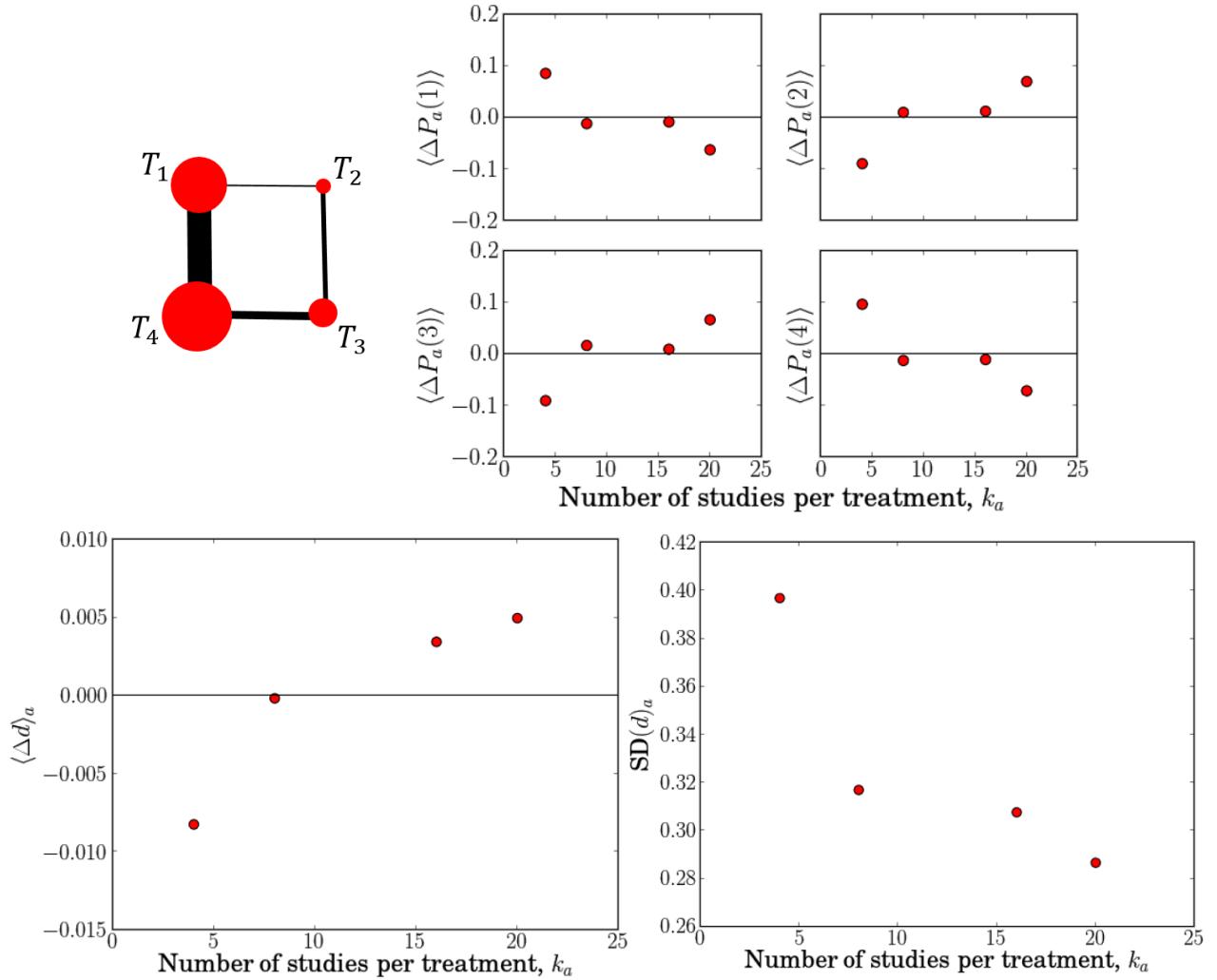


FIG. S4. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a loop network with $\mathbf{K} = (1, 0, 15, 3, 0, 5)$.

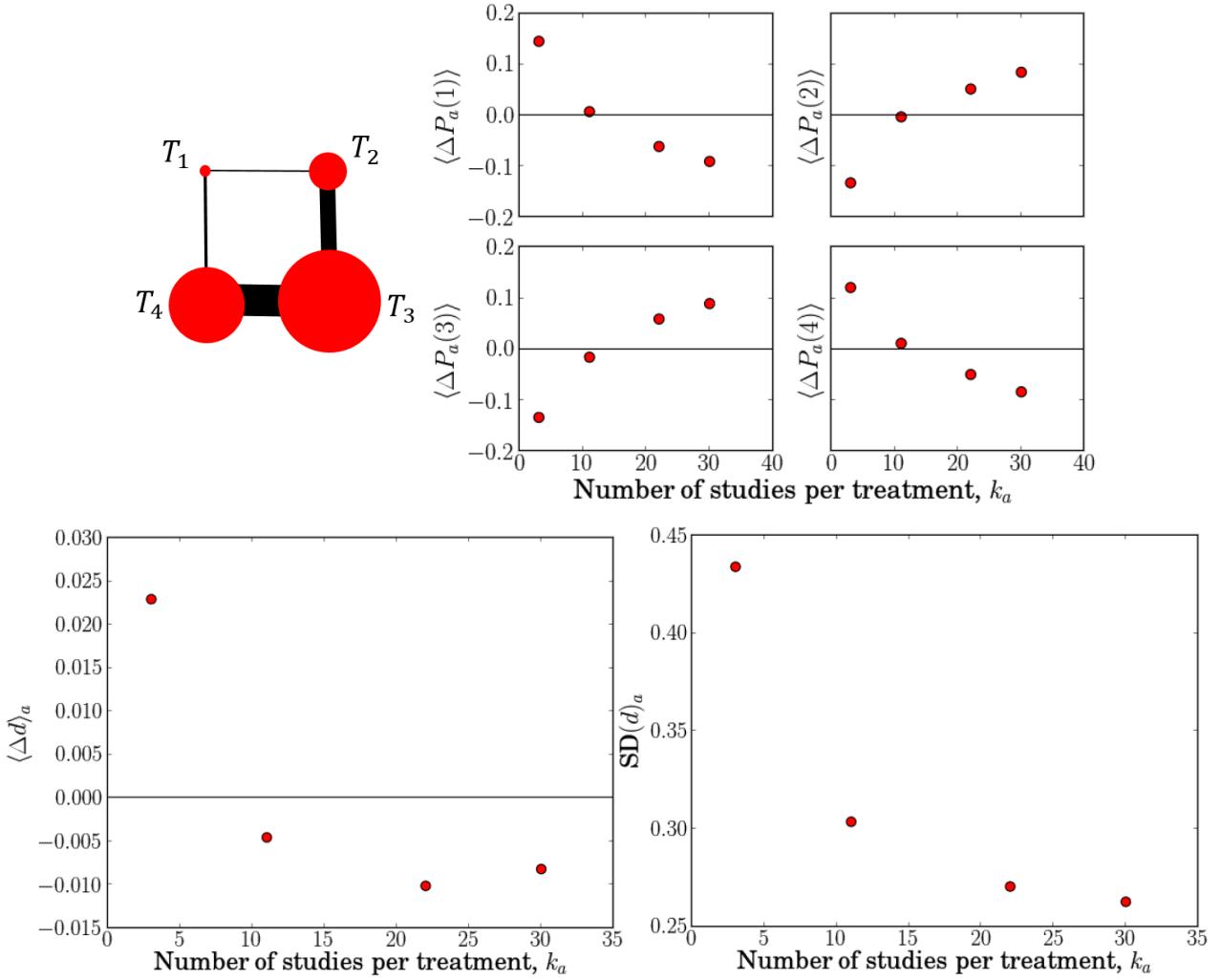


FIG. S5. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a loop network with $\mathbf{K} = (1, 0, 2, 10, 0, 20)$.

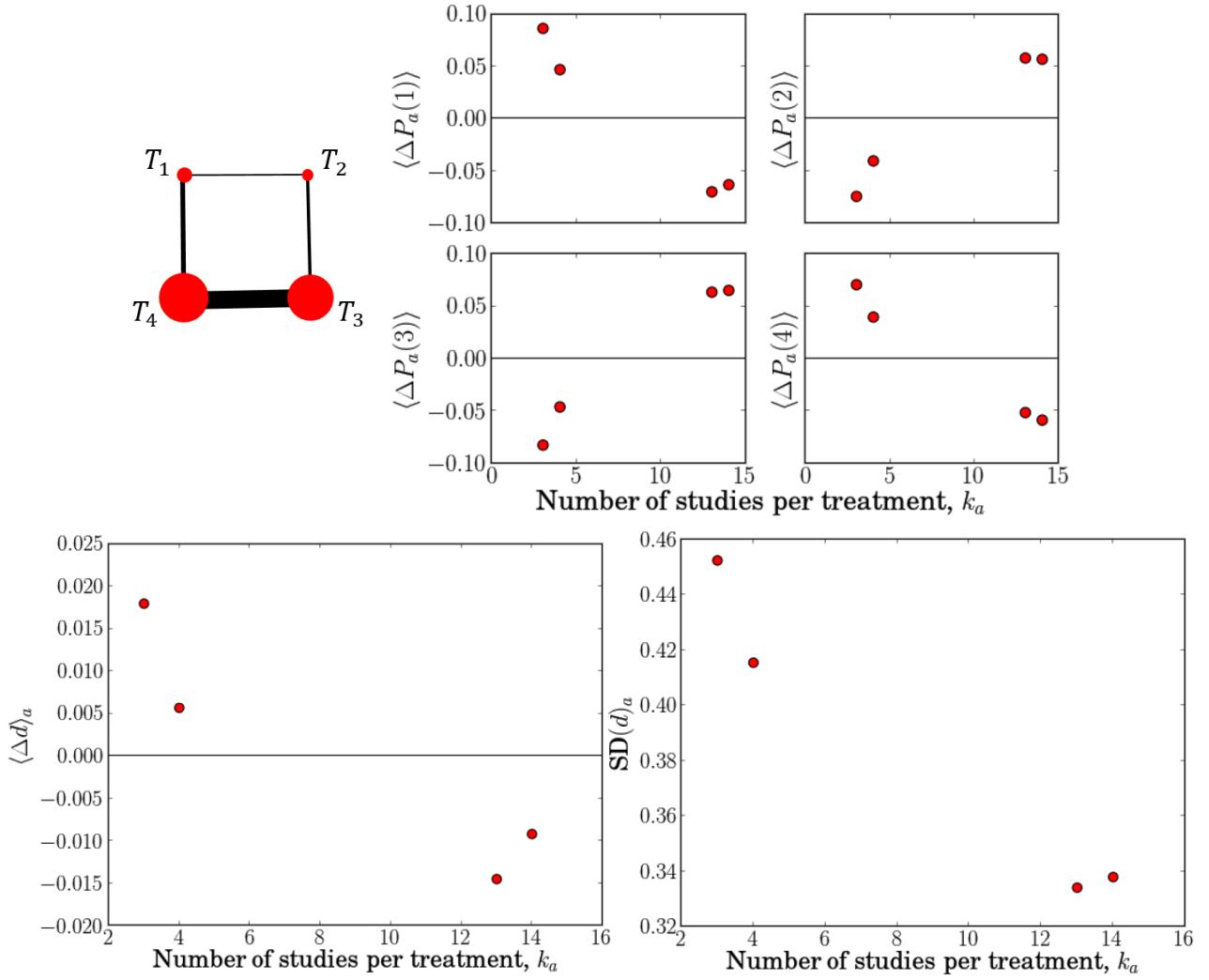


FIG. S6. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a loop network with $\mathbf{K} = (1, 0, 3, 2, 0, 11)$.

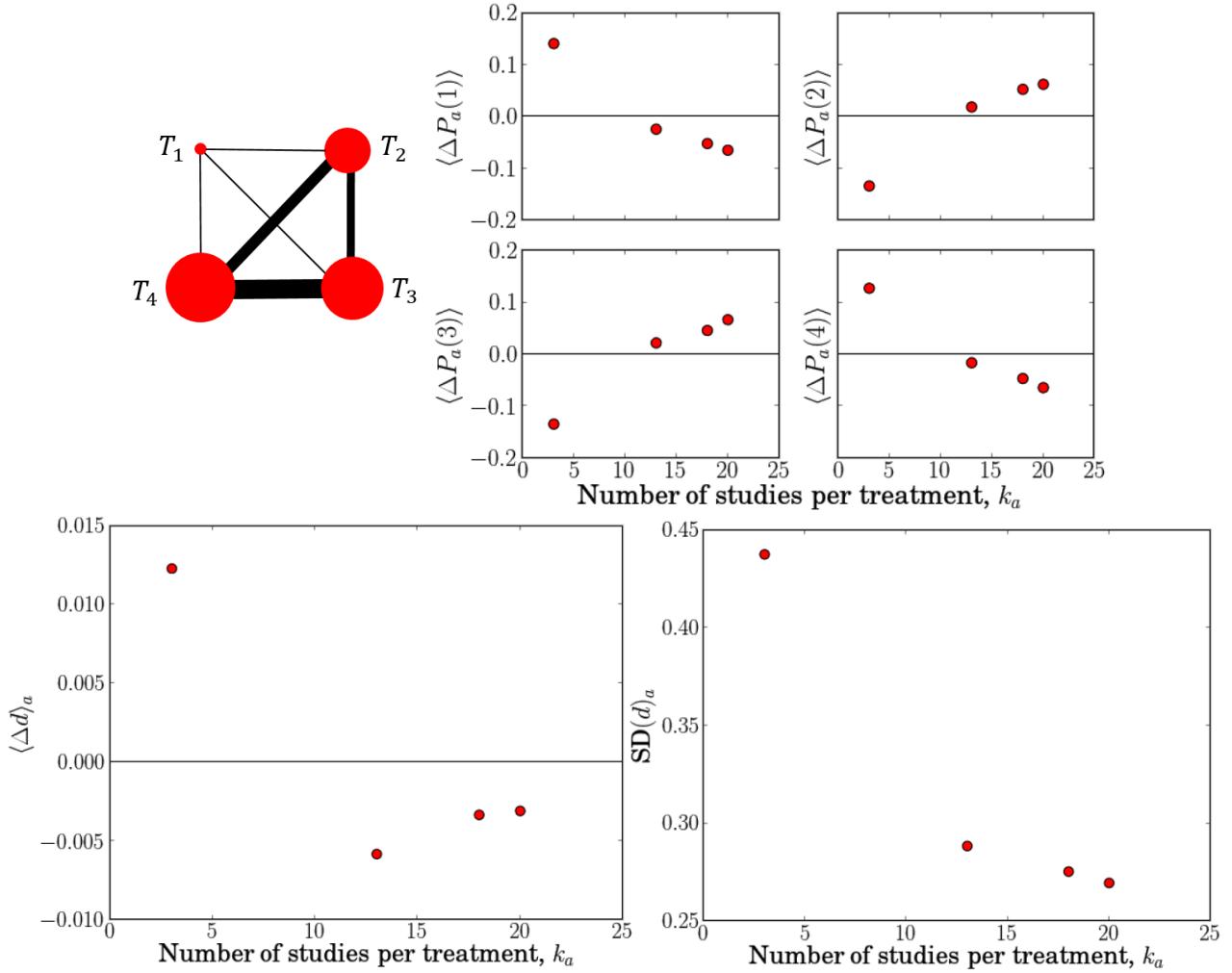


FIG. S7. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (1, 1, 1, 5, 7, 12)$.

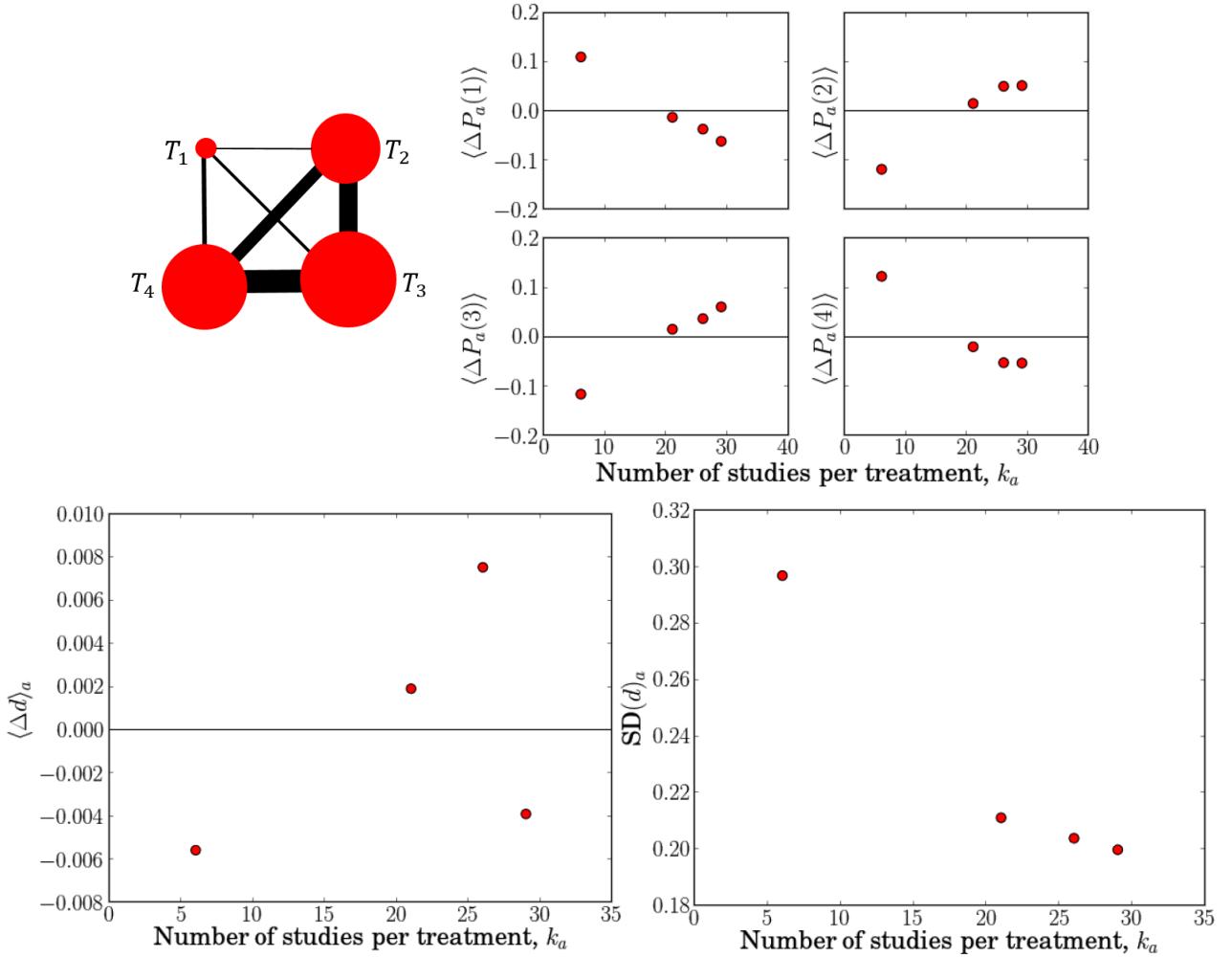


FIG. S8. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (1, 2, 3, 12, 8, 15)$.

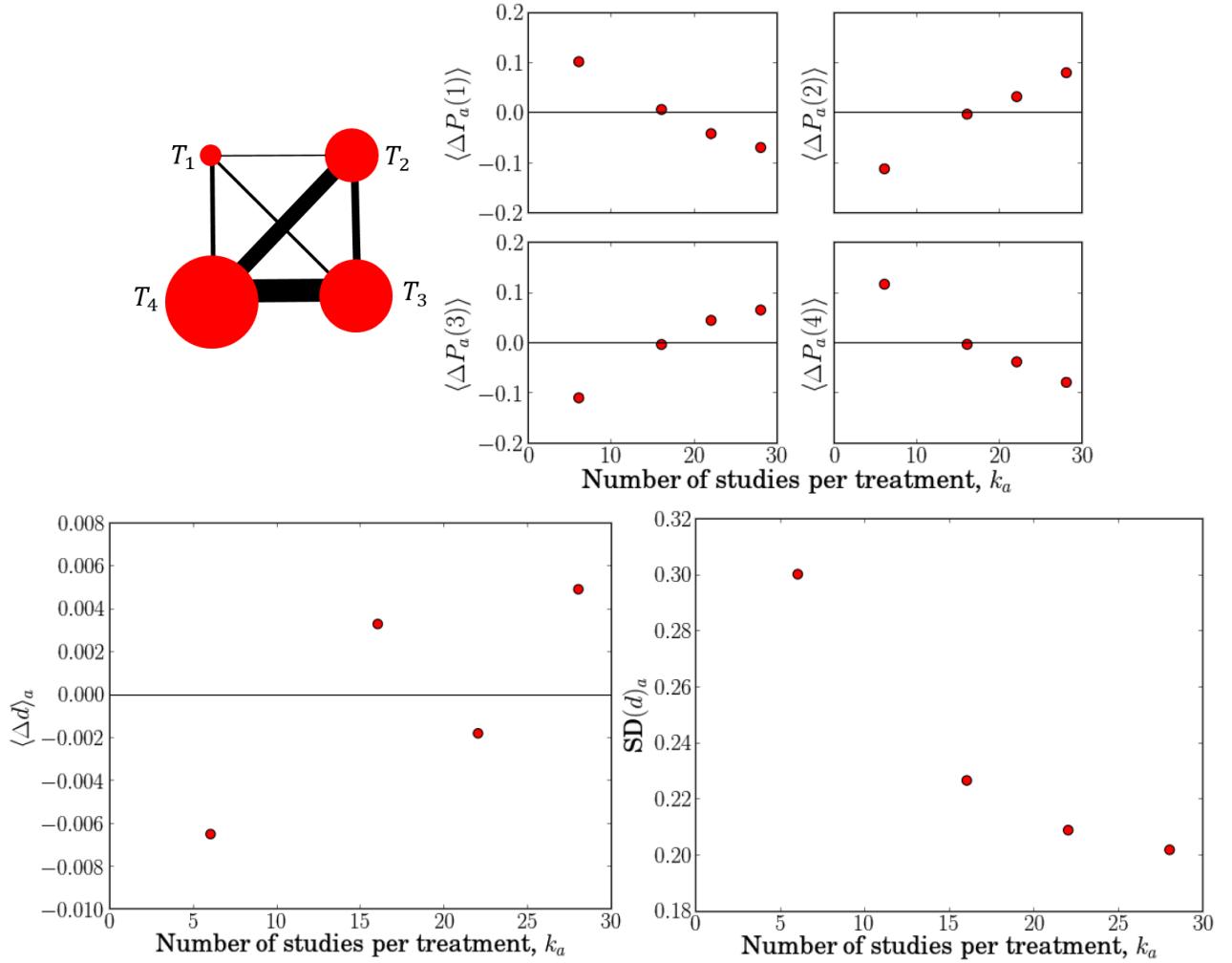


FIG. S9. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (1, 2, 3, 5, 10, 15)$.

