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Article

Converting Medians and Ranges to Means and Standard Deviations: A Practical Guide for Evidence Synthesis

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Abstract

Quantitative pooling in meta-analysis requires standardized effect measures, typically expressed as mean differences or standardized mean differences. However, many primary studies report continuous outcomes as medians with ranges or interquartile ranges (IQR), particularly when data are skewed. This reporting practice complicates evidence synthesis because means and standard deviations (SD) are required for conventional meta-analytic models. Over the past two decades, multiple statistical methods have been developed to convert medians and dispersion measures into approximate means and SDs, each with specific assumptions and limitations. This tutorial provides a structured overview of the main approaches, illustrates their application through simulated examples, and discusses their strengths and weaknesses in different scenarios. Practical guidance is offered on software implementation, interpretation of skewed data, and best practices to ensure transparency. These methods enable the inclusion of studies that would otherwise be excluded, but their use requires caution, explicit reporting, and acknowledgment of inferential limitations.

Keywords: meta-analysis; interquartile range; median to mean conversion; skewed data; standard deviation estimation; statistical methodology

Introduction

In evidence synthesis, quantitative pooling depends on the ability to standardize effect measures across studies. For continuous outcomes, the standard practice is to compare mean differences (or standardized mean differences), which requires studies to report the mean and standard deviation (SD). However, in primary clinical research, continuous variables are often expressed as medians with ranges or interquartile ranges (IQR), particularly when the data are skewed. While this choice more accurately reflects the underlying distribution, it creates a practical obstacle for meta-analysts [1]. This challenge remains unresolved, as highlighted by recent evaluations showing both the increasing prevalence of median-based reporting [2] and the persistent methodological uncertainty regarding conversion approaches [3]. For instance, operative time in surgical studies is commonly reported as a median with interquartile range: while most procedures finish within a predictable window, a small number of complicated cases can last far longer, pulling the mean upward. This reporting choice makes clinical sense but creates difficulties for meta-analysts, who need means and standard deviations for standard pooling methods. Simply discarding studies that report medians introduces bias. In contrast, inappropriate conversions may misrepresent the underlying distribution.

The problem is not merely technical. It reflects the reality that clinical data—such as length of stay, operative time, or biomarkers—often deviate from a symmetric distribution. The choice between reporting the mean or the median embodies a tension between statistical convention and clinical interpretability. This tutorial aims to clarify the methodological basis for converting medians and

ranges/IQRs to means and SDs, illustrate step-by-step calculations, and highlight both the utility and limitations of these methods for meta-analysis.

Understanding the Data: Distributions and Skewness

Before addressing conversion formulas, it is essential to recognize the differences between measures of central tendency and dispersion.

The mean is sensitive to outliers and asymmetry, while the median is more robust under skewness. When data are normally distributed, the two measures converge; however, in skewed distributions, they can diverge substantially. For instance, postoperative length of stay is often right-skewed: a minority of patients remain hospitalized for very long periods, pulling the mean upward while leaving the median closer to the “typical” patient. A similar logic applies to dispersion: while the SD reflects variability around the mean under the assumption of approximate normality, the IQR and range are less sensitive to extreme values and are therefore frequently reported when distributions are skewed.

This distinction is critical for meta-analysis. Effect sizes based on mean differences require both the mean and SD, but primary studies often provide only the median with an IQR or range. To overcome this, numerous methods have been designed, each with its assumptions and particularities. This tutorial aims to present these approaches clearly and practically and to provide guidance on how to choose among them. Thus, while conversion enables inclusion of otherwise ineligible studies, it does not neutralize the underlying distributional problem.

Understanding Available Conversion Methods

Hozo et al. (2005): First Practical Range-Based Rules

Hozo et al. [4] introduced the first widely recognized framework for converting medians and ranges into means and SDs. Their method relied on the median together with the minimum, maximum, and sample size to approximate the mean. It used simple functions of the range to approximate the SD, with different adjustments depending on whether the sample size was small, moderate, or large. In their formulation, Hozo et al. concluded that for samples larger than 25, the median is the best estimator of the mean, while for smaller samples, they proposed specific formulas. This approach was groundbreaking at the time because it provided a practical way to include studies that did not report means and SD, which had previously been excluded from quantitative synthesis. Its simplicity and minimal data requirements explain its popularity and longevity in the meta-analytic literature. Nevertheless, the method has major shortcomings: it assumes approximate symmetry, it tends to underestimate variability, and its reliance on crude range-based rules limits accuracy, especially in skewed distributions or when quartiles are available but ignored.

