Redefining the Risk Quotient: A Generalized Framework for Fragility Analysis Across Study Designs

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Abstract

The Risk Quotient was introduced to normalize the Relative Risk Index, offering an interpretable alternative to fragility metrics tied to P values. However, the initial formulation defined the Risk Quotient as the Relative Risk Index divided by the total sample size, limiting interpretability and comparability. We propose a unified definition: the Relative Risk Index is the average absolute residual between the observed table and the neutrality table (expected counts under therapeutic neutrality), and the Risk Quotient is the Relative Risk Index normalized by the average cell count. This definition yields a Risk Quotient ranging from 0 (perfect neutrality) to 1 (maximum possible deviation), which makes it directly interpretable as the minimum percent of outcomes that must change to eliminate any observed treatment effect. We demonstrate its extension from 2×2 tables to contingency tables of any size, including continuous outcomes reframed as contingency

tables. This refinement standardizes the Risk Quotient across study types, resolves definitional conflicts, and enables a common interpretive framework for evidence robustness.

1. Introduction

Statistical practice has long relied on P values as the benchmark of trial evidence, yet they capture only threshold-based significance and not robustness to small perturbations. Fragility metrics, including the Fragility Index (1) and the Fragility Quotient (2), quantify sensitivity of statistical significance to small data changes, but they remain tied to prespecified α levels.

The Relative Risk Index (RRI) reframes the question around therapeutic neutrality. In a 2×2 contingency table with cells {a, b, c, d} and total sample size n, the RRI equals $|ad - bc|/n$. It measures deviation from neutrality but is still sample size dependent. The Risk Quotient (RQ) was introduced to normalize this quantity and was originally defined as the RRI divided by the total sample size (3). However, that definition is also sample size dependent and impedes comparability across studies.

We propose a unified definition: continue to define the RRI as the average absolute residual per cell between the observed table and the neutrality table (expected counts under therapeutic neutrality with fixed margins), and redefine the RQ as the RRI divided by the average cell count instead of the total sample size. This definition yields a bounded 0–1 scale that is directly interpretable as the minimum percent of outcomes that must change to achieve neutrality. The same construction applies to contingency tables of any size and to continuous outcomes via contingency tabulation.

2. Methods

2.1 Definitions

- Let $k = R \times C$.
- For $i = 1,..., k$: O_i = observed count in cell i; $E_i =$ expected count under therapeutic neutrality (fixed margins). When tabulating continuous data, O_i and E_i may be noninteger.
- Total $n = \sum_{i=1}^{k} O_i = \sum_{i=1}^{k} E_i$.
- O and E denote the tables, not scalars.

2.2 RRI

$$RRI = \sum_{i=1}^{k} |O_i - E_i| / k$$

where

- k = total number of cells in the contingency table.
- O_i = observed count in cell i.
- E_i = expected count in cell i.
- O is the table of observed counts.
- E is the neutrality table with the same margins as O.

RRI is the average absolute residual per cell between what was observed and what would be expected if there were no difference between study arms. When tabulating continuous data, O_i and E_i may be noninteger.

2.3 RQ

$$RQ = (\frac{k}{n})\, RRI = \frac{1}{n}\sum_{i=1}^{k} |O_i - E_i|$$

where

- RQ range, 0 to 1 (i.e. $RQ \in [0, 1]$).
- k = total number of cells in the contingency table
- n = total sample size

RQ is the minimum percent of outcomes that must change to eliminate the observed treatment effect. RQ can be computed directly without first computing RRI.

3. Worked Examples

3.1 A 2×2 Contingency Table

Observed and expected tables under neutrality (fixed margins):

Observed

	Outcome A	**Outcome B**	**Total**
Arm A	14	15	29
Arm B	6	13	19
Total	20	28	48

Expected (neutrality, same margins)

	Outcome A	**Outcome B**	**Total**
Arm A	12.0833	16.9167	29
Arm B	7.9167	11.0833	19
Total	20	28	48

Absolute residuals |O−E|

	Outcome A	**Outcome B**	**Total**
Arm A	1.9167	1.9167	3.8333
Arm B	1.9167	1.9167	3.8333
Total	3.8333	3.8333	7.6667

RRI and RQ

- k=4, n=48
- RRI (mean absolute residual per cell): 1.9167
- Average cell count (n/k): 12.0000
- RQ = RRI / (n/k) = 1.9167 / 12.0000 = 0.1597 (15.97%).