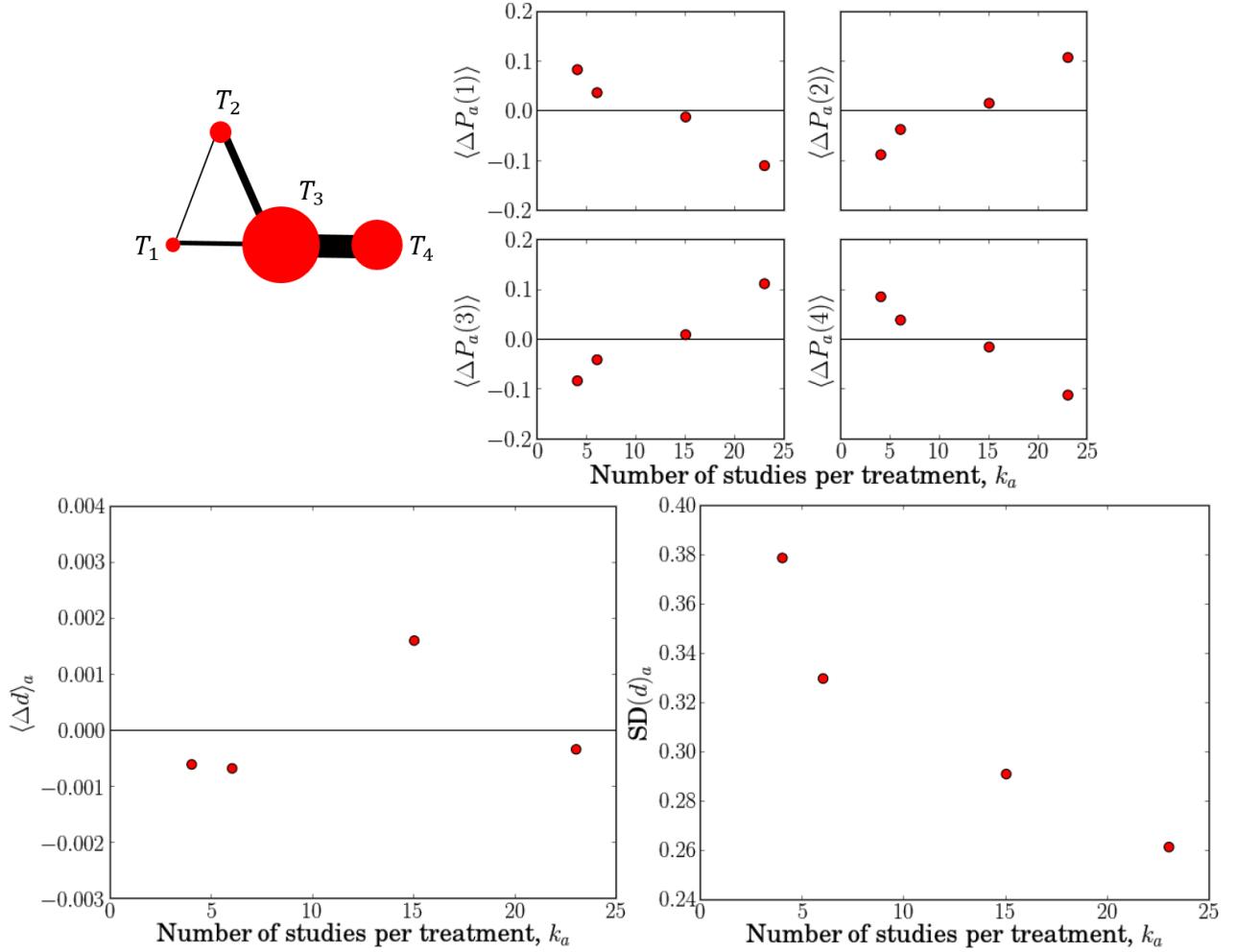


FIG. S10. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a tadpole network with $\mathbf{K} = (1, 3, 0, 5, 0, 15)$.

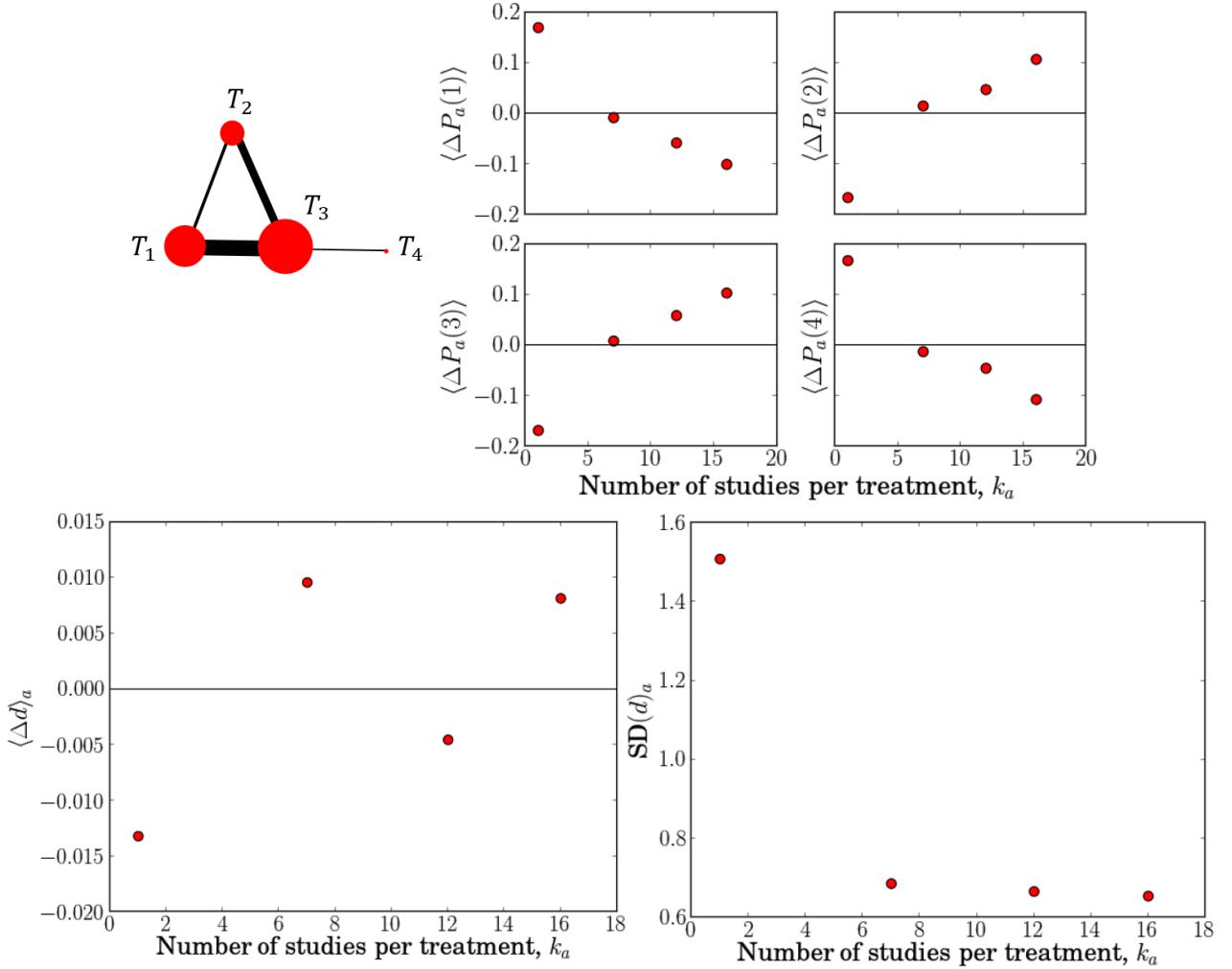


FIG. S11. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a tadpole network with $\mathbf{K} = (2, 10, 0, 5, 0, 1)$.

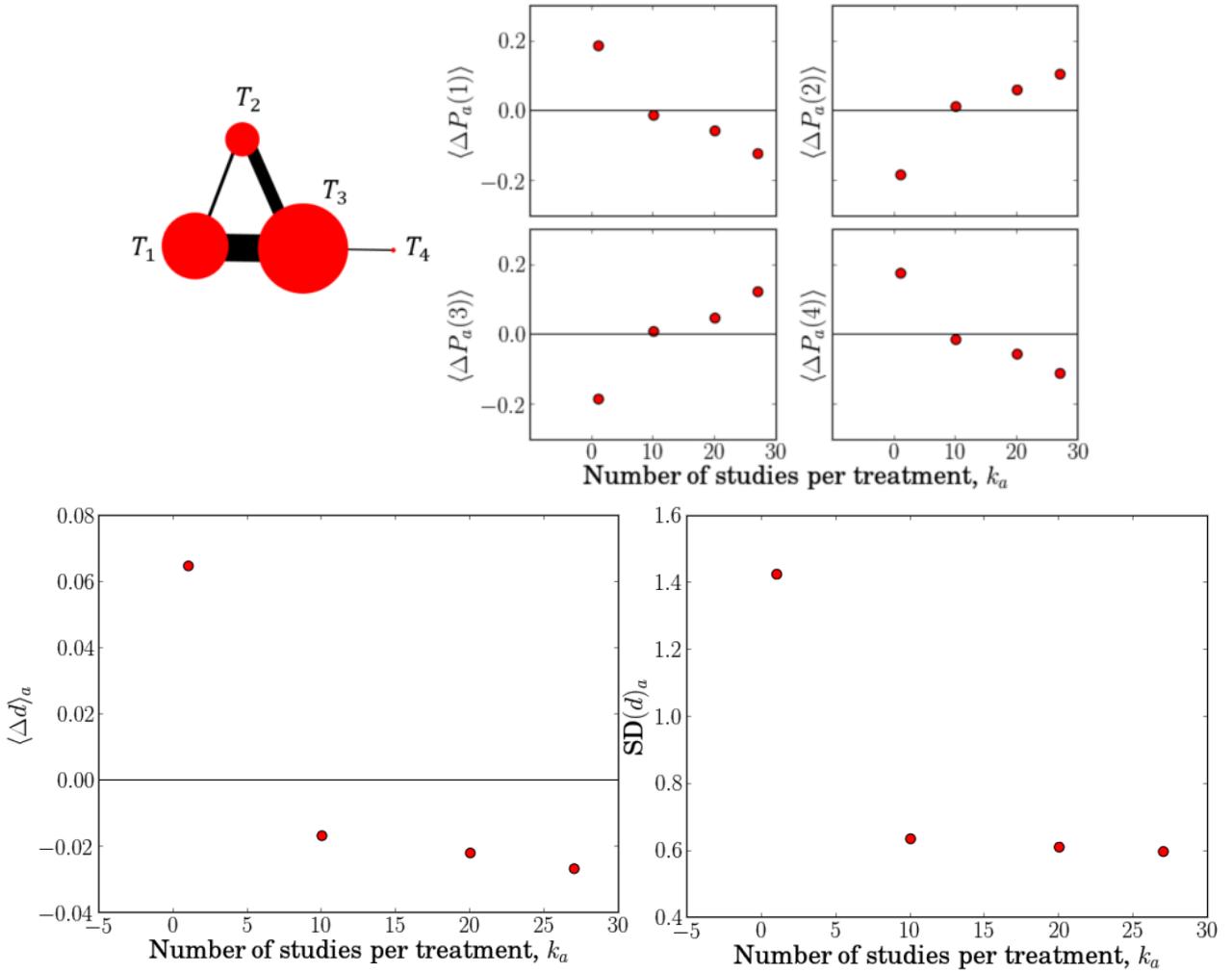


FIG. S12. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a tadpole network with $\mathbf{K} = (2, 18, 0, 8, 0, 1)$.

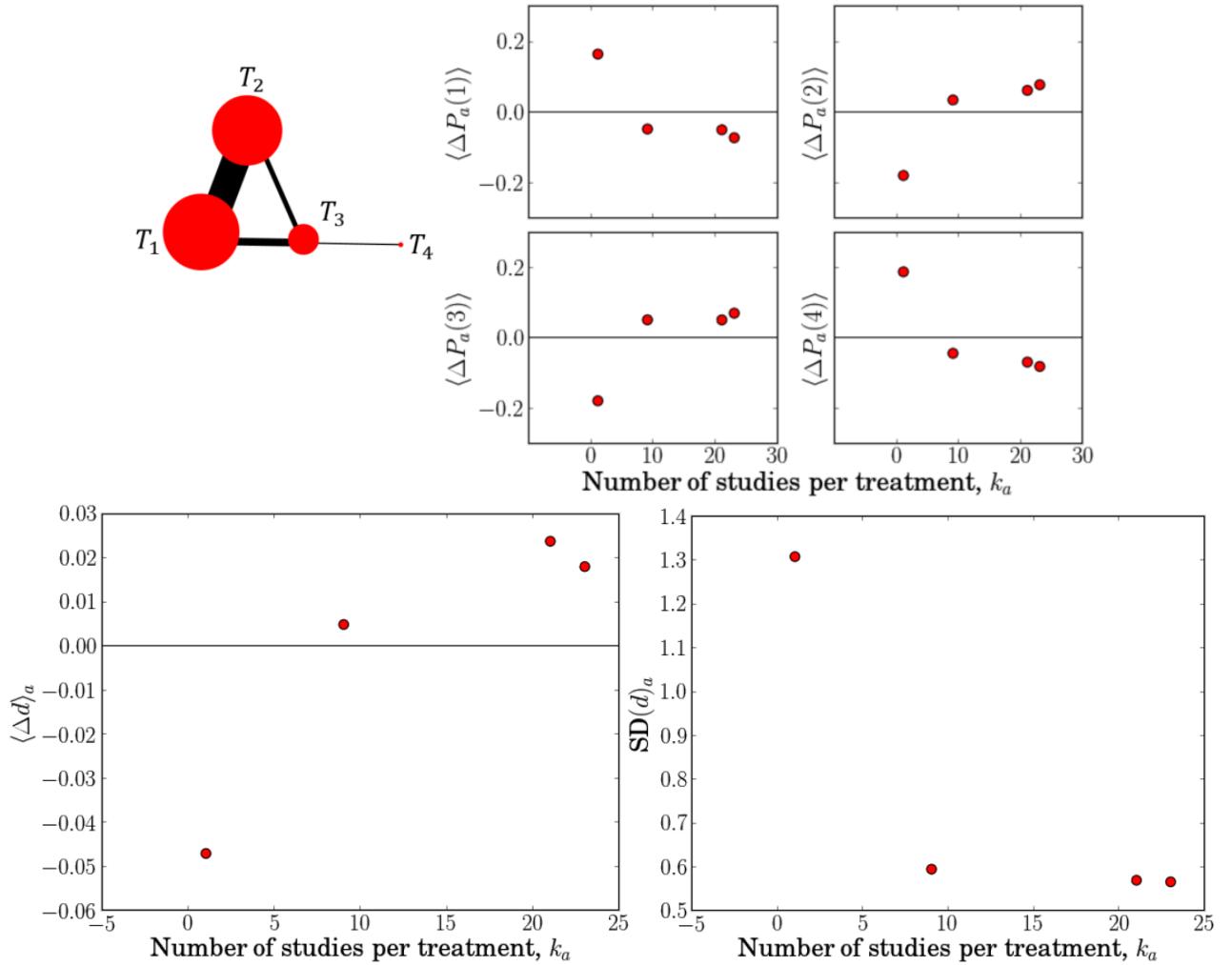


FIG. S13. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a tadpole network with $\mathbf{K} = (18, 5, 0, 3, 0, 1)$.

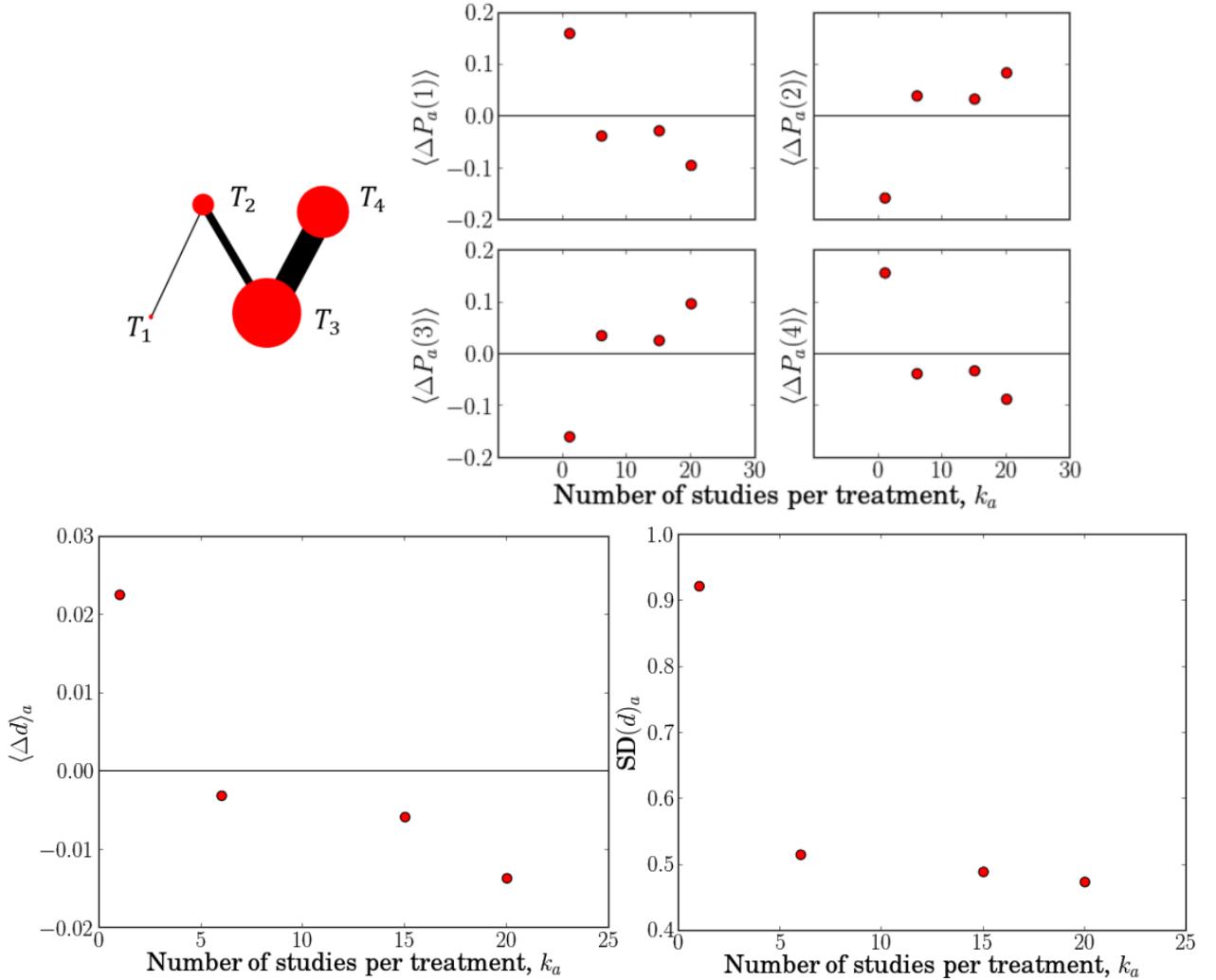


FIG. S14. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a ladder network with $\mathbf{K} = (1, 0, 0, 5, 0, 15)$.