Wan et al. (2014): Systematic Use of Range and IQR

Wan et al. [5] advanced the field by providing refined estimators for the mean and SD that made systematic use of both range and quartile information, adapting the formulas to three distinct reporting scenarios: median with range, median with IQR, and the full five-number summary. Unlike Hozo’s simple *ad hoc* rules, Wan’s approach derived estimators grounded in order statistics and sample size distributions, which markedly improved the accuracy of variance estimation. Their extensive simulation studies showed that the proposed SD estimators were nearly unbiased under normality and retained reasonable performance under mild skewness. This contribution was highly influential because it offered a flexible and unified toolkit for the formats most commonly encountered in clinical research reporting. However, their formulas for the mean still largely extended previous heuristics rather than being formally optimized, leaving some residual bias when applied to skewed data.

Bland (2015): Integrating the Full Five-Number Summary

M. Bland [6] proposed a straightforward estimator that combines information from the minimum, maximum, quartiles, and median to approximate the mean and SD. The appeal of this method lies in its transparency: it makes fuller use of the available summary statistics than earlier rules such as Hozo's, while avoiding the complexity of more advanced approaches. Simulation studies showed that Bland's approach improved on the cruder estimators but remained less accurate than later methods, particularly in small samples or skewed distributions, since it does not incorporate adjustments for sample size or distributional shape. It should be noted that in Bland's approach, the formula for the mean does not depend on sample size, whereas his formula for the SD does include a dependence on n . Wan et al. later criticized this specific aspect, noting that Bland's SD approximation may overestimate variability in large samples and underestimate it in small ones.

Luo et al. (2018): Optimal Estimation of the Mean Across Sample Sizes

Luo et al. [7] built on these earlier methods by proposing a more flexible way to estimate the mean. Hozo and Wan had relied on fixed rules that changed abruptly with sample size—for example, Hozo suggested that once a study had more than 25 participants, the median itself could be treated as the mean, while for smaller samples a correction formula was needed. Such stepwise rules often produced unstable results. Luo instead introduced an "optimal" estimator that adjusts smoothly, combining information from the median, range, and quartiles in a balanced way. This reduced bias and made estimates more stable across different study sizes and reporting formats. The approach performed particularly well when quartile data were available, but as with earlier methods, accuracy still declined when the underlying data were highly skewed.

Shi et al. (2020–2023): Improved SD Estimation and Skewness Detection

Shi et al. [8] focused on improving the estimation of the SD. Building on Wan's framework, they used the full five-number summary (minimum, quartiles, median, maximum) to generate more precise estimates of variability. Their simulation studies showed that these estimators outperformed earlier ones, particularly when both range and quartile information were available. In later work [9], they went a step further by developing a simple test to detect skewness using only the five-number summary and sample size. This test operates by comparing the relative distances between quartiles and extremes: under symmetry, the spacing between $Q1$ –median– $Q3$ should be balanced, whereas systematic elongation of one tail indicates skewness. Because it requires only basic summary statistics, the test is simple to apply in practice. This was important because it offered analysts practical guidance on whether conversion to mean and SD was appropriate or whether the data were too skewed to be reliably transformed. The strength of this approach lies in its greater accuracy and its diagnostic component, but its limitation is clear: when data are heavily skewed, no formula can fully solve the problem, and exclusion or alternative modelling remains necessary.

McGrath et al. (2020): Reconstructing the Underlying Distribution

McGrath et al. [10] questioned the entire premise of forcing medians into means. They emphasized that authors often report medians precisely because the data are skewed, making normality-based conversions questionable. Instead of relying on approximate formulas, they proposed methods that model the underlying distribution directly from reported quantiles, allowing the mean and SD to be reconstructed even when data depart from symmetry. Their simulations showed clear advantages over traditional conversions in scenarios common in clinical research, such as log-normal or skew-normal distributions seen with outcomes like length of stay or blood loss. The strength of this approach is its adaptability to real-world skewed data, while its limitations are mainly practical: the methods are more complex, less familiar to most analysts, and not yet widely implemented in standard meta-analysis software, which has slowed their adoption.

Cai et al. (2021): Flexibility Through Transformations

Lastly, Cai et al. [11] introduced a method known as MLN (Method for Unknown Non-Normal distributions), which enhances flexibility when underlying distributions depart from normality. This approach applies a Box–Cox transformation to the available summary statistics (e.g., median, range, IQR), estimates mean and SD in the transformed space via maximum likelihood, and then back-transforms the estimates to the original scale. This strategy improves accuracy in situations where clinical biomarkers exhibit skewed or non-normal distributions. However, its performance depends on the success of the transformation in approximating normality and may still be challenged by complex or multimodal distributions.