Interpretation: ~16% of outcomes would need to change allocation to reach neutrality.

3.2 Multi-arm Categorical (3×3)

Observed and expected tables under neutrality (fixed margins):

Observed

	Outcome A	**Outcome B**	**Outcome C**	**Total**
Arm A	10	6	15	31
Arm B	13	16	9	38
Arm C	16	10	11	37
Total	39	32	35	106

Expected (neutrality, same margins)

	Outcome A	Outcome B	Outcome C	Total
Arm A	11.4057	9.3585	10.2358	31
Arm B	13.9811	11.4717	12.5472	38
Arm C	13.6132	11.1698	12.2170	37
Total	39	32	35	106

Absolute residuals |O−E| by cell

	Outcome A	Outcome B	Outcome C	Total
Arm A	1.4057	3.3585	4.7642	9.5283
Arm B	0.9811	4.5283	3.5472	9.0566
Arm C	2.3868	1.1698	1.2170	4.7736
Total	4.7736	9.0566	9.5283	23.3585

RRI and RQ

- k=9, n=106
- RRI (mean absolute residual per cell): 2.5954
- Average cell count (n/k): 11.7778
- RQ = 2.5954 / 11.7778 = 0.2204 (22.04%).

Interpretation: ~22% of outcomes would need to change allocation to achieve neutrality across arms and outcomes.

3.3 Continuous Data (paired)

Paired continuous values from two groups (n=30 pairs). To apply RQ:

1. Construct a 30×2 table of observed values.
2. Define the neutrality table with fixed margins.
3. Compute residuals |O−E|.
4. Calculate RRI (average residual) and RQ (fractional normalization).

Observed averages:

- Mean residual ≈ **0.1937**
- Mean observed cell ≈ **0.6204**
- RQ = **0.3122** (**31%**).

Interpretation: 31% of outcomes would need to change to eliminate the observed effect.

Raw data for this worked example is in Supplement A.

5. Discussion

This updated definition of RQ improves interpretability and generalizes across data structures. Clinically, it enables statements like: “31% of outcomes would need to change to eliminate the observed benefit.” Methodologically, it aligns with regulatory emphasis on clinically meaningful effects rather than pure statistical significance.

Limitations: For continuous data, neutrality-table construction requires explicit assumptions (equal margins). Small samples remain sensitive.

Recommended thresholds: RQ<0.10 fragile; 0.10–0.29 moderate; ≥0.30 robust. These thresholds at this time are not validated and require domain-specific calibration.

Future work: Apply RQ to survival and ordinal outcomes, test calibration in real trial datasets, and compare predictive utility against FI, FQ, and robustness index measures.

6. Conclusion

We recommend standardizing RQ to equal the minimum percent change in outcomes required to eliminate any treatment effect. This definition yields a bounded, interpretable metric applicable to contingency tables of any size and even continuous paired outcomes. It extends fragility analysis beyond P value thresholds and strengthens the clinical relevance of robustness assessment.

Keywords

Risk Quotient; Relative Risk Index; fragility metrics; robustness; therapeutic neutrality; contingency tables; continuous outcomes

Consolidation Notice

This analysis is part of an exploratory methodological series. Related briefs may be consolidated into a master synthesis prior to journal submission.

Declarations

- **Submission status:** Original methodological work; not submitted elsewhere.

- **Data availability:** All data is provided in the manuscript and Supplement A.

- **Funding:** None.

- **Conflicts of interest:** None declared.