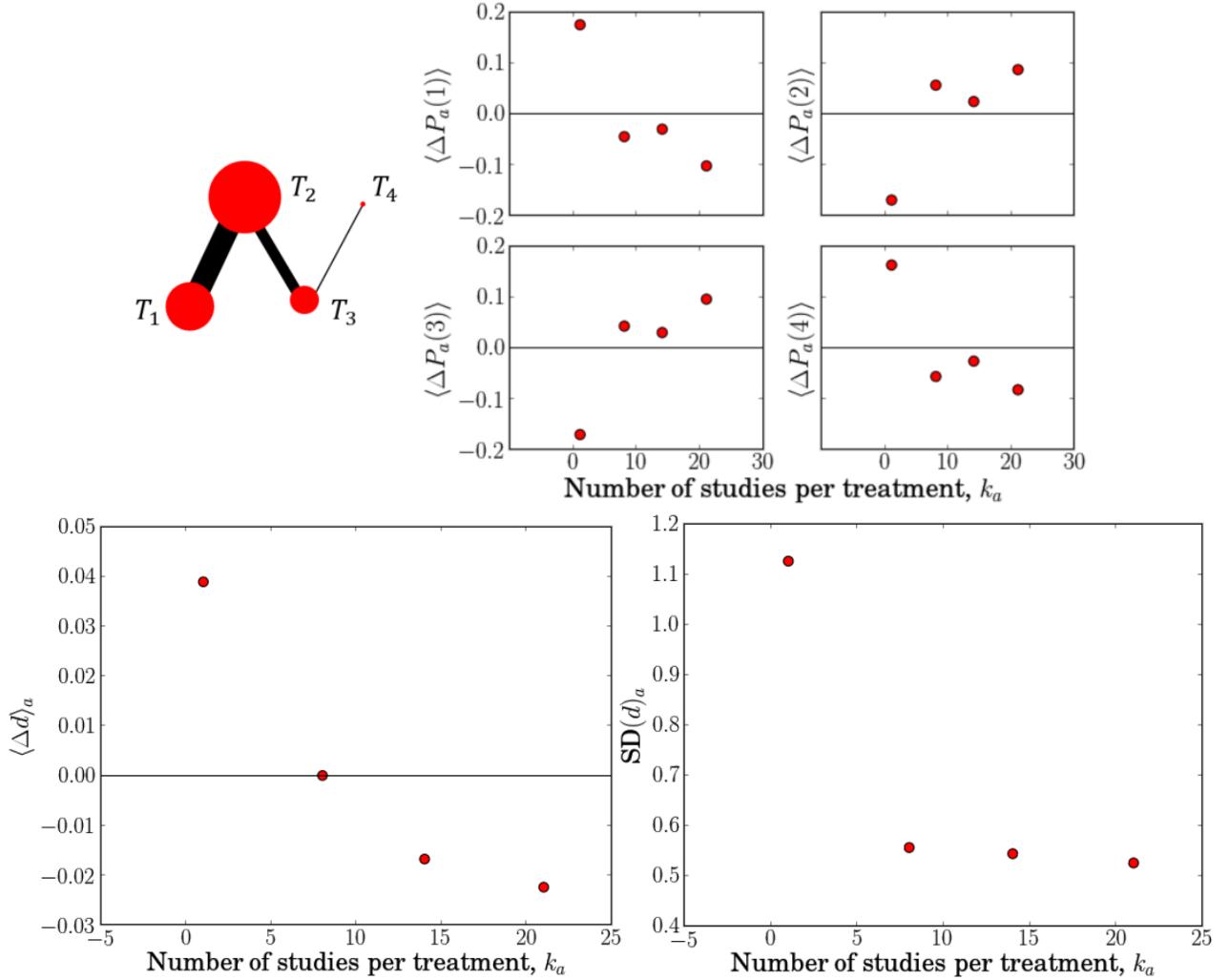


FIG. S15. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a ladder network with $\mathbf{K} = (14, 0, 0, 7, 0, 1)$.

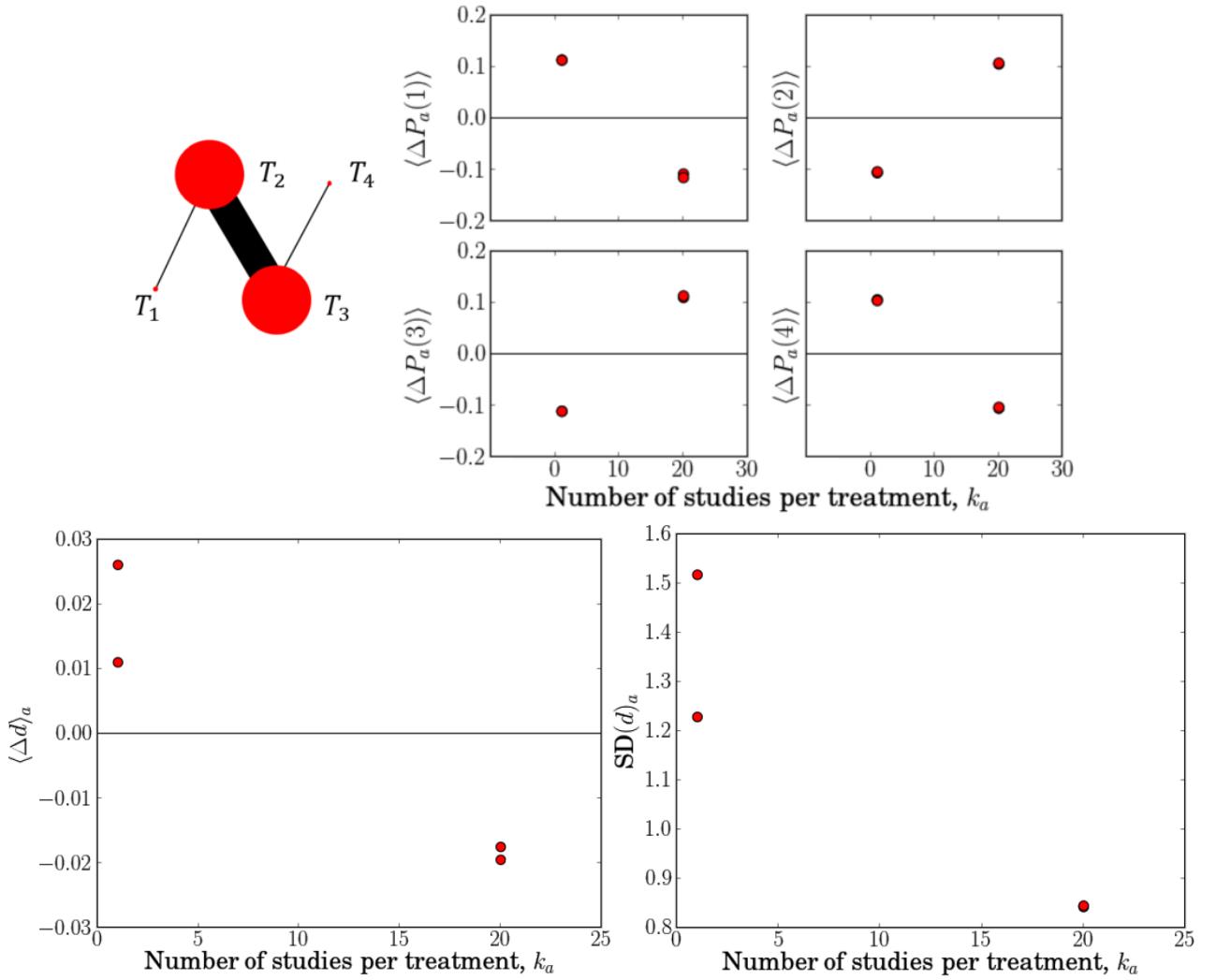


FIG. S16. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a ladder network with $\mathbf{K} = (1, 0, 0, 19, 0, 1)$.

S4. WITHIN NETWORK PLOTS: BIAS ON SUCRA

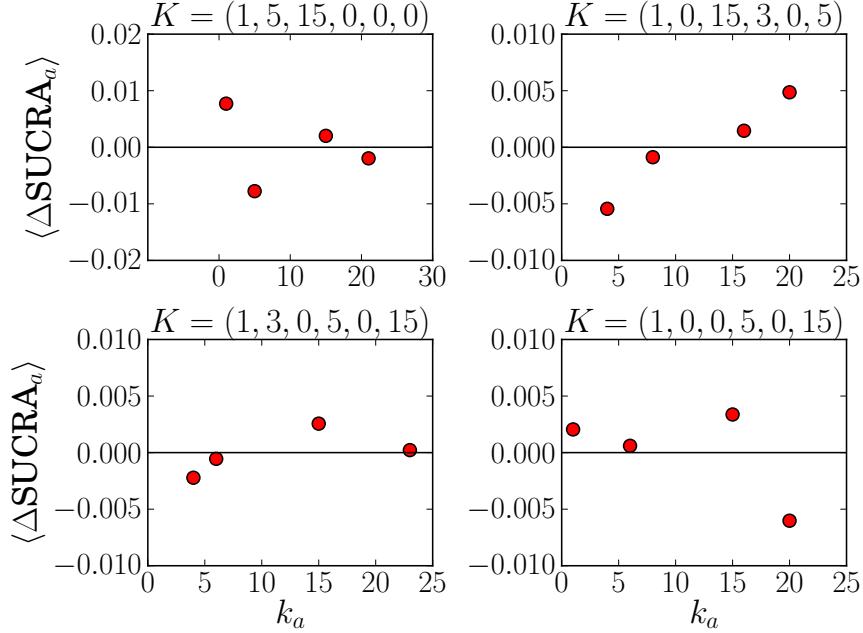


FIG. S17. Some examples of the effect of the number of studies per treatment on SUCRA_a for different network geometries. For these examples $\mathbf{d} = (0, 0, 0)$ and the networks are made up of exclusively 2-arm trials.

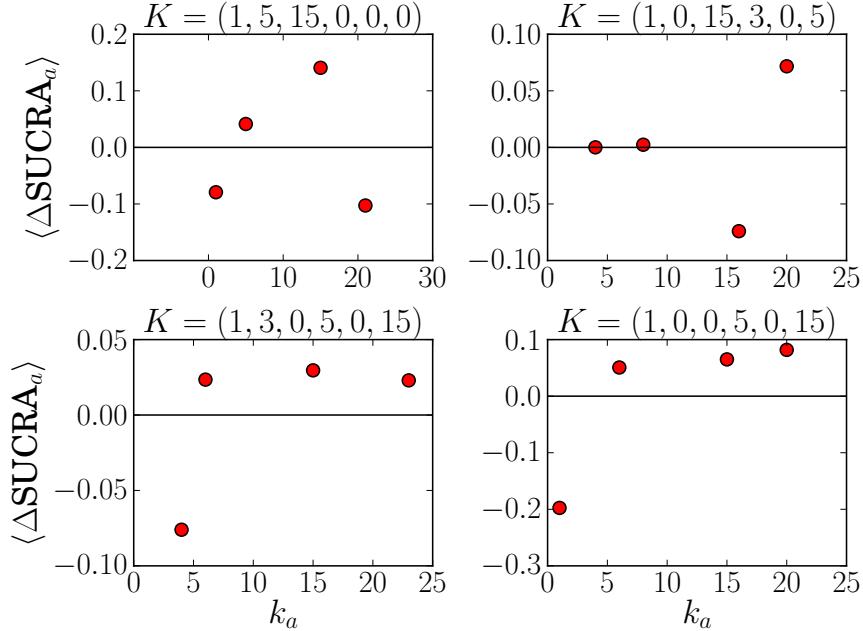


FIG. S18. Some examples of the effect of the number of studies per treatment on SUCRA_a for different network geometries. For these examples $\mathbf{d} = (0.5, 1.0, 1.4)$ and the networks are made up of exclusively 2-arm trials.

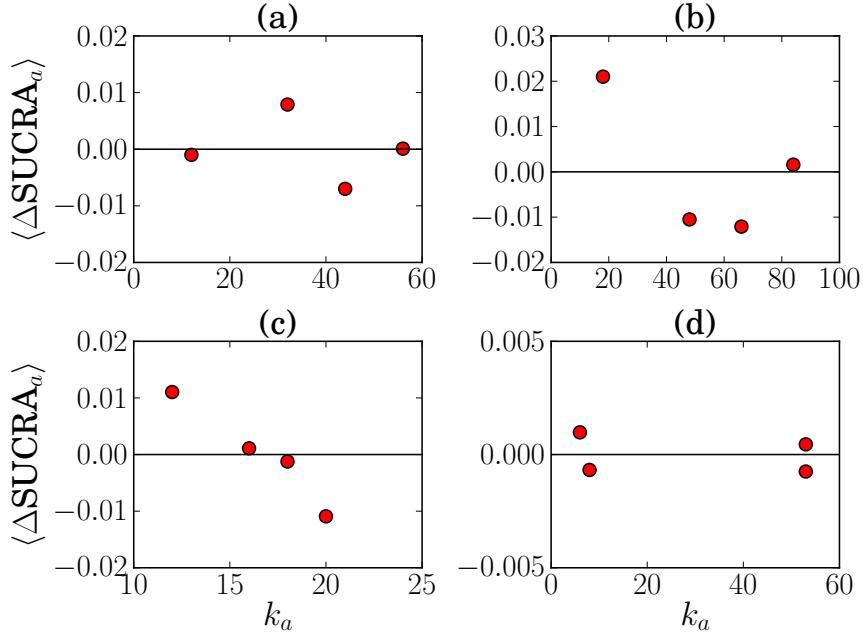


FIG. S19. Some examples of the effect of the number of studies per treatment on SUCRA_a for different network geometries. For these examples $\mathbf{d} = (0, 0, 0)$ and the networks contain multi-arm trials. We use n_m to indicate the number of m -arm trials. Figure (a): $\mathbf{K} = (2, 4, 6, 10, 20, 30)$ ($n_2, n_3, n_4 = (66, 0, 1)$), Figure (b): $\mathbf{K} = (3, 6, 9, 15, 30, 45)$ ($n_2, n_3, n_4 = (90, 4, 1)$), Figure (c): $\mathbf{K} = (3, 4, 5, 6, 7, 8)$ ($n_2, n_3, n_4 = (21, 4, 0)$), Figure (d): $\mathbf{K} = (2, 2, 2, 3, 3, 48)$ ($n_2, n_3, n_4 = (48, 0, 2)$).

S5. WITHIN NETWORK PLOTS: RANK PROBABILITY FOR NON-EQUALLY EFFECTIVE TREATMENTS

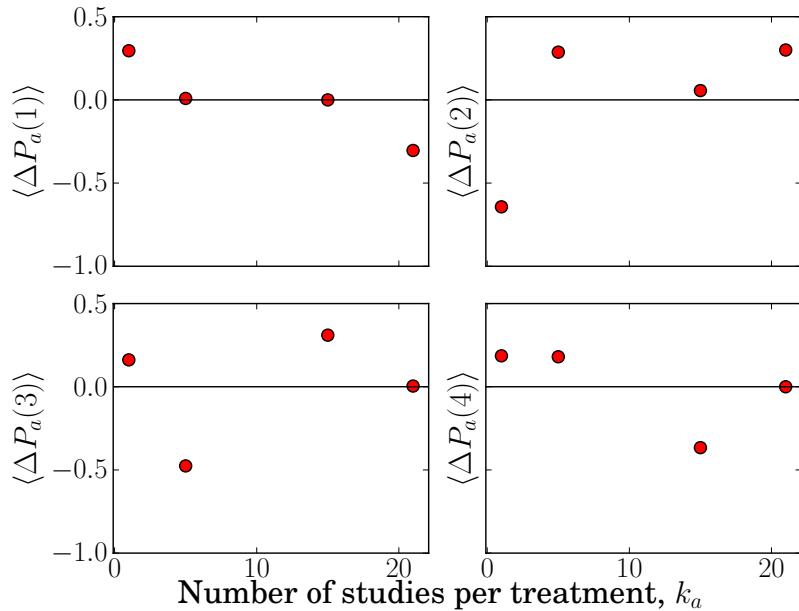


FIG. S20. Bias of rank probability against the number of studies per treatment for a star network with $\mathbf{K} = (1, 5, 15, 0, 0, 0)$ and non-equally effective treatments, $\mathbf{d} = (0.5, 1.0, 1.4)$.

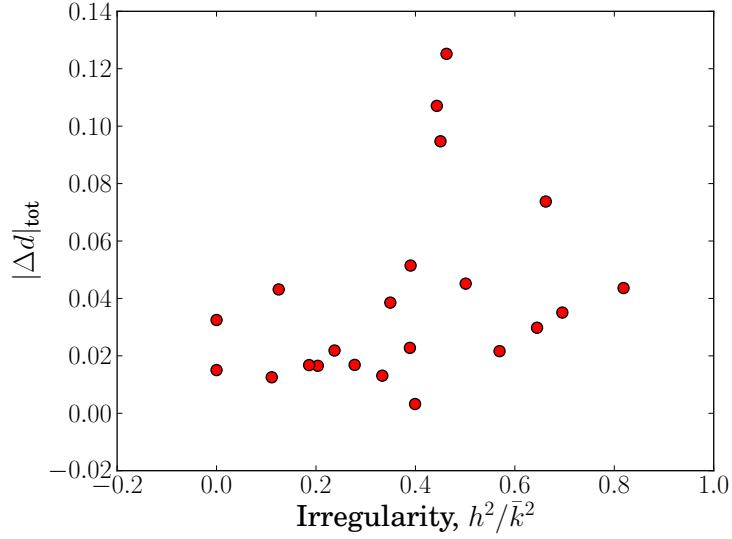
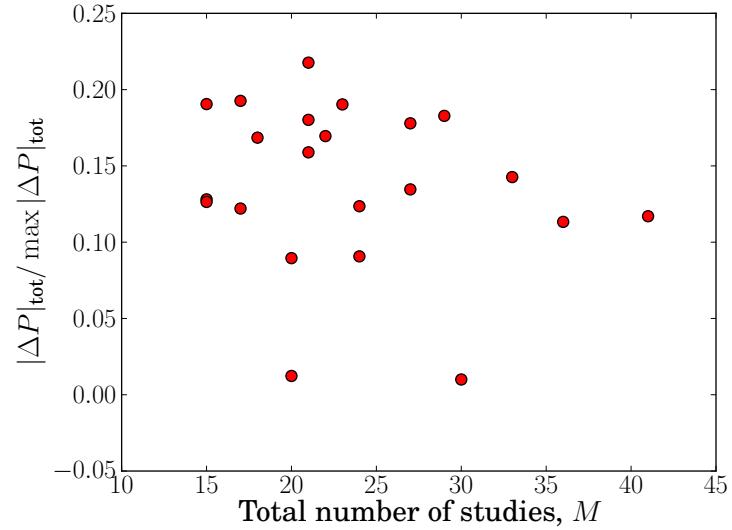
S6. BETWEEN NETWORK PLOTS: TREATMENT EFFECT BIAS AND IRREGULARITY


FIG. S21. The effect of irregularity on the total bias of treatment effects.

S7. BETWEEN NETWORK PLOTS: THE EFFECT OF THE TOTAL NUMBER OF STUDIES


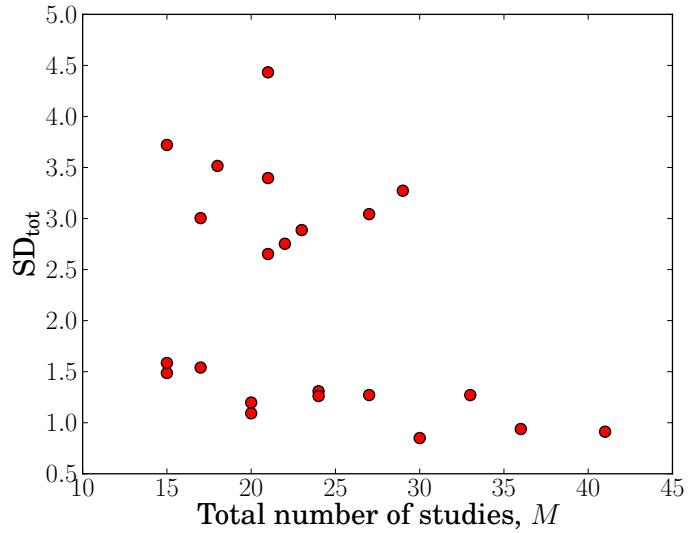


FIG. S23. The effect of the total number of studies in the network on the network's total standard deviation on treatment effect estimates.