Table 1 provides a structured comparison of the main conversion methods, summarizing their required inputs, strengths, limitations, and susceptibility to skewness in a format tailored for clinical readers.

Table 1. Overview of main conversion methods from median-based to mean-based summary statistic.

Method (Author, Year)	Required Summary Statistics	Key Features	Limitations	Susceptibility to Skewness	Implementation
Hozo et al., 2005 [4]	Median, minimum, maximum, sample size	First systematic method; simple rules for estimating mean and SD when only minimal data are available	Crude approximations; underestimates variability; arbitrary thresholds; poor accuracy with skewed data	High – performs poorly under skewness or outliers	Wan spreadsheet [5]
Wan et al., 2014 [5]	Median, range and/or quartiles, sample size	Widely adopted; separate formulas depending on whether only range, only IQR, or a full five-number summary is available	Sensitive to the type of summary used: range-based formulas inflate SD in the presence of outliers; IQR-based formulas underestimate SD when distributions are skewed; five-number summary performs better and provides the closest approximation	Moderate – accuracy decreases under skewness, but is more robust than Hozo	Wan spreadsheet [5], Hong Kong Baptist University converter
M Bland, 2015 [6]	Median, minimum, maximum, quartiles, sample size	Straightforward estimator combining the full five-number summary (min, Q1, median, Q3, max); simple to apply and transparent; extends information use beyond Hozo’s range rules	Mean estimator does not depend on sample size; SD estimator depends on n but has been criticized for inaccuracy at extremes; less precise than later methods (Luo, Shi, Cai, McGrath)	Moderate to High – performs better than Hozo under mild asymmetry but unstable under strong skew or small samples	Wan spreadsheet [5]
Luo et al., 2018 [7]	Median, range and/or quartiles, sample size	Introduced “optimal” estimator for the mean; smooth weighting avoids arbitrary cut-offs; more stable across sample sizes	Assumes approximate symmetry; accuracy declines with heavy skewness	Moderate – robust under mild asymmetry but not extreme skew	Hong Kong Baptist University converter
Shi et al., 2020, 2023 [8,9]	Quartiles, sample size (also proposed skewness test)	Provided improved SD estimation and a diagnostic to flag skewness	Skewness test may misclassify; the method still assumes roughly normal data once flagged	Moderate to High – performs well in near-normal data, unstable under strong skew	Hong Kong Baptist University converter

McGrath et al., 2020 [10]	Any combination of median, range, quartiles, sample size	Flexible framework combining all available summaries; maximizes use of reported data	More computationally complex; still assumes moderate symmetry	Low to Moderate – more resilient, but not immune to skewness	R (<i>estmeansd</i> , <i>metamedian</i>)
Cai et al., 2021 [11]	Quartiles, range, sample size	Designed specifically for skewed data; adjusts estimates to reduce bias under asymmetry	Less validated in practice; requires more detailed input	Lower – better suited to handle skewed distributions, although performance may deteriorate under extreme asymmetry.	R (<i>estmeansd</i> , <i>metamedian</i>)

Cochrane Recommendations for Handling Medians and Ranges/IQRs

The Cochrane Handbook provides specific guidance on the use of medians and non-parametric summaries in meta-analysis of continuous outcomes. In Chapter 6, Section 6.5.2.9, it is noted that the median may occasionally substitute for the mean when the distribution is symmetrical, but that means and medians can diverge substantially under skewness—a frequent reason why medians are reported in the first place. Early conversion methods, such as Hozo et al. (2005), and later refinements, such as Wan et al. (2014) and Bland (2015), are explicitly cited, with simulation evidence suggesting that the Wan method performs better in many scenarios (Weir et al. 2018).

In Section 6.5.2.7, the Handbook warns about missing variability measures. When SDs cannot be derived, imputation may be considered (e.g., borrowing SDs from other studies), but this should remain exceptional, limited to a small fraction of studies, and always accompanied by sensitivity analyses.

Finally, Chapter 10, Section 10.5.3 emphasizes that meta-analyses based on means assume approximate normality; when distributions are skewed, the validity of conversions is limited. Practical checks for skewness (e.g., Altman and Bland’s ratio method) and the use of transformations (often log transformations) are recommended. Whenever possible, trialists should be contacted to provide appropriate summaries or individual participant data.