References

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Supplement A

Worked Example 3.3			
OBSERVED	**GROUP A**	**GROUP B**	**TOTAL**
1	0.7363	1.1292	1.8654
2	0.4329	1.2556	1.6885
3	0.7143	0.6932	1.4075
4	0.9296	0.2008	1.1304
5	0.1647	1.1407	1.3054
6	0.7872	0.9345	1.7217
7	0.2612	1.0117	1.2729
8	0.7905	0.5700	1.3606
9	0.9010	0.6115	1.5126
10	0.6108	1.0789	1.6897

11	0.1204	0.8666	0.9870
12	0.9816	0.2795	1.2611
13	0.1499	0.6231	0.7730
14	0.2872	0.7429	1.0301
15	0.9851	0.3308	1.3159
16	0.4276	1.0668	1.4944
17	0.2684	0.6208	0.8892
18	0.4655	0.7766	1.2421
19	0.7583	0.8197	1.5779
20	0.0437	0.9762	1.0199
21	0.4556	0.0145	0.4700
22	0.3057	0.9062	1.2118
23	0.4329	1.2308	1.6636

24	0.6518	0.7834	1.4352
25	0.7297	1.1964	1.9260
26	0.1846	0.0299	0.2145
27	0.1024	0.1775	0.2799
28	0.9009	0.8214	1.7223
29	0.5278	0.8250	1.3529
30	0.2891	0.1128	0.4019
TOTAL	15.3966	21.8269	37.2235

EXPECTED	**GROUP A**	**GROUP B**	**TOTAL**
1	0.7716	1.0938	1.8654
2	0.6984	0.9901	1.6885
3	0.5822	0.8253	1.4075

4	0.4676	0.6629	1.1304
5	0.5400	0.7655	1.3054
6	0.7121	1.0096	1.7217
7	0.5265	0.7464	1.2729
8	0.5628	0.7978	1.3606
9	0.6256	0.8869	1.5126
10	0.6989	0.9908	1.6897
11	0.4082	0.5787	0.9870
12	0.5216	0.7395	1.2611
13	0.3197	0.4533	0.7730
14	0.4261	0.6040	1.0301
15	0.5443	0.7716	1.3159
16	0.6181	0.8763	1.4944

17	0.3678	0.5214	0.8892
18	0.5138	0.7283	1.2421
19	0.6527	0.9253	1.5779
20	0.4218	0.5980	1.0199
21	0.1944	0.2756	0.4700
22	0.5013	0.7106	1.2118
23	0.6881	0.9755	1.6636
24	0.5936	0.8416	1.4352
25	0.7967	1.1294	1.9260
26	0.0887	0.1258	0.2145
27	0.1158	0.1642	0.2799
28	0.7124	1.0099	1.7223
29	0.5596	0.7933	1.3529

30	0.1662	0.2357	0.4019
TOTAL	15.3966	21.8269	37.2235
RESIDUALS	**GROUP A**	**GROUP B**	**TOTAL**
1	0.0353	0.0353	0.0706
2	0.2655	0.2655	0.5310
3	0.1322	0.1322	0.2643
4	0.4621	0.4621	0.9241
5	0.3752	0.3752	0.7505
6	0.0751	0.0751	0.1501
7	0.2653	0.2653	0.5305
8	0.2278	0.2278	0.4555
9	0.2754	0.2754	0.5508

10	0.0881	0.0881	0.1762
11	0.2879	0.2879	0.5758
12	0.4600	0.4600	0.9200
13	0.1698	0.1698	0.3396
14	0.1389	0.1389	0.2778
15	0.4408	0.4408	0.8816
16	0.1905	0.1905	0.3811
17	0.0994	0.0994	0.1988
18	0.0483	0.0483	0.0966
19	0.1056	0.1056	0.2112
20	0.3782	0.3782	0.7564
21	0.2612	0.2612	0.5223
22	0.1956	0.1956	0.3912

23	0.2553	0.2553	0.5105
24	0.0582	0.0582	0.1163
25	0.0670	0.0670	0.1340
26	0.0959	0.0959	0.1918
27	0.0134	0.0134	0.0268
28	0.1885	0.1885	0.3770
29	0.0318	0.0318	0.0635
30	0.1228	0.1228	0.2457
TOTAL	5.8108	5.8108	11.6215
RRI =	**0.1937**		
RQ =	**0.3122**		