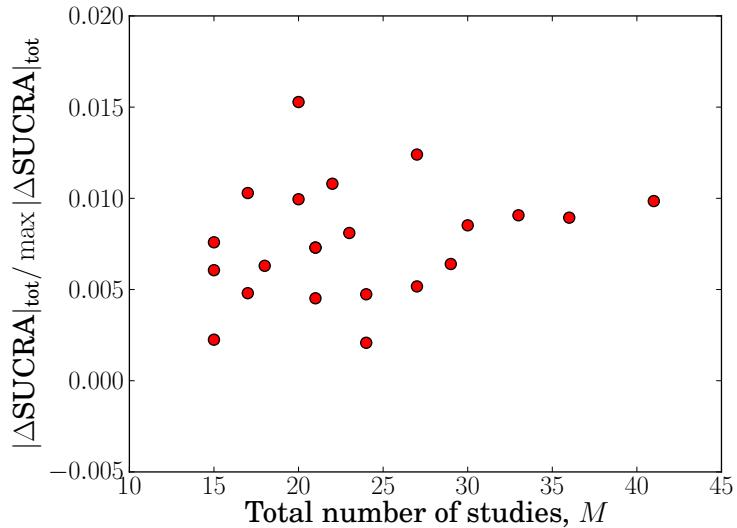


FIG. S24. The effect of the total number of studies in the network on a network's total bias on SUCRA values. Total bias is plotted as a proportion of the maximum total SUCRA bias.

S8. MULTI-ARM STUDIES: WITHIN NETWORK PLOTS

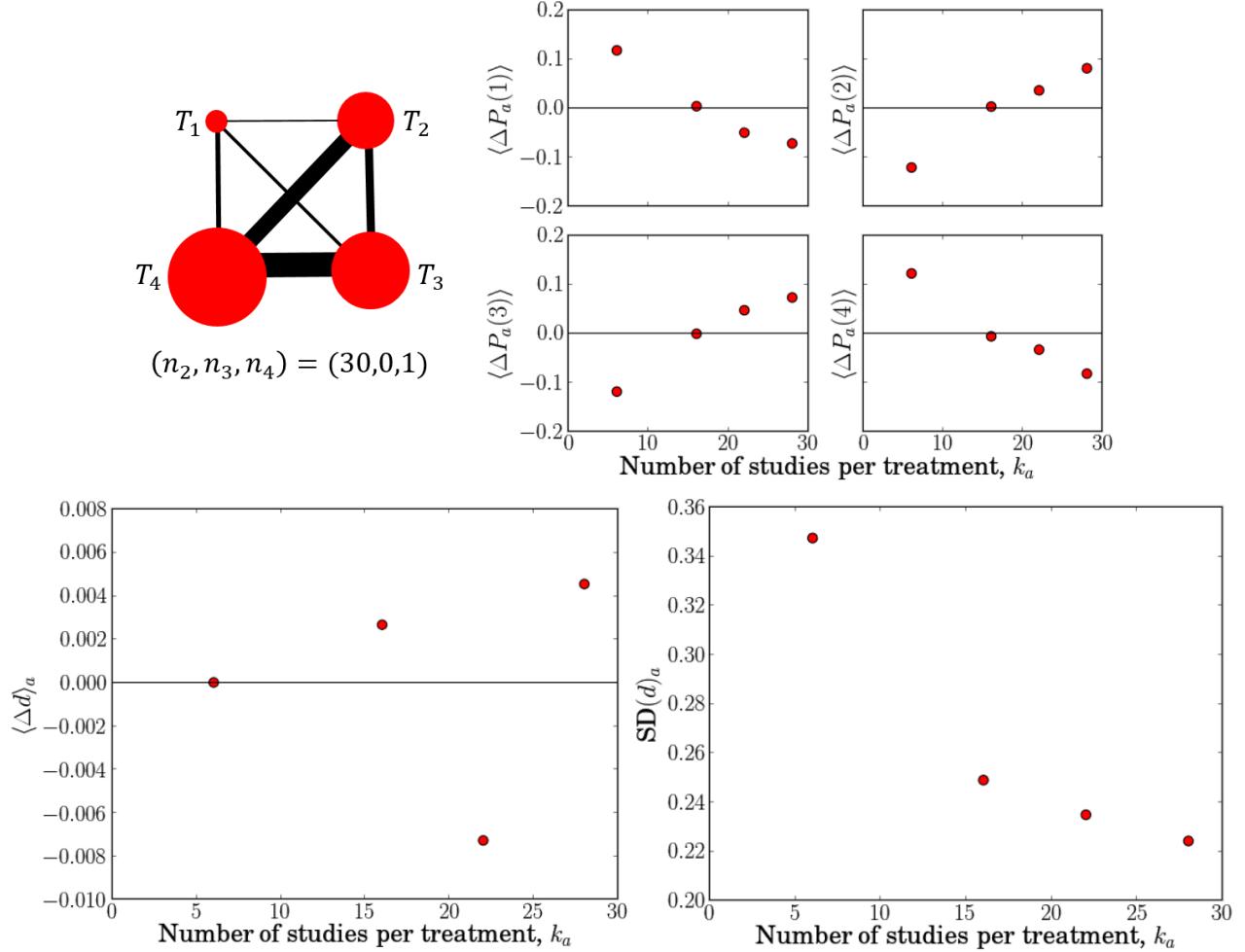


FIG. S25. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $K = (1, 2, 3, 5, 10, 15)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (30, 0, 1)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.203704$.

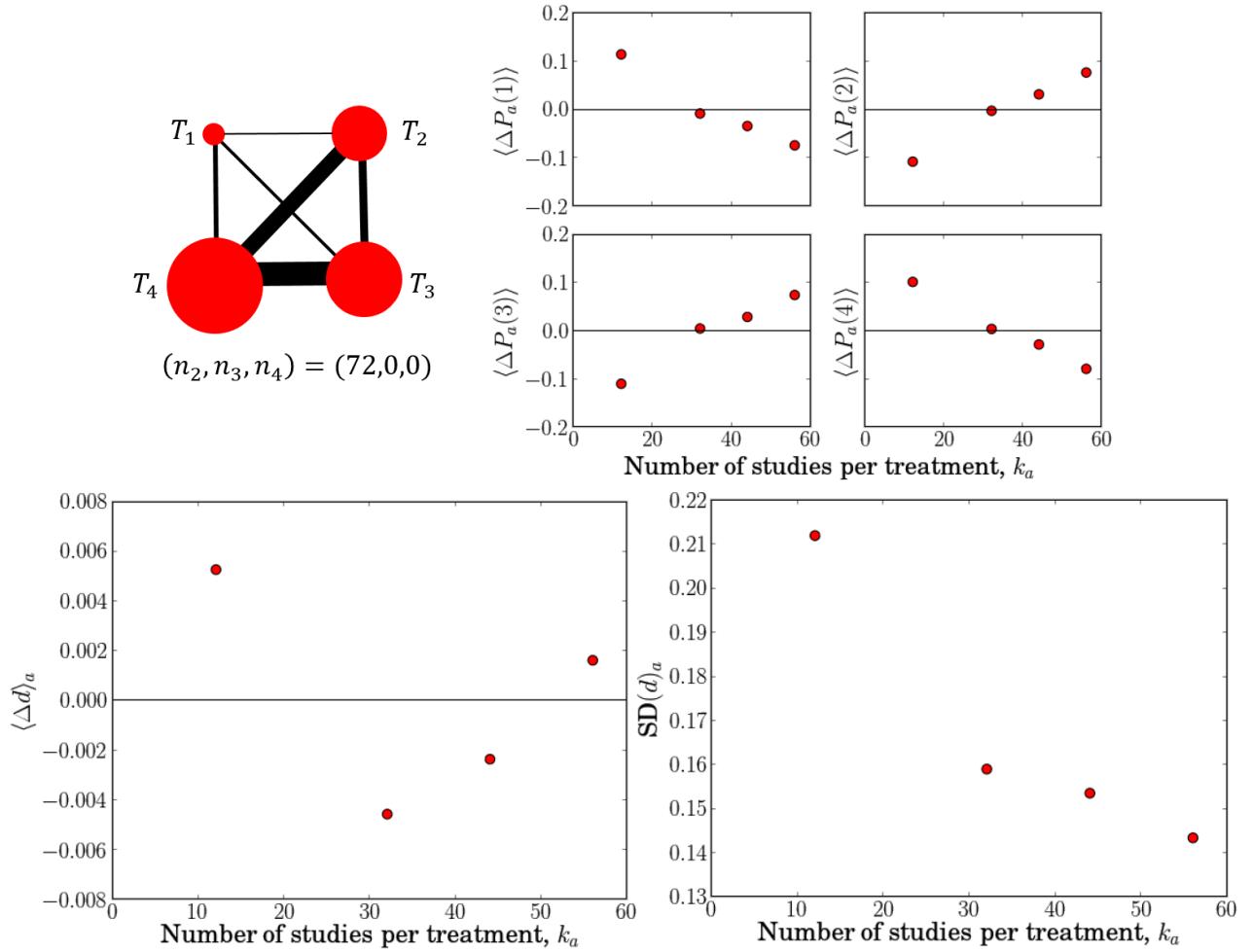


FIG. S26. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (2, 4, 6, 10, 20, 30)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (72, 0, 0)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.203704$.

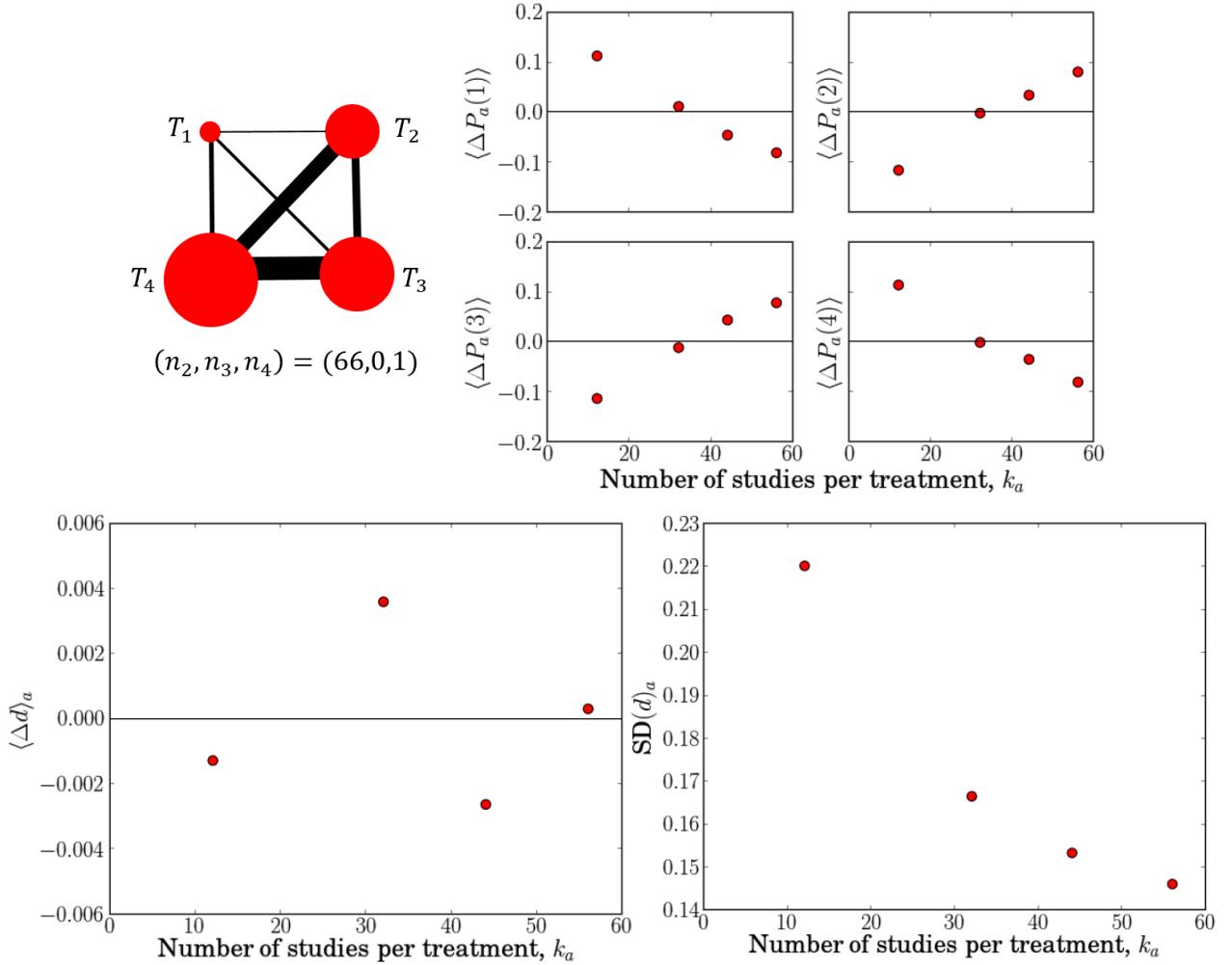


FIG. S27. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (2, 4, 6, 10, 20, 30)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (66, 0, 1)$. The irregularity of the network is $h^2/k^2 = 0.203704$.

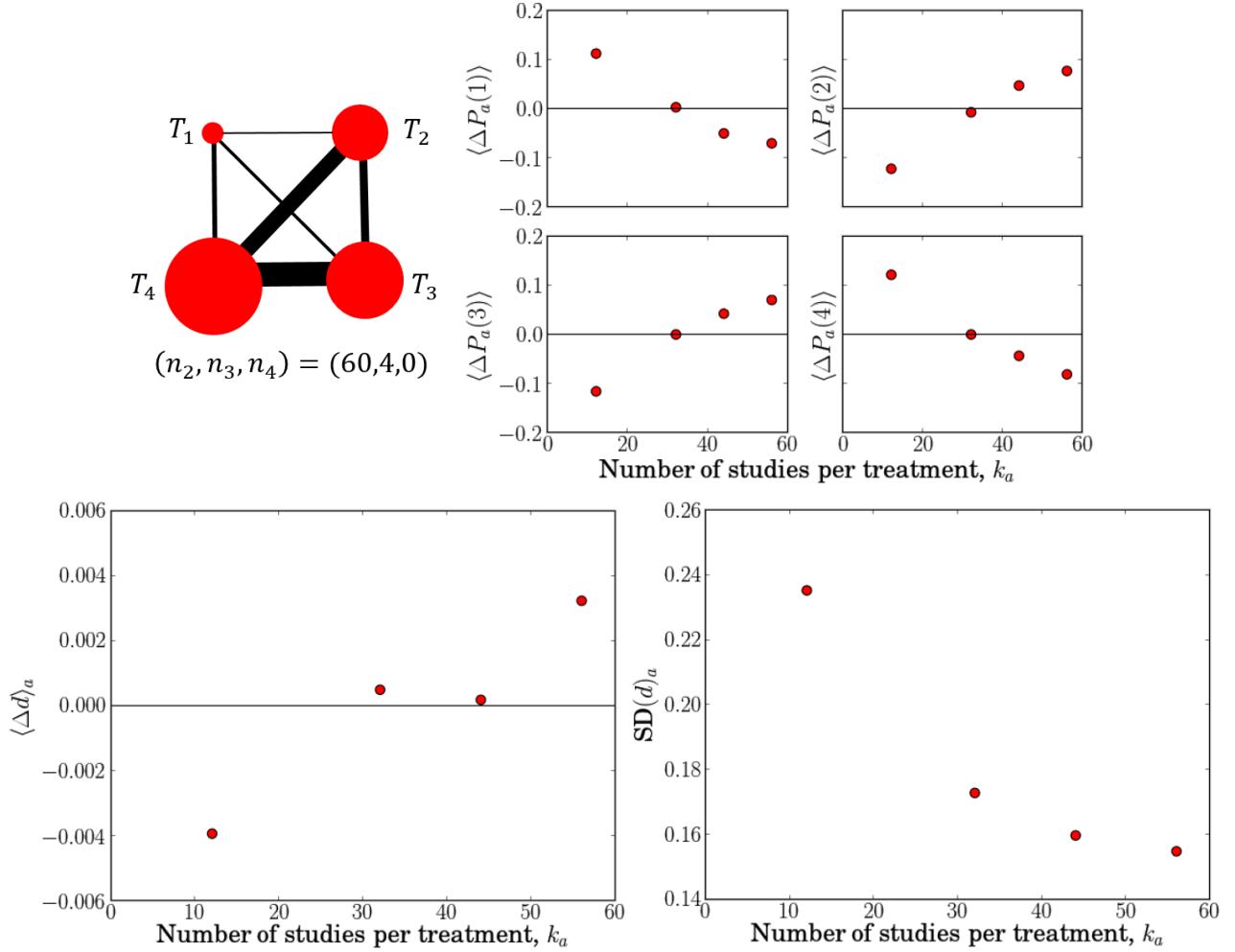


FIG. S28. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (2, 4, 6, 10, 20, 30)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (60, 4, 0)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.203704$.

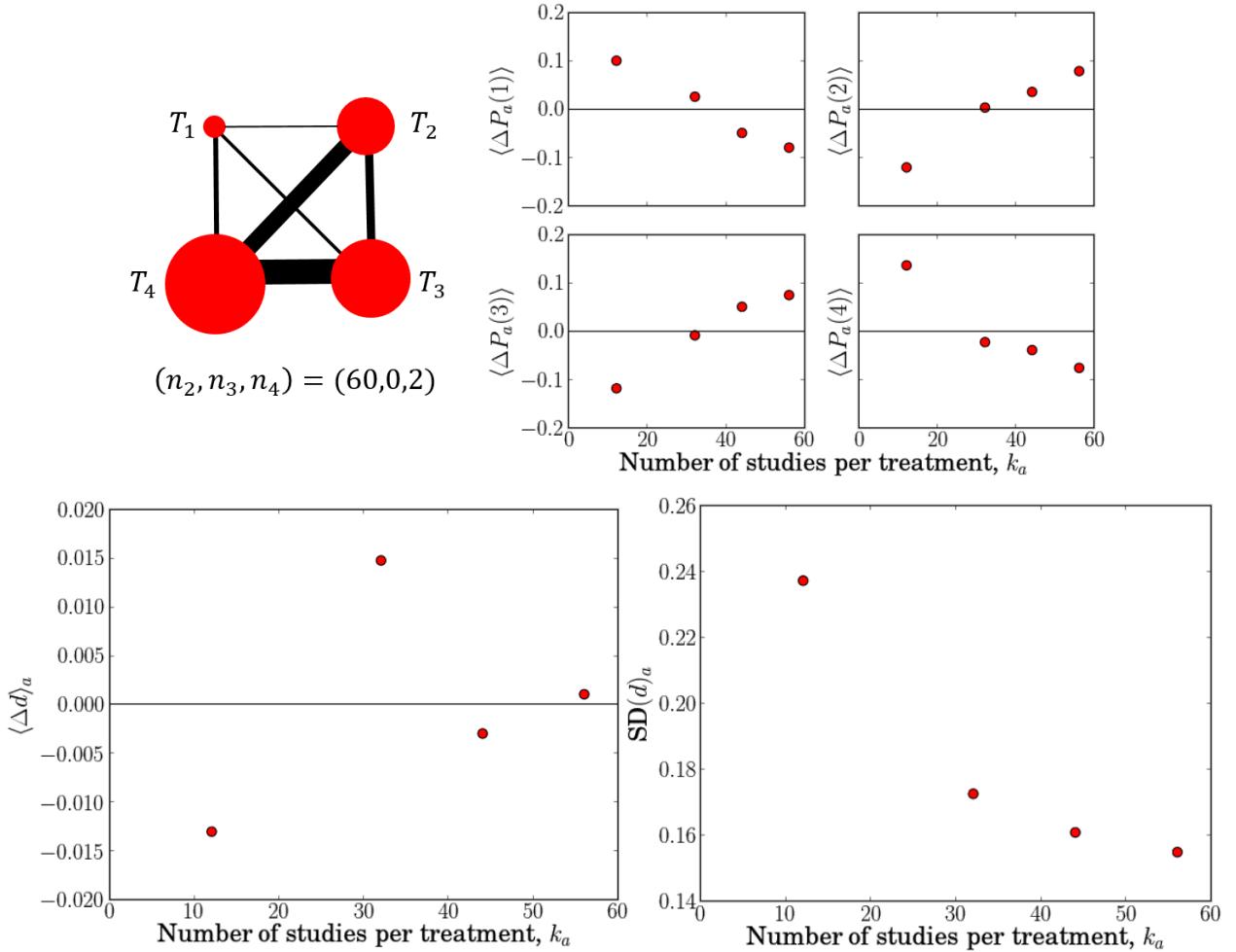


FIG. S29. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (2, 4, 6, 10, 20, 30)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (60, 0, 2)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.203704$.