Taken together, the Cochrane guidance underscores three principles: (1) means and SDs remain the preferred format; (2) conversions from medians and ranges/IQRs can be used judiciously, but with awareness of underlying distributional assumptions; and (3) sensitivity analyses are essential to evaluate the robustness of any imputed or converted values. Notably, while the Handbook references early approaches (Hozo, Wan, Bland), it does not yet address more recent methods such as those proposed by Luo, Shi, Cai, or McGrath. These advances provide more flexible and accurate estimators, particularly when quartile data are available or when skewness is present, underscoring the need to complement existing guideline recommendations with updated methodological evidence. Therefore, a key objective of this tutorial is to provide researchers with access to modern, more accurate methods that have not yet been formally incorporated into major guidelines, thereby bridging the gap between methodological innovation and evidence synthesis practice.

Software Resources

Although the previous section has outlined the conceptual foundations of each conversion method, the mathematical formulas they employ are often too complex for clinical researchers to implement manually. To facilitate their application in practice, several user-friendly tools have been developed:

1. Some of the original methodological articles (e.g., Wan et al.) include dynamic Excel spreadsheets as supplementary materials that automate the necessary calculations.
2. Online calculators are available for practical use—for example, an interactive converter hosted by Hong Kong Baptist University allows direct input of summary statistics to obtain estimated means and SDs (<https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html>).
3. Dedicated software packages integrate these methods into commonly used analytic environments. For example, in R, the *estmeansd* package [12] implements the conversion methods proposed by McGrath et al. [10] and Cai et al. [11], supporting a variety of reported summary data formats. Additionally, the *metamedian* package builds on this functionality and provides tools for meta-analyses of median-based outcomes [13].

An Applied Example

To illustrate the performance of different conversion methods, a simulated dataset (Supplementary File 1) was generated to represent six pedagogical scenarios of biomarker reporting. Each scenario was designed to capture a typical situation in clinical research while highlighting the strengths and weaknesses of different approaches.

1. A small pilot study ($n = 12$) with an approximately symmetric distribution reported only the median and range, as often occurs in early investigations of novel biomarkers.
2. A large cohort study ($n = 200$) with a symmetric distribution, but reported using the median and IQR rather than the conventional mean and SD.
3. A moderate-sized study ($n = 60$) with a symmetric distribution, reported with full five-number summaries.
4. Another moderate-sized study ($n = 60$) with an approximately symmetric distribution, also reported with full summary statistics (range and quartiles). This scenario, with characteristics very similar to the previous one but with different data, was used to demonstrate the reproducibility of the methods under ideal conditions.
5. A study with $n = 100$ and a markedly right-skewed distribution, reported with a full five-number summary to illustrate the challenges of applying conversion methods in the presence of strong asymmetry.
6. A moderate-sized study ($n = 42$) with a symmetric core distribution but influenced by extreme outliers, where only the median and range were reported.

These scenarios provide a consistent clinical framework for a structured comparison of methods across varying sample sizes, distributional shapes, and reporting formats.

- **Scenario 1 (Small sample, range only, $n=12$, symmetric):** Luo's and McGrath's mean estimators were closest to the truth (error ~3%). For the SD, all methods performed poorly, ranging from underestimation (Hozo) to mild overestimation (McGrath), confirming the unreliability of range-based rules in small samples.
- **Scenario 2 (Large sample, IQR only, $n=200$, symmetric):** All modern mean estimators (Luo, Cai, McGrath, Wan) reproduced the mean accurately (errors <1%). However, every SD estimator underestimated dispersion by ~7–8%, reflecting the loss of tail information when only IQRs are reported.
- **Scenario 3 (Moderate sample, five-number summary, $n=60$, symmetric):** All modern methods performed well, with mean and SD estimates very close to the truth. McGrath's SD was almost exact, and Cai's mean was the most accurate. Hozo's rule, relying on the median, was highly biased, showing that quartiles should always be used when available.

- **Scenario 4 (Moderate sample, five-number summary, n=60, symmetric):** Again under ideal conditions, all modern methods (Wan, Luo, Shi, Cai, McGrath) achieved excellent accuracy, with most errors below 2%.
- **Scenario 5 (Moderate sample, five-number summary, n=100, strongly skewed):** Here, the limitations of all methods became evident. In this scenario, Bland's method yielded the closest estimate of the mean, whereas McGrath and Cai markedly underestimated it. All approaches showed the expected downward bias under right skewness, but the extent of error varied considerably. For the SD, Bland again provided the most accurate result, with McGrath slightly underestimating and both Cai and Shi producing severe underestimates of variability. Overall, range-based estimators generated distorted values, while even methods designed for skewed data failed to capture the true variability, confirming that strong skewness remains problematic