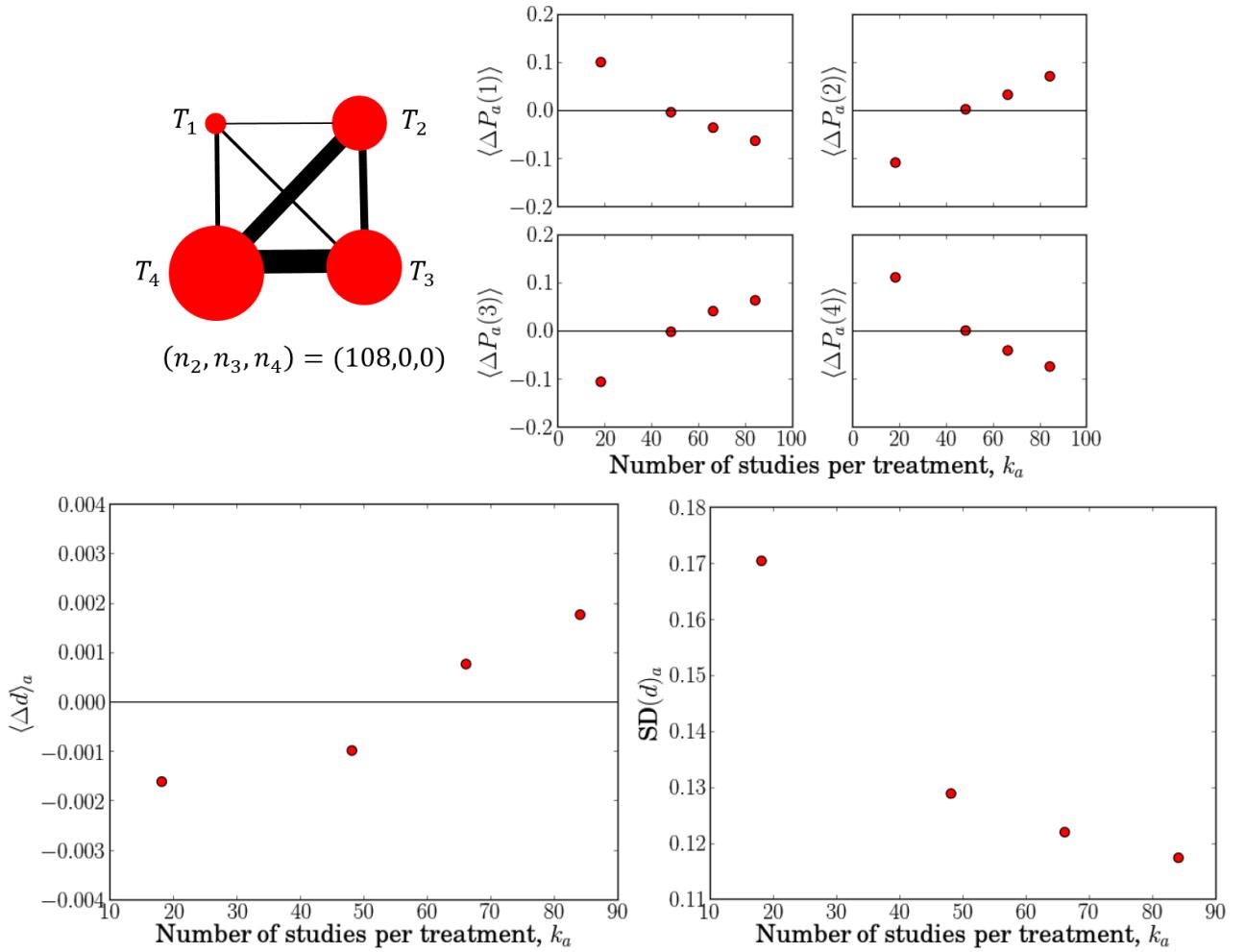


FIG. S30. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $K = (3, 6, 9, 15, 30, 45)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (108, 0, 0)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.203704$.

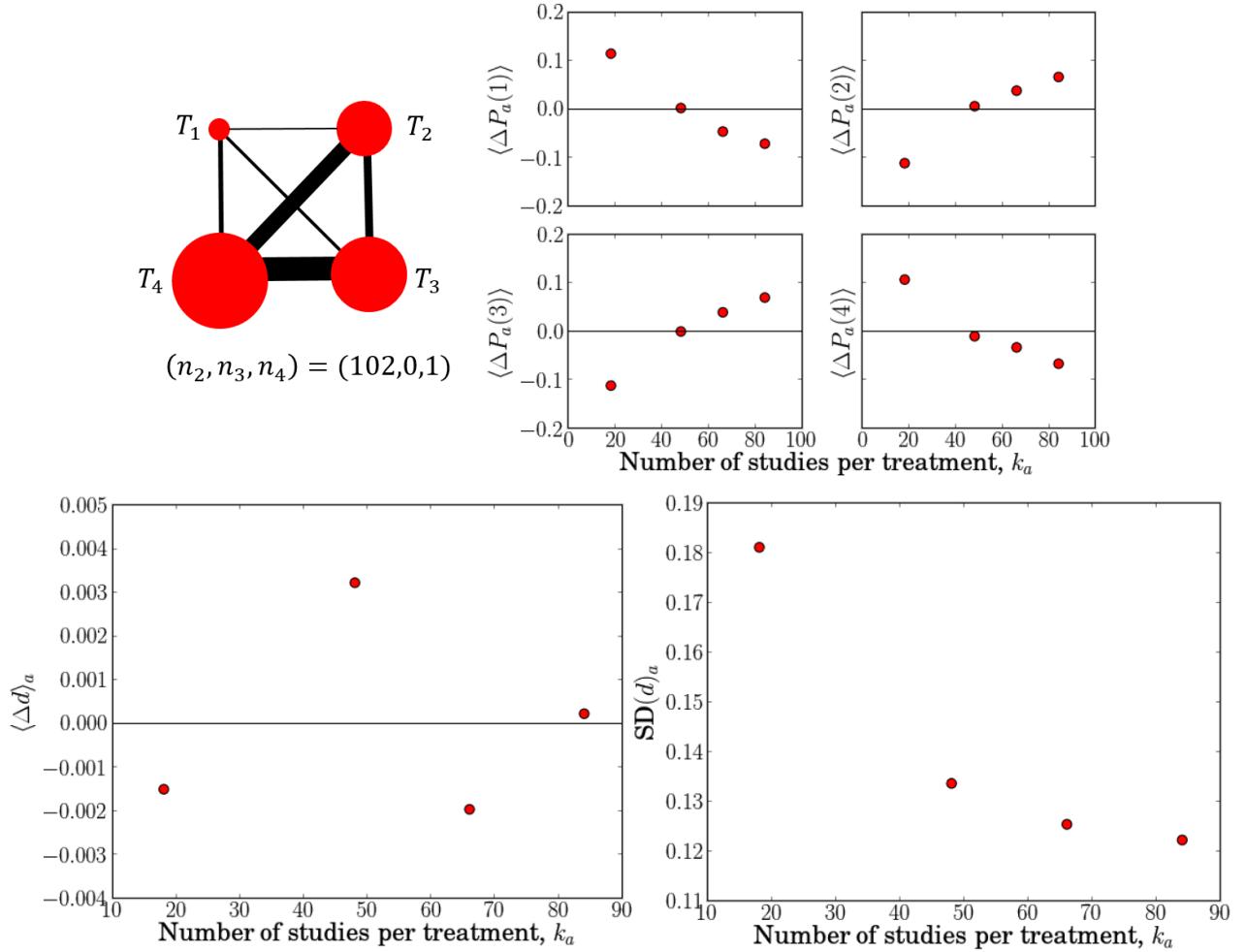


FIG. S31. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (3, 6, 9, 15, 30, 45)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (102, 0, 1)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.203704$.

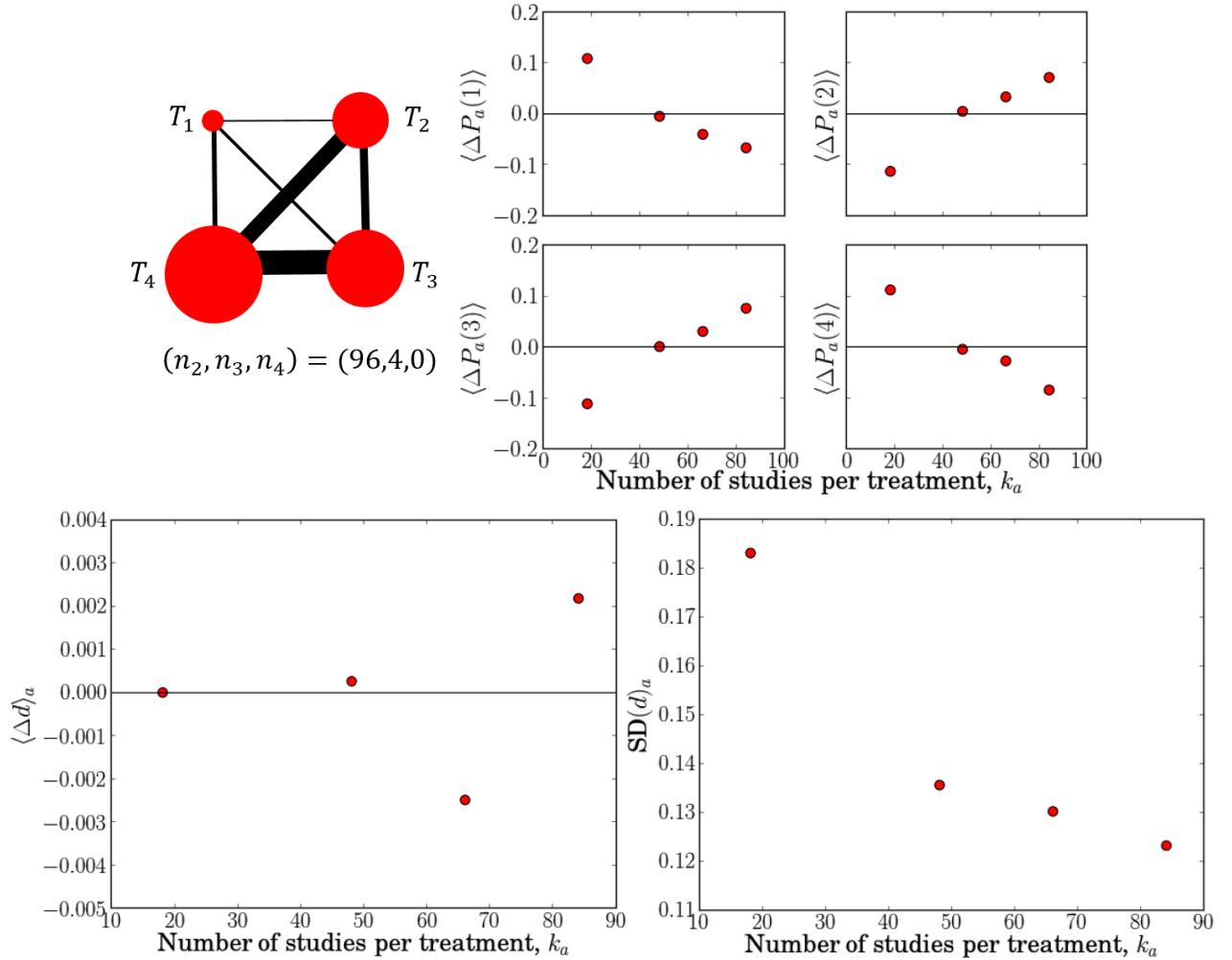


FIG. S32. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (3, 6, 9, 15, 30, 45)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (96, 4, 0)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.203704$.

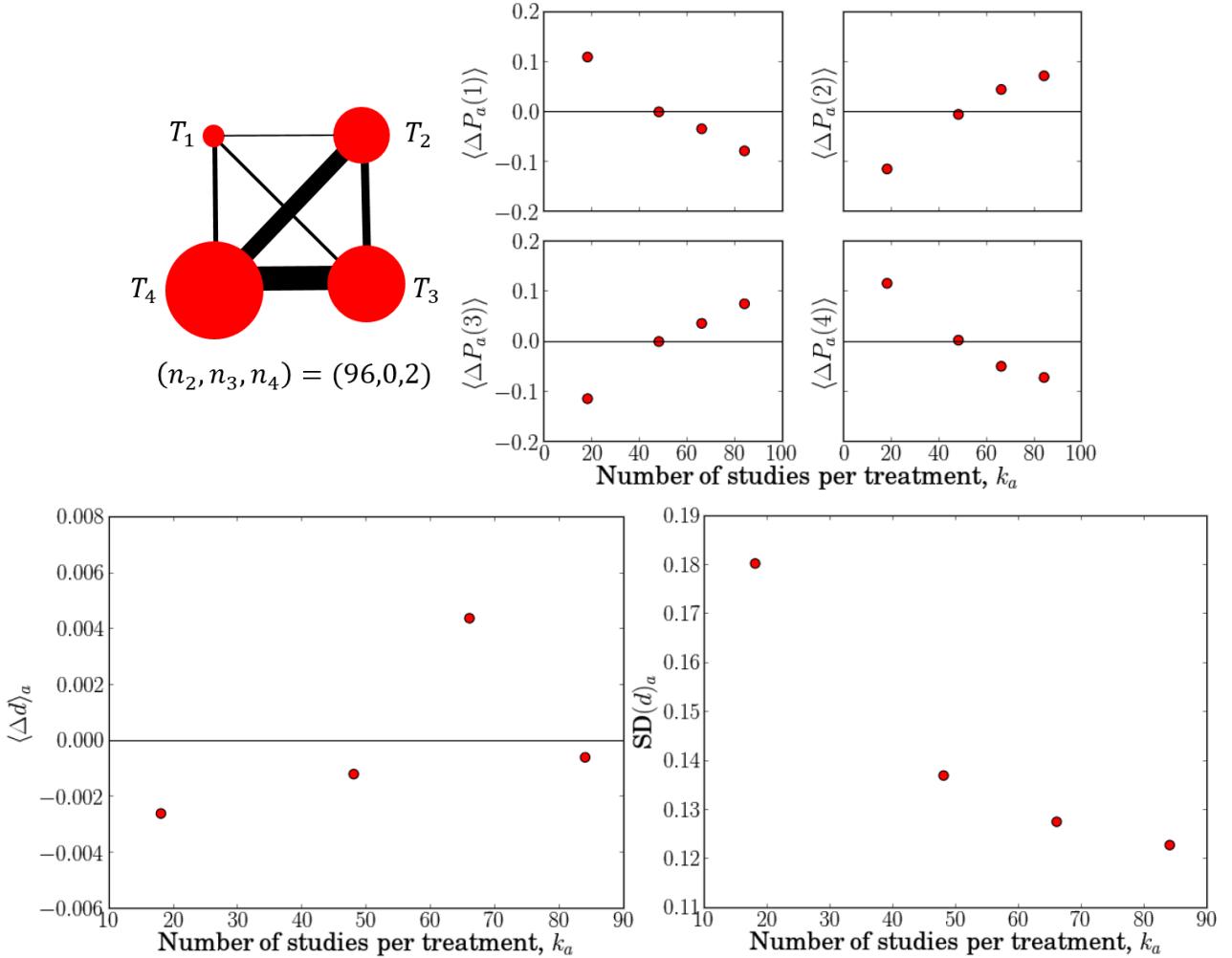


FIG. S33. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (3, 6, 9, 15, 30, 45)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (96, 0, 2)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.203704$.

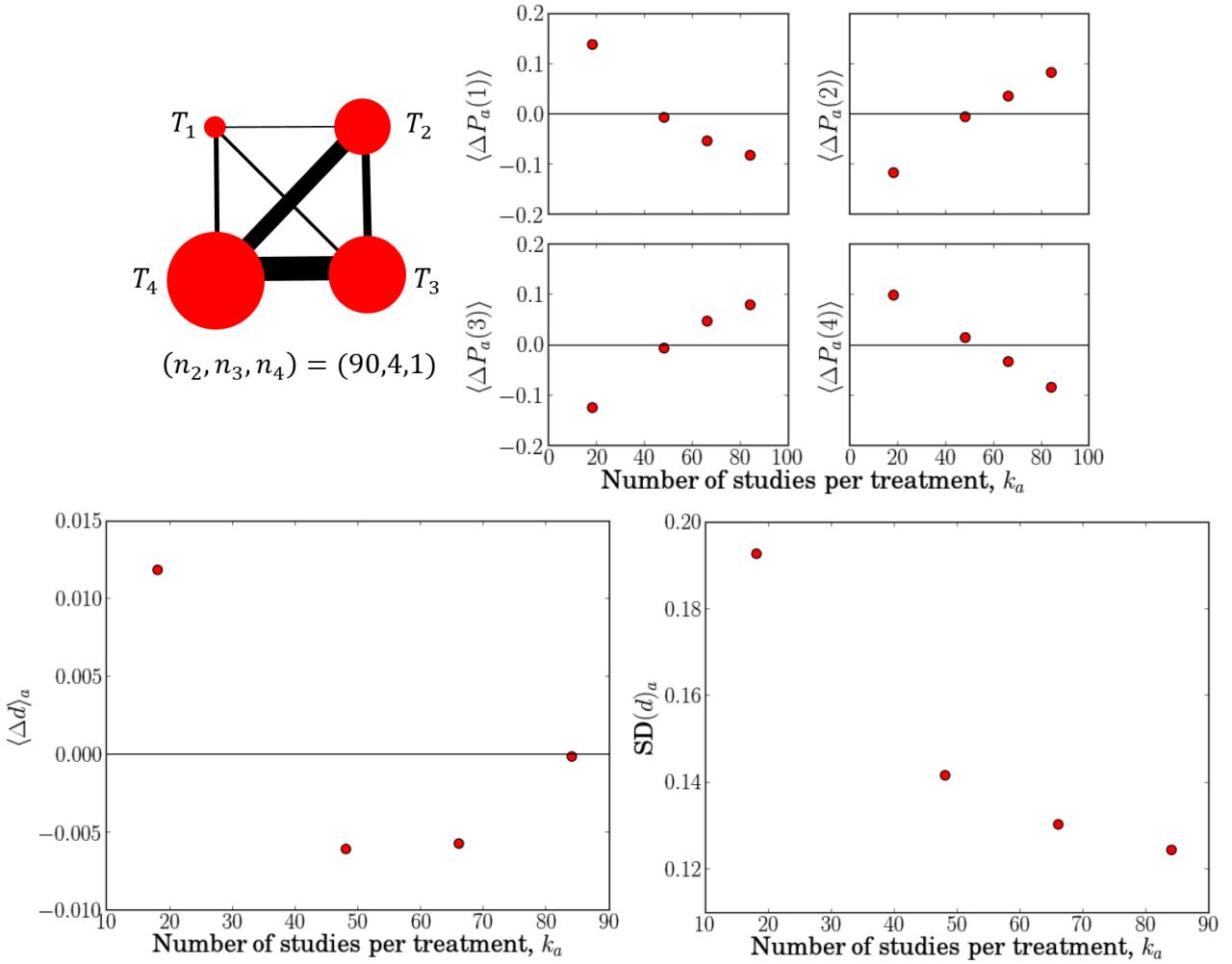


FIG. S34. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (3, 6, 9, 15, 30, 45)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (90, 4, 1)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.203704$.

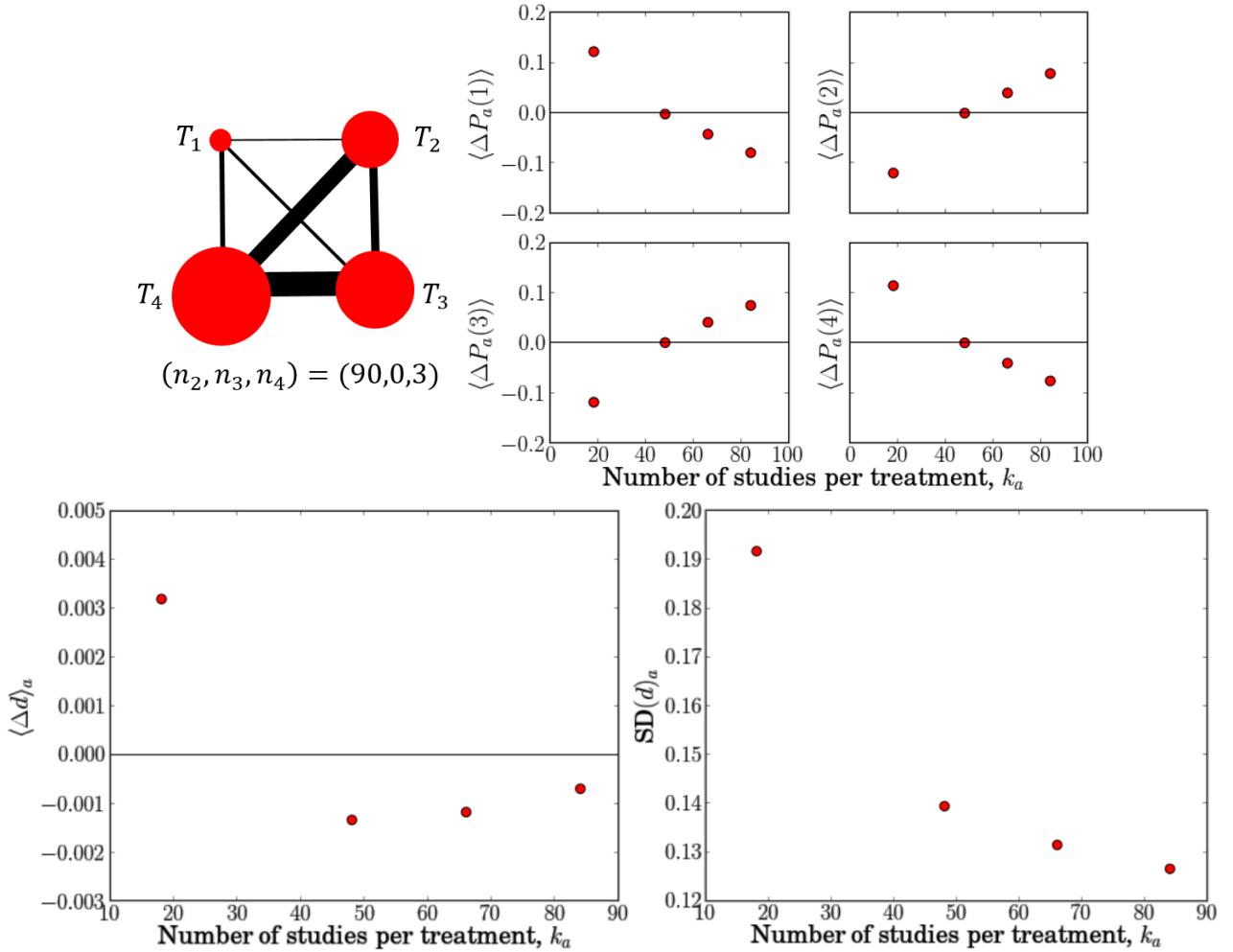


FIG. S35. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (3, 6, 9, 15, 30, 45)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (90, 0, 3)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.203704$.

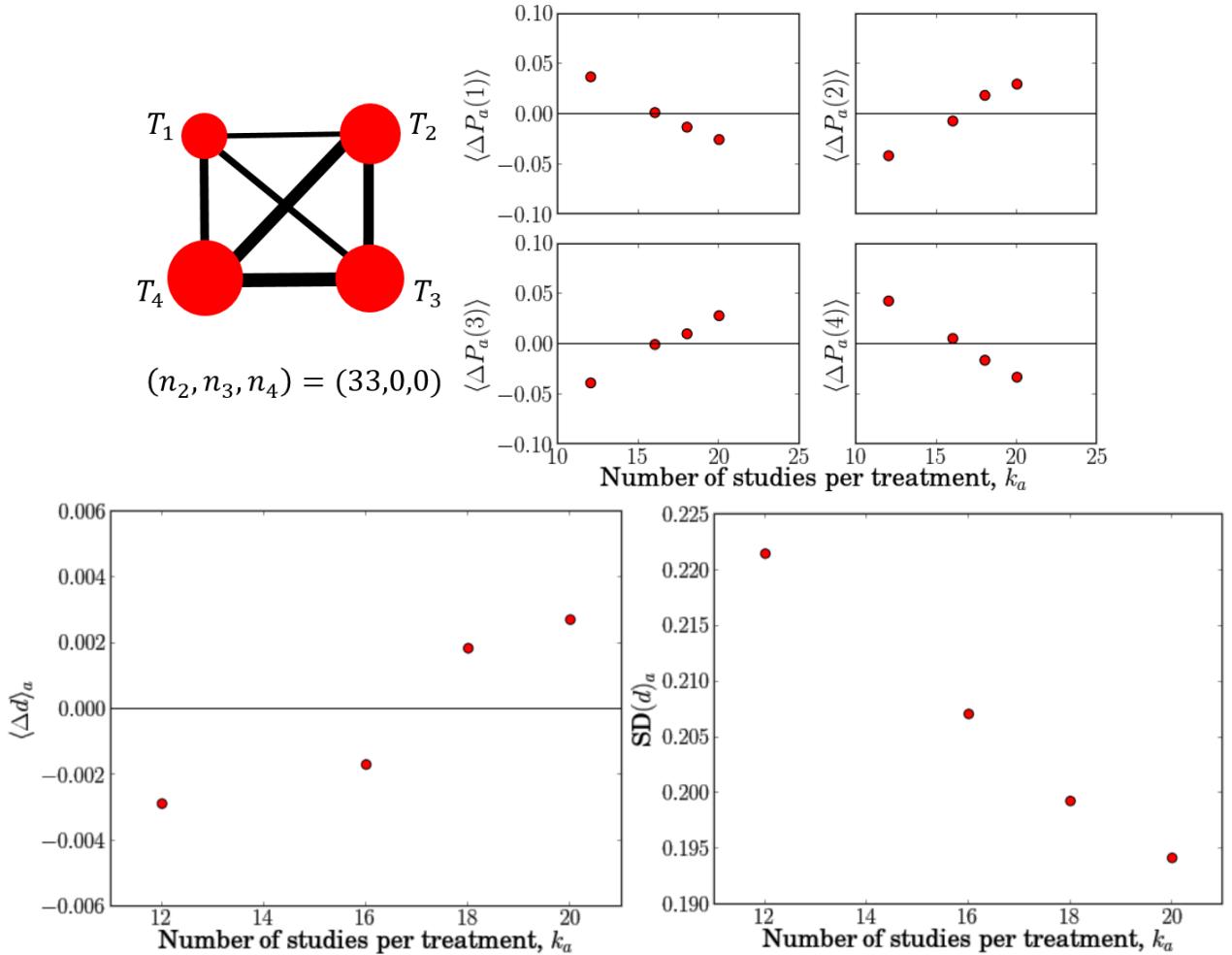


FIG. S36. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (3, 4, 5, 6, 7, 8)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (33, 0, 0)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.032140$.

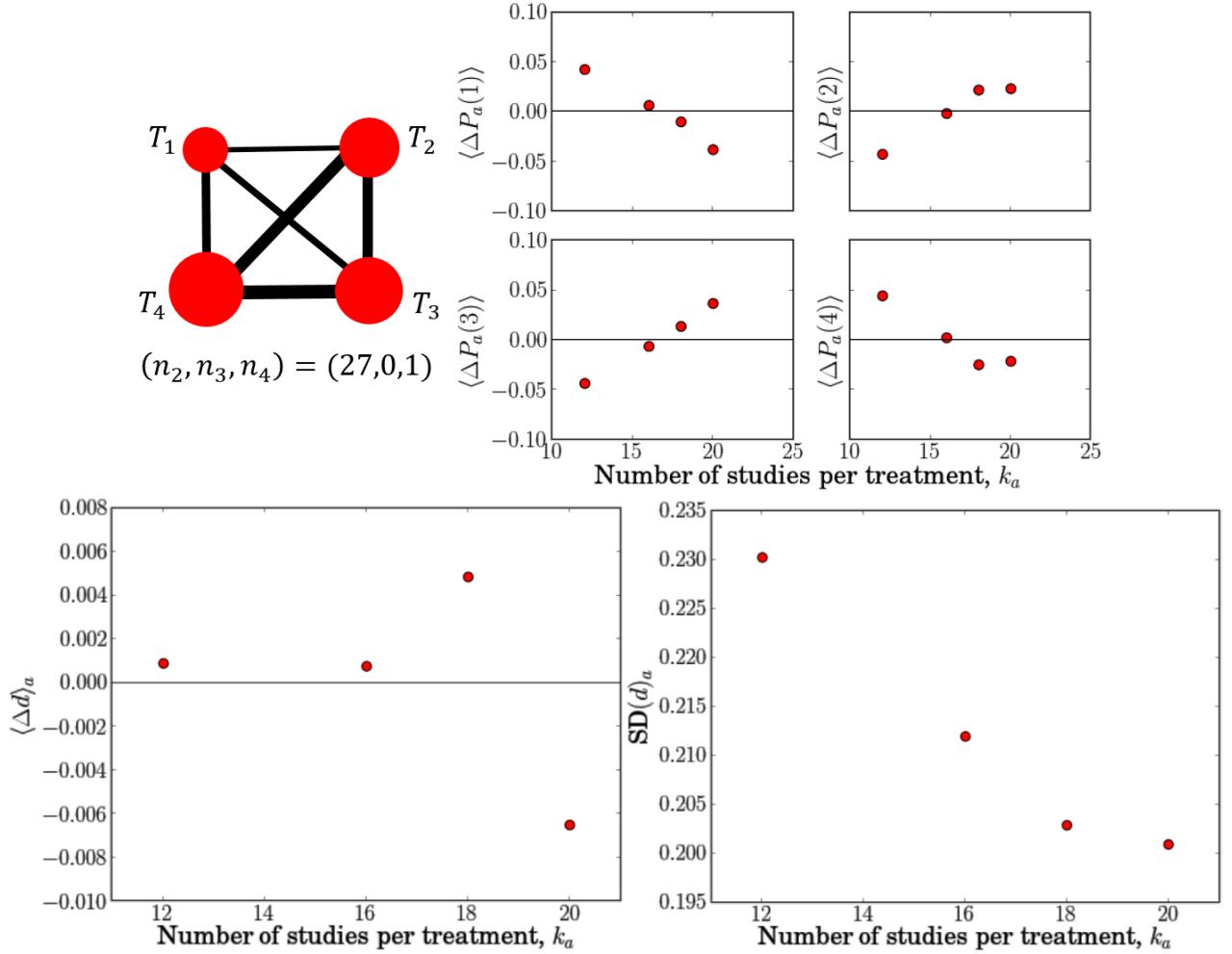


FIG. S37. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (3, 4, 5, 6, 7, 8)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (27, 0, 1)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.032140$.

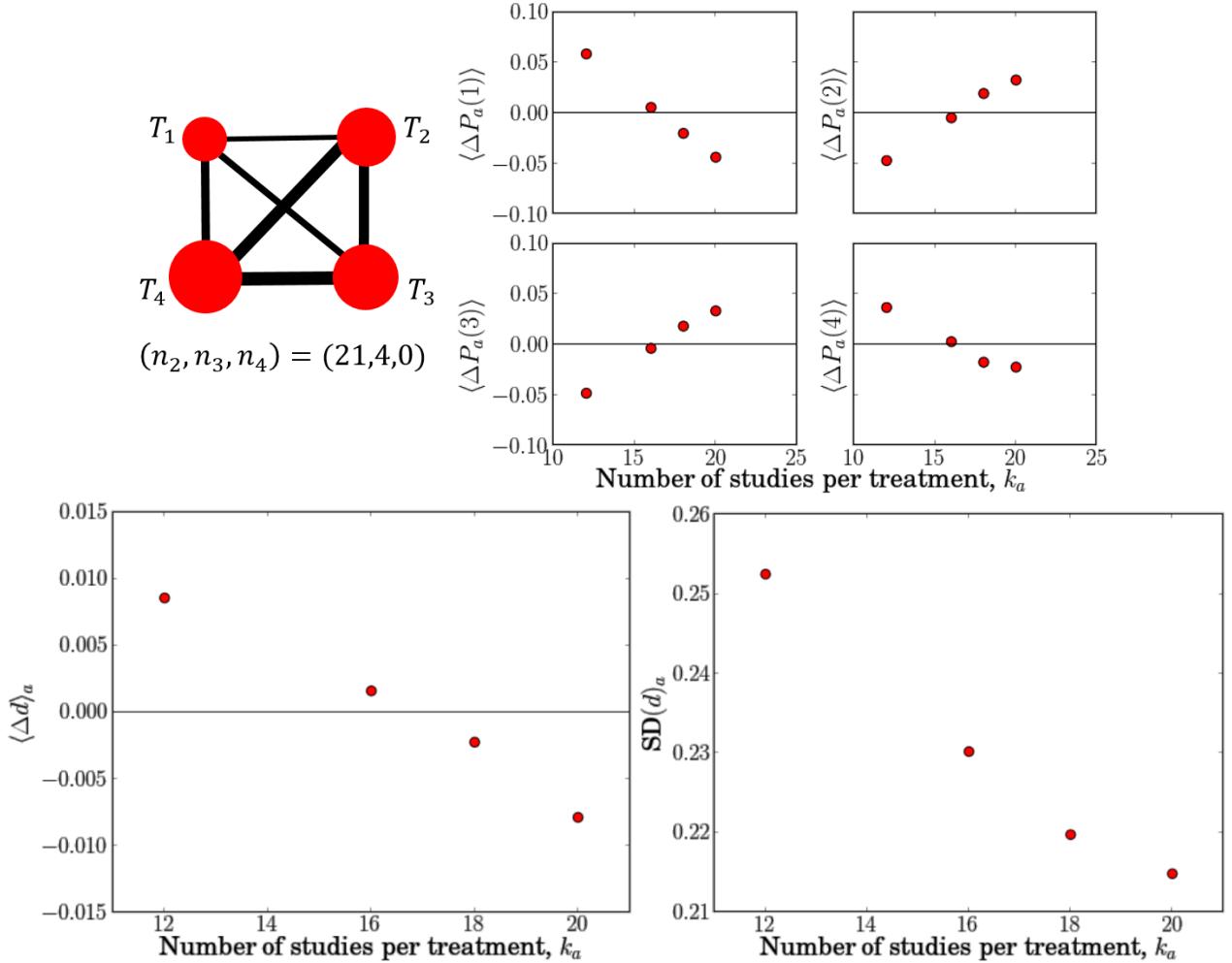


FIG. S38. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (3, 4, 5, 6, 7, 8)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (21, 4, 0)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.032140$.

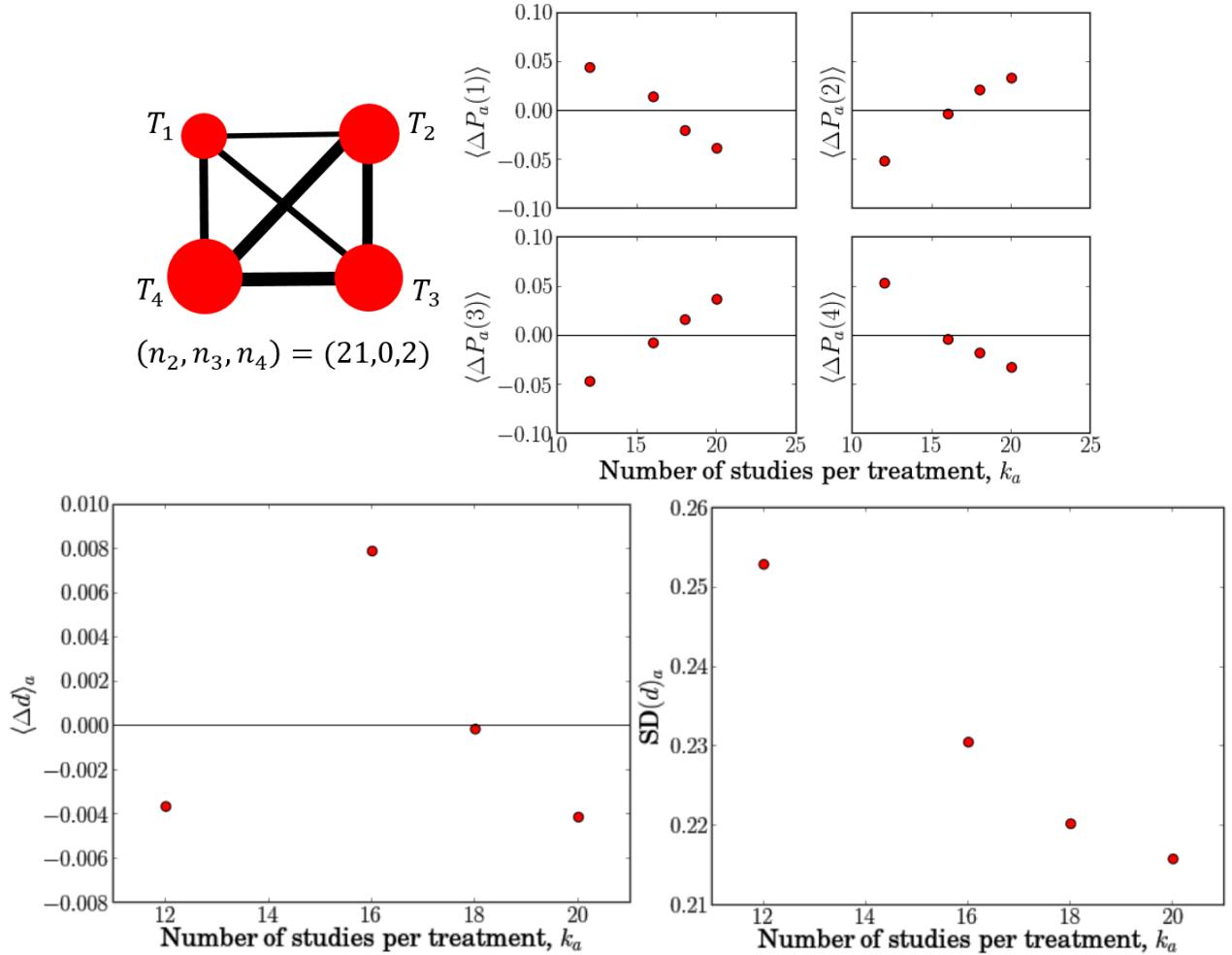


FIG. S39. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (3, 4, 5, 6, 7, 8)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (21, 0, 2)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.032140$.

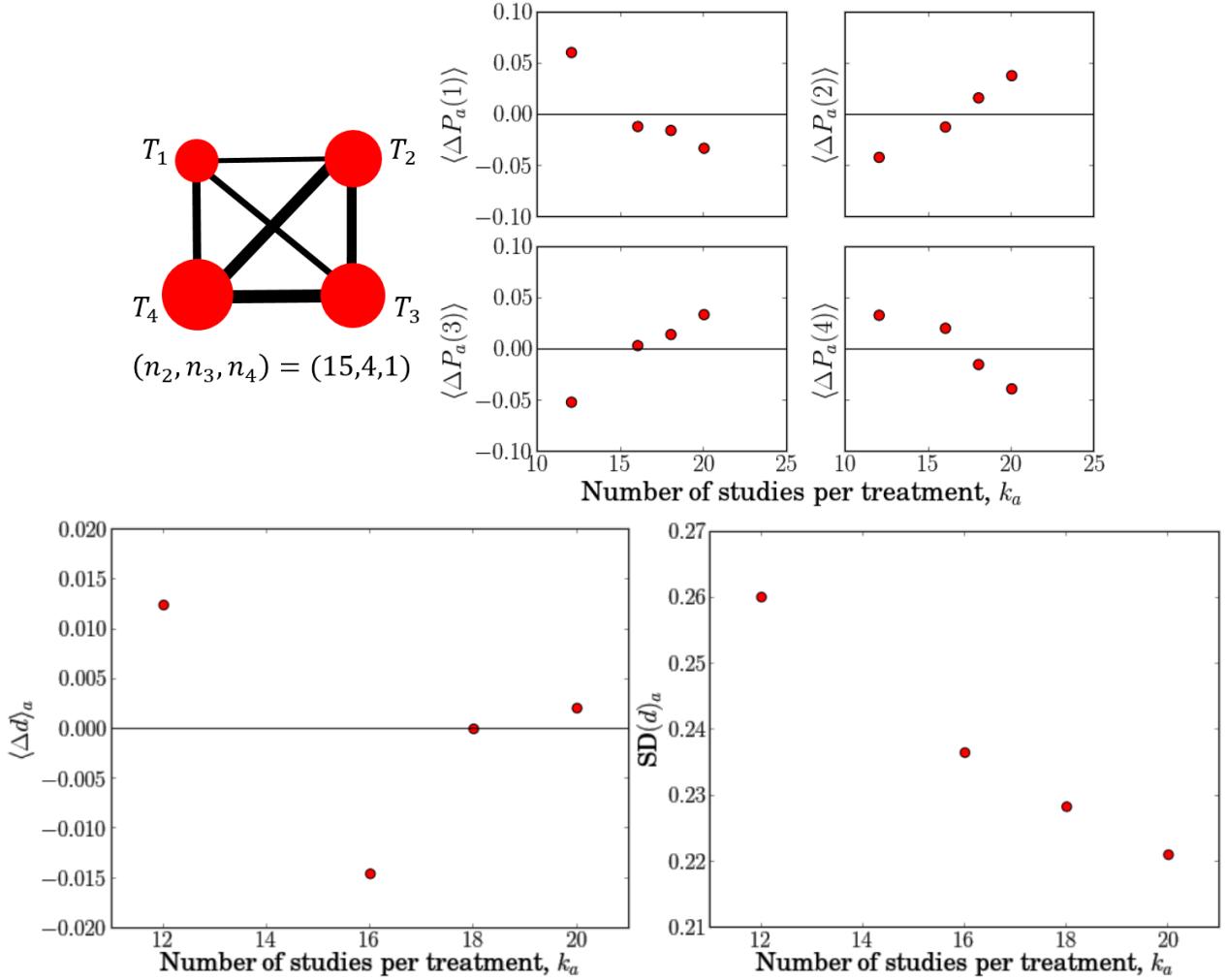


FIG. S40. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (3, 4, 5, 6, 7, 8)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (15, 4, 1)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.032140$.

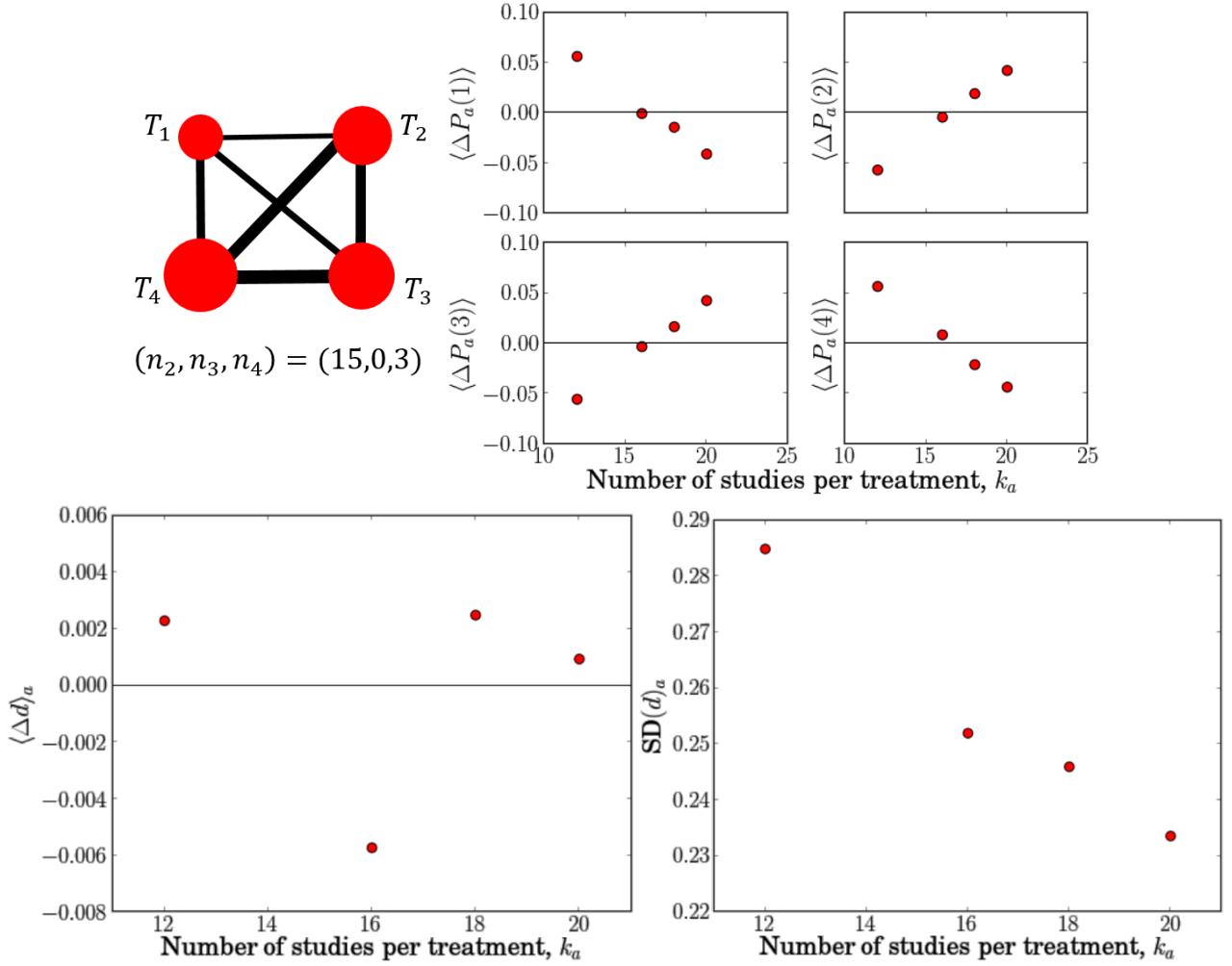


FIG. S41. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (3, 4, 5, 6, 7, 8)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (15, 0, 3)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.032140$.

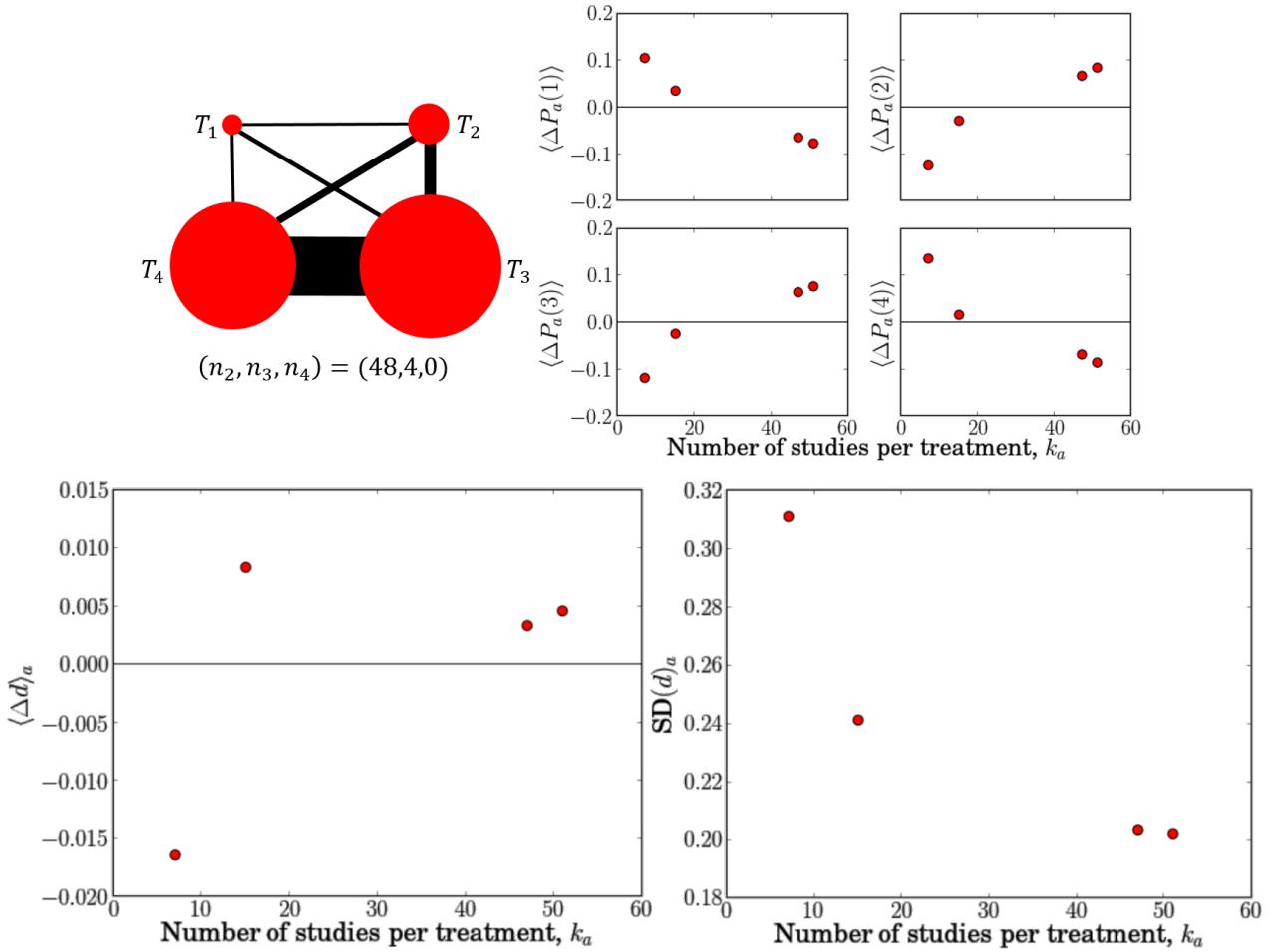


FIG. S42. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (2, 3, 2, 8, 5, 40)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (48, 4, 0)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.412222$.

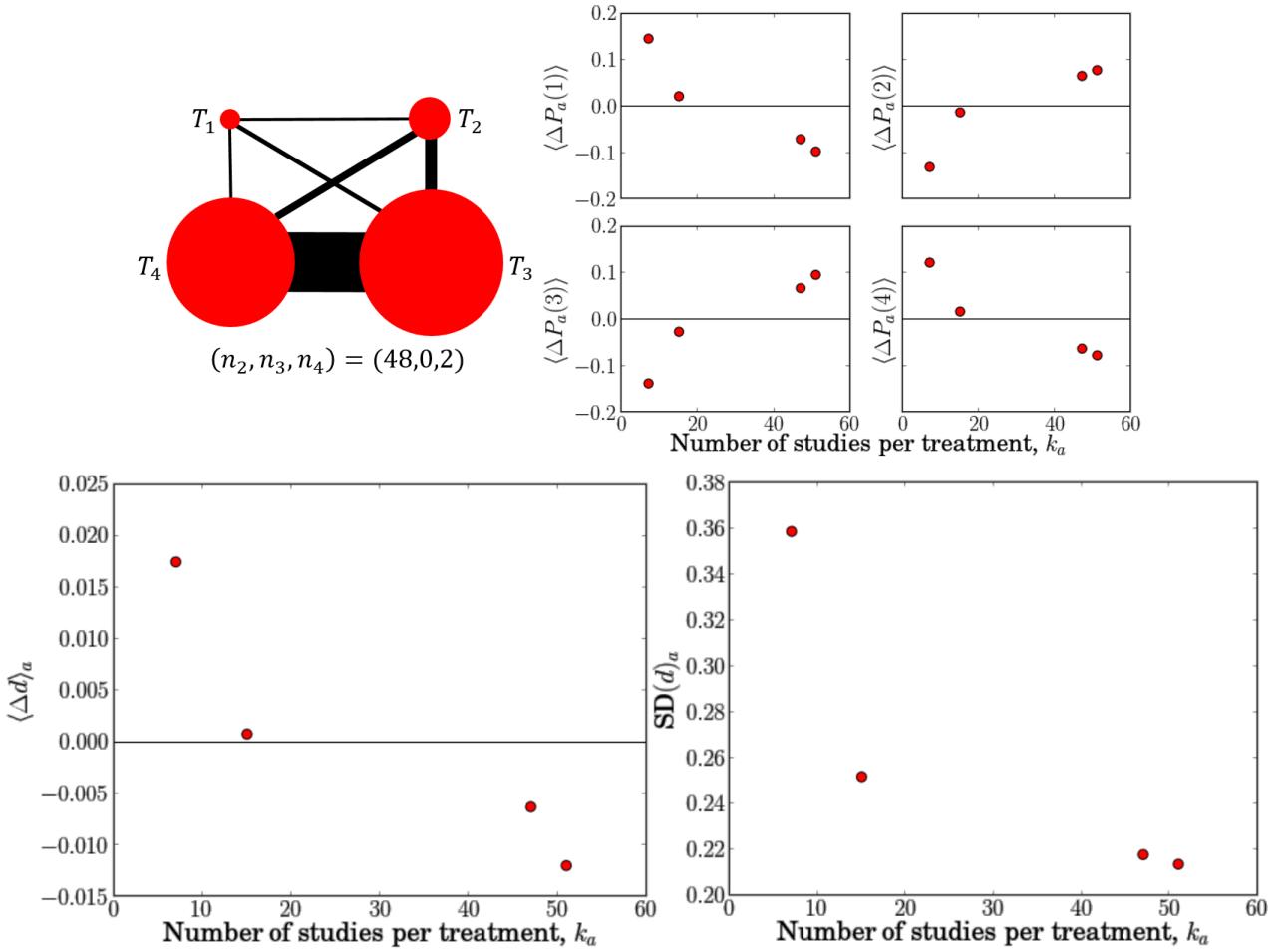


FIG. S43. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (2, 3, 2, 8, 5, 40)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (48, 0, 2)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.412222$.

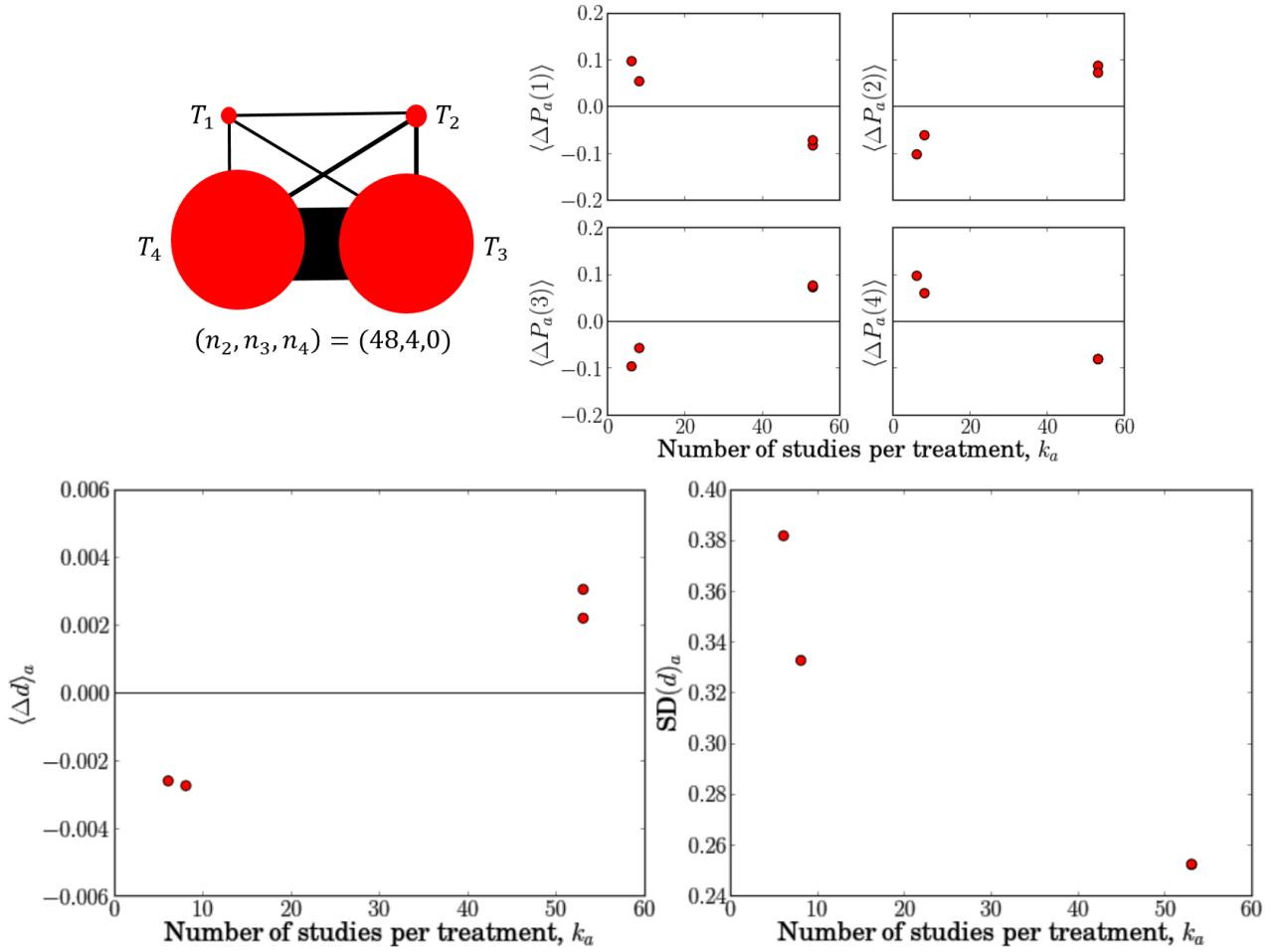


FIG. S44. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (2, 2, 2, 3, 3, 48)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (48, 4, 0)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.588333$.

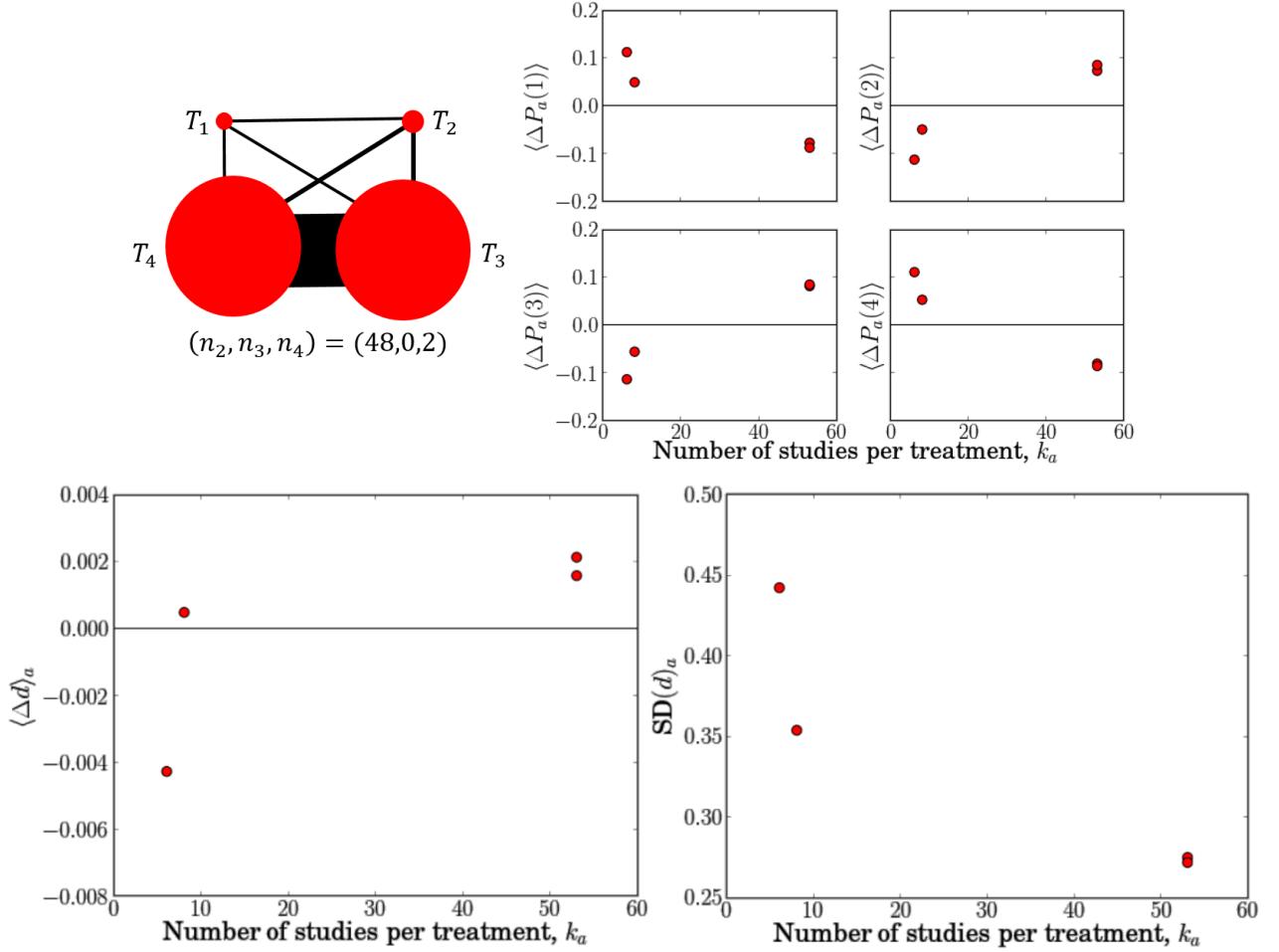


FIG. S45. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (2, 2, 2, 3, 3, 48)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (48, 0, 2)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.588333$.

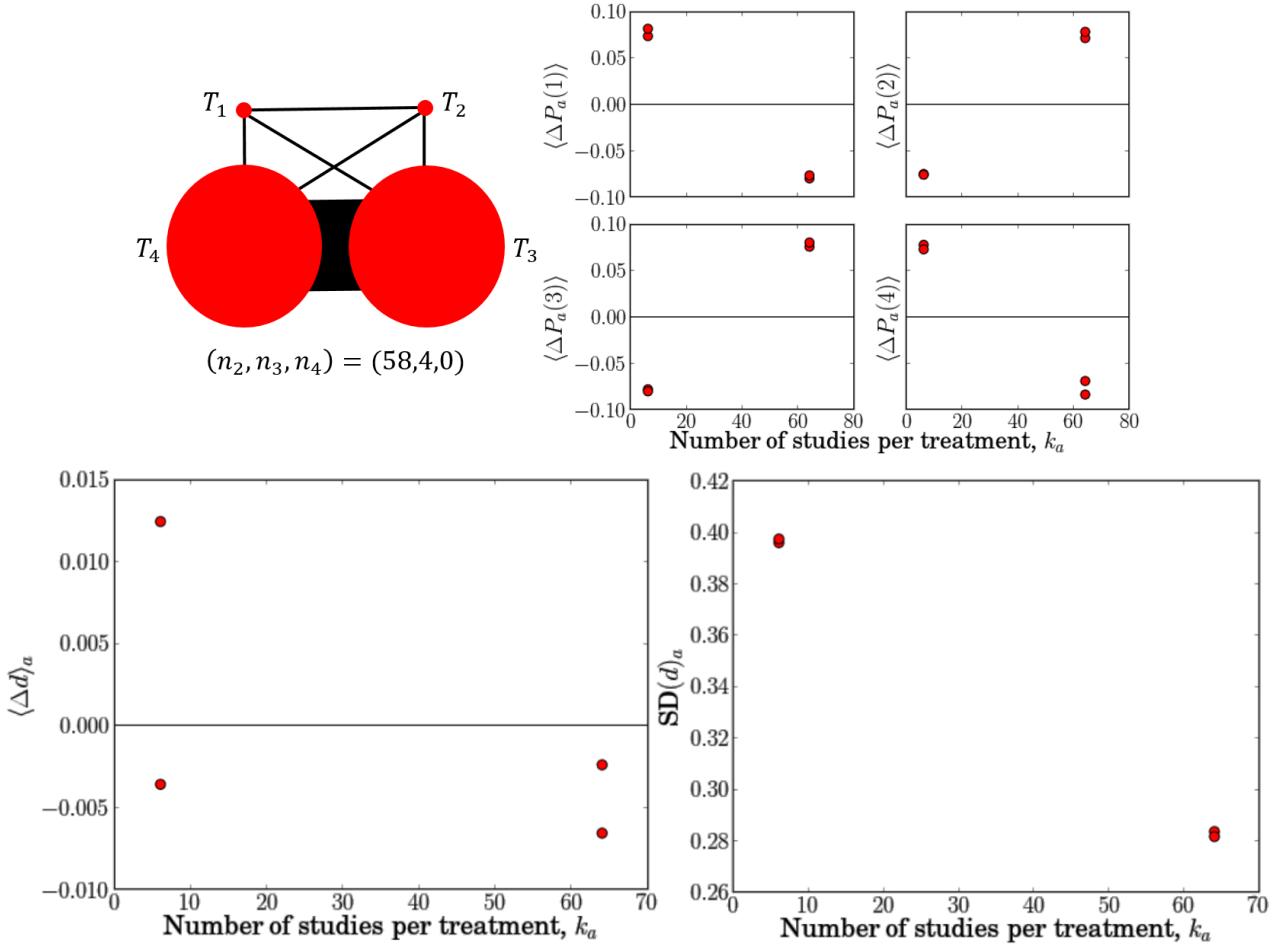


FIG. S46. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (2, 2, 2, 2, 2, 60)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (58, 4, 0)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.686531$.

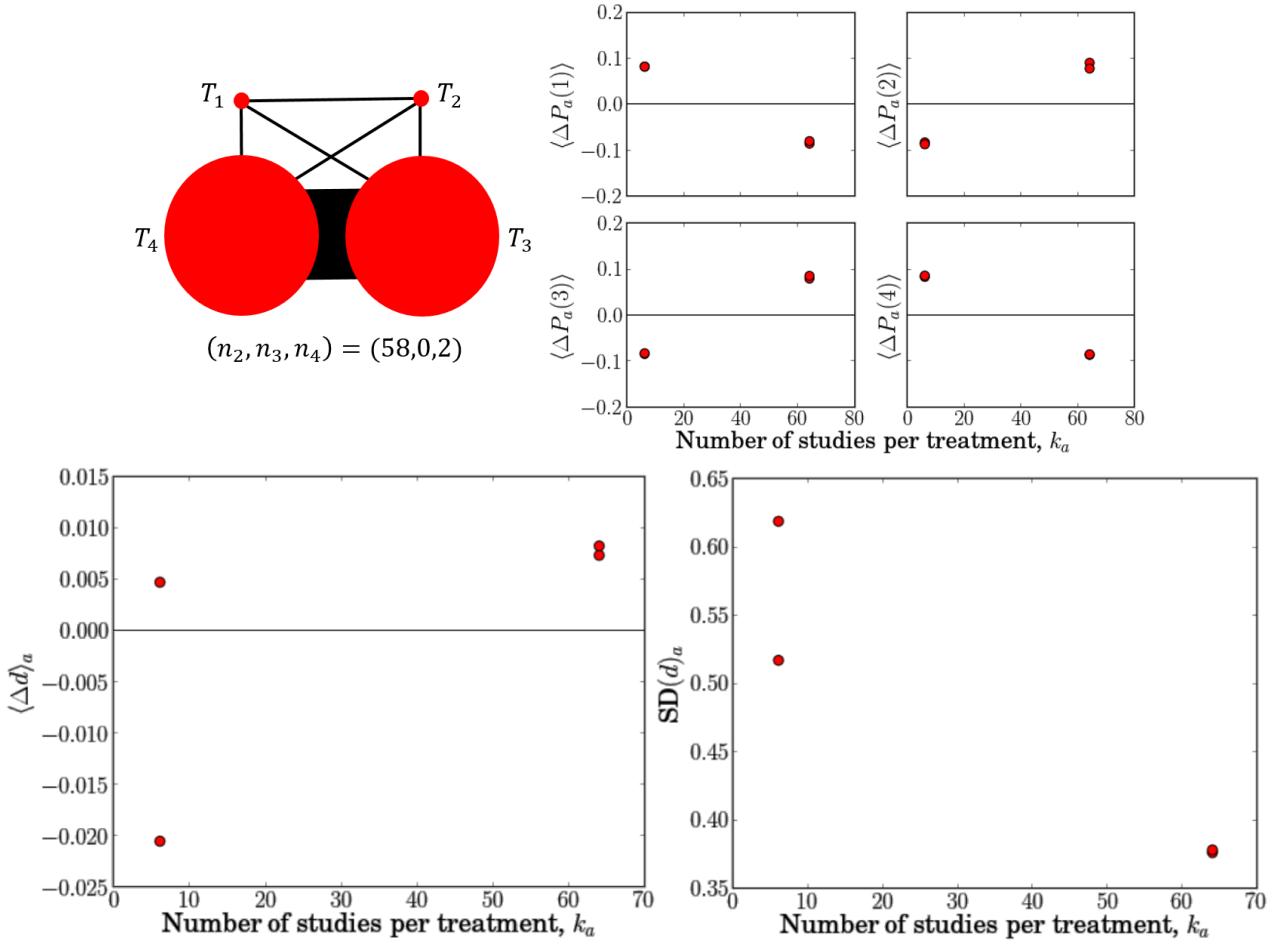


FIG. S47. The number of studies per treatment versus bias of rank probabilities, and treatment-specific bias and standard deviation of treatment effects for a complete loop network with $\mathbf{K} = (2, 2, 2, 2, 2, 60)$. The number of two, three and four arm studies included is $(n_2, n_3, n_4) = (58, 0, 2)$. The irregularity of the network is $h^2/\bar{k}^2 = 0.686531$.

S9. COMPARING DATA-GENERATING MODELS

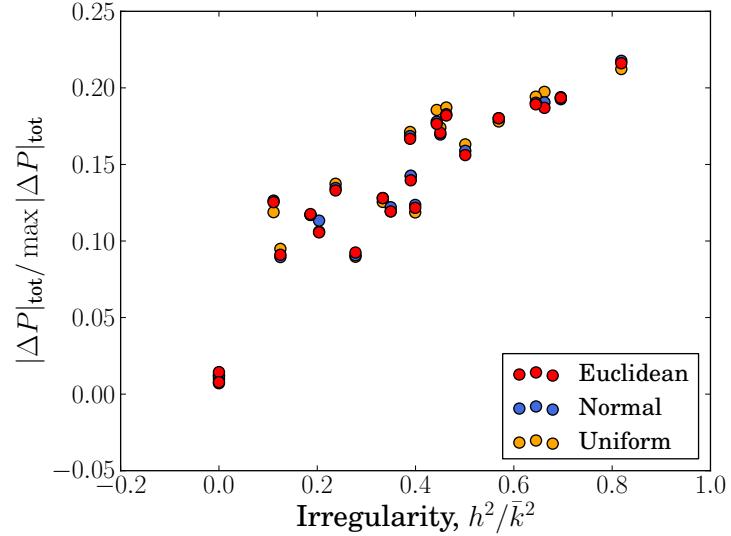


FIG. S48. Comparing plots of network irregularity versus total rank probability bias for different data-generating models.

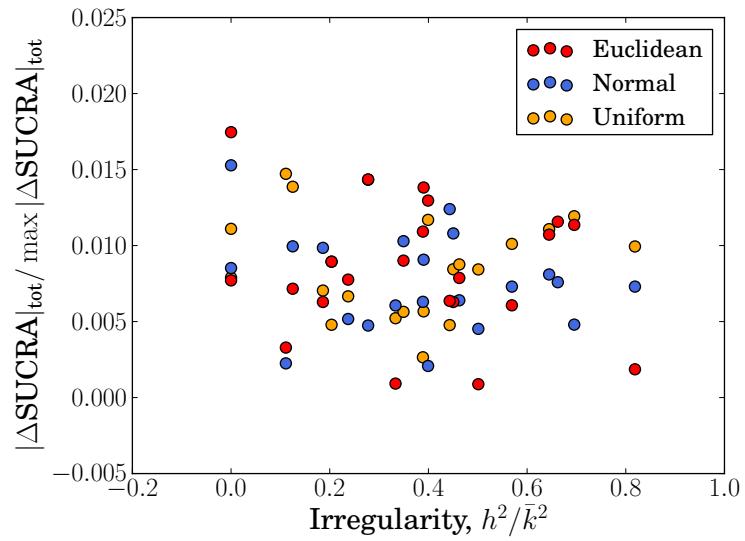


FIG. S49. Comparing plots of network irregularity versus total SUCRA bias for different data-generating models.

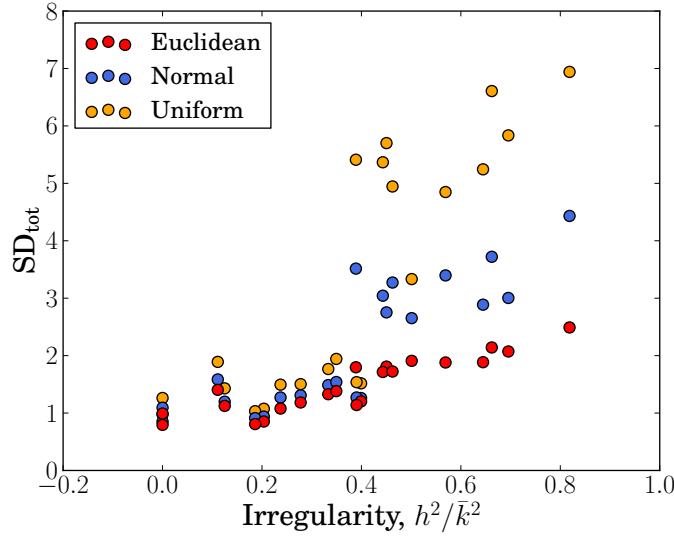


FIG. S50. Comparing plots of network irregularity versus total standard deviation for different data-generating models. Standard deviation is lowest for the ‘Euclidean’ method as this DGM is the most restrictive in the variation of binomial probabilities sampled. Uniform has the greatest standard deviation because it is the least restrictive.

S10. BIAS OF BETWEEN-TRIAL VARIANCE

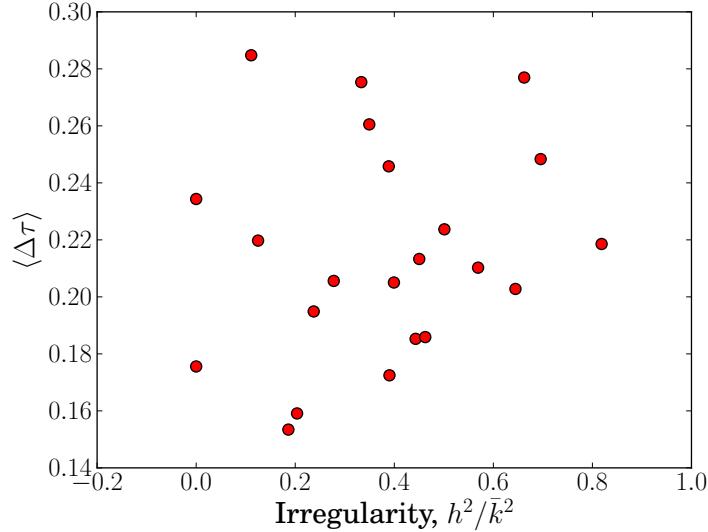


FIG. S51. The effect of network irregularity on the accuracy of τ estimation. This is for networks with $d = (0, 0, 0)$ and made up of exclusively 2-arm trials.

S11. TESTING ROBUSTNESS

A. More than four treatments

To test if our results generalised to networks with more than four treatments we simulated four networks of ten treatments, each with different irregularity. The first network was the ‘original’ and is shown on the left in Figure S52. This network contains 20 trials in total; 12 trials comparing treatments T_1 and T_2 , one trial connecting each of T_3 , T_4 , T_5 and T_6 to T_1 and one trial connecting each of T_7 , T_8 , T_9 and T_{10} to T_2 . The other three networks (networks (a) to (c) in Figure S52) are made from the original network and eight extra studies.

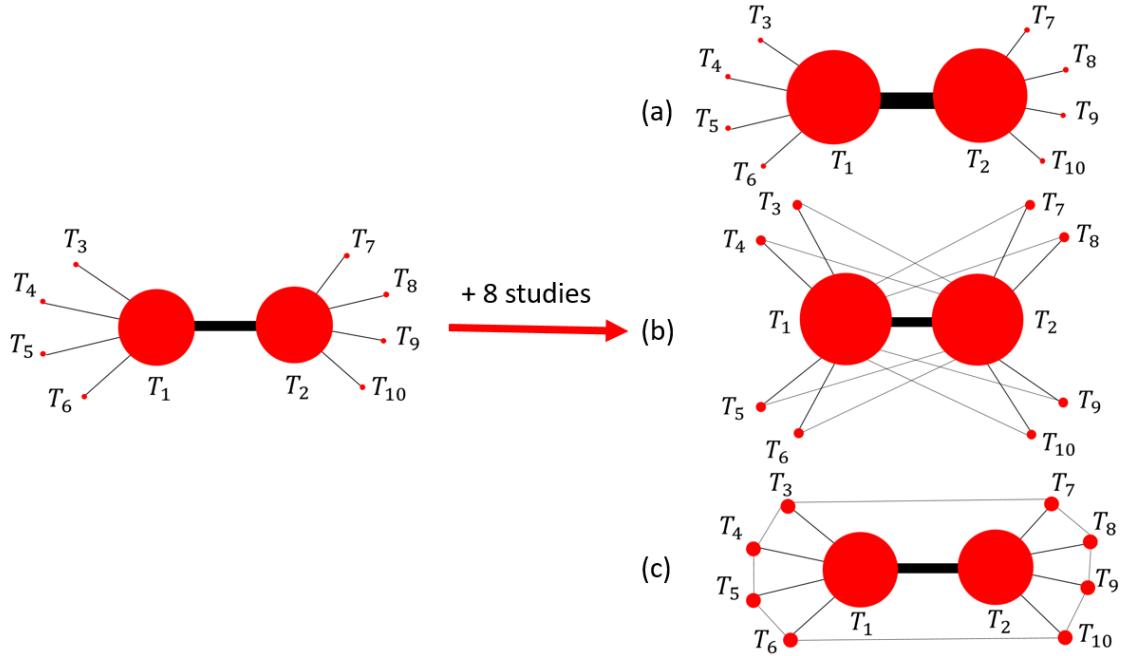


FIG. S52. Network diagrams showing the networks simulated with $N = 10$ treatments. The original network has 12 ($T_1 - T_2$) studies, and 1 study comparing the other connected treatments to T_1 or T_2 . Networks (a), (b) and (c) have 8 studies added to them. In (a) all 8 are added to the ($T_1 - T_2$) study, and in (b) and (c) each new connecting line represents one study. The results of these simulations can be found in Table S1.

Network (a) has the highest irregularity and network (c) has the lowest irregularity. Table S1 summarises the results from these simulations and shows that high degree irregularity is associated with high rank probability bias and high SD_{tot} . Therefore we find that our results hold for networks with more than four treatments.

TABLE S1. Degree irregularity and quality of NMA outcome for the networks in Figure S52.

Network	M	h^2/\bar{k}^2	SD_{tot}	$ \Delta P _{tot}$
Original:	20	2.25	16.76	2.94
(a):	28	2.70	16.72	3.06
(b):	28	1.65	6.82	2.76
(c):	28	0.86	5.64	1.79

B. Unequal participants per arm

In our second robustness test, simulations were done for six networks where the number of participants per arm, rather than being assigned a fixed value, was randomly generated from a uniform distribution between 20 and 100. Figures S53 and S54. show that the results of these simulations are consistent with our previous findings.

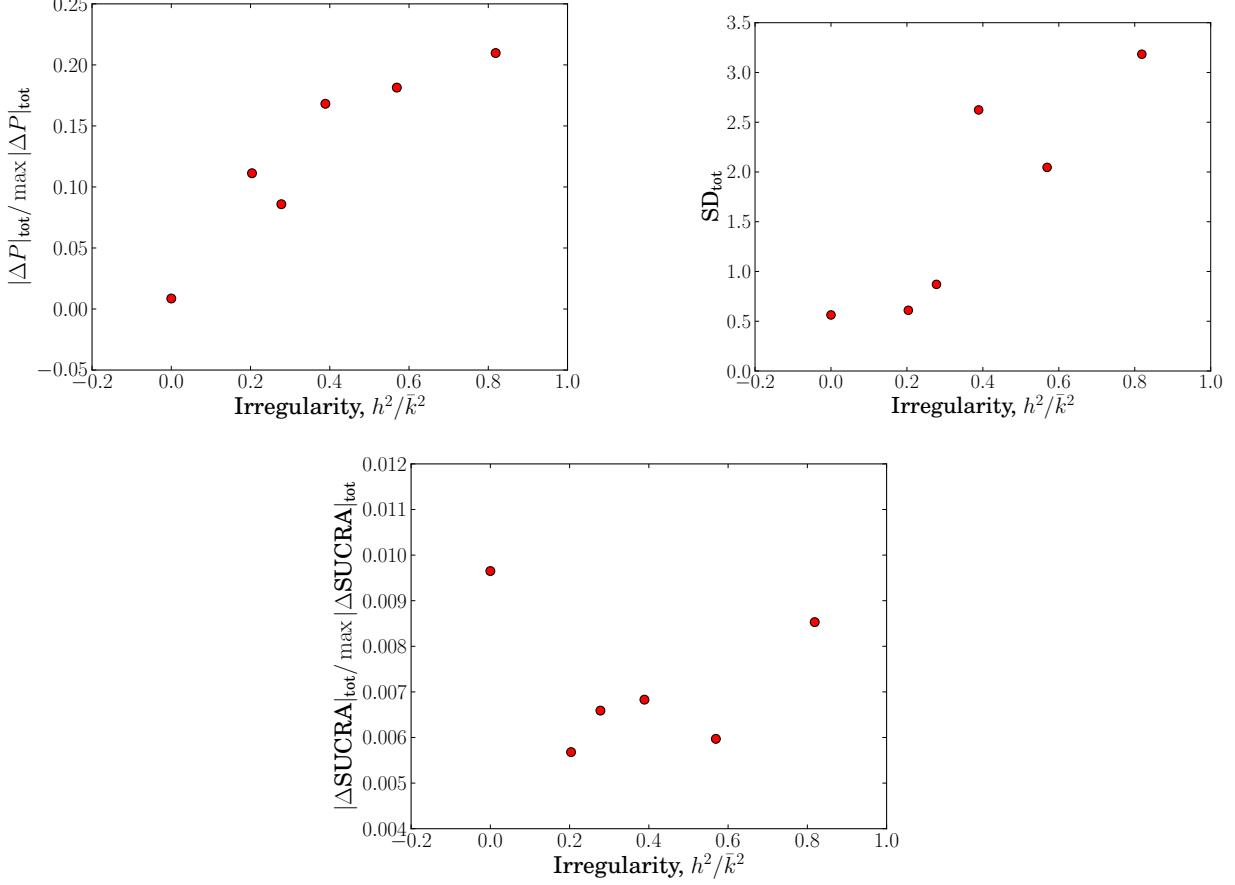


FIG. S53. The effect of degree irregularity on a network's (a) total rank probability bias, (b) total standard deviation of treatment effect estimates, and (c) total SUCRA bias for networks with an unequal number of participants per arm. These networks have equally effective treatments and contain only 2-arm trials.

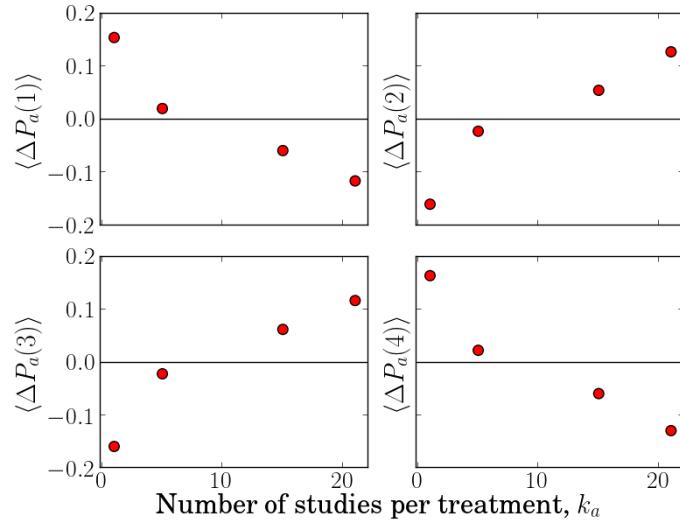


FIG. S54. The effect of the number of studies per treatment on the bias on rank probabilities, $\Delta P_a(r)$, for $r = 1, 2, 3, 4$. These plots are for a star network with $\mathbf{K} = (1, 5, 15, 0, 0, 0)$ and for networks with an unequal number of participants per arm.

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- [1] S. H. Hurlbert. The nonconcept of species diversity: A critique and alternative parameters. *Ecology*, 52(4), 1971.
 - [2] G. Salanti, J. Higgins, A. Ades, and J. Ioannidis. Evaluation of networks of randomized trials. *Stat Methods Med Res*, 17(3):279–301, 2008.
 - [3] G. Salanti, F. K. Kavvoura, and J. P. A. Ioannidis. Exploring the geometry of treatment networks. *Ann Intern Med*, 148(7):544–53, 2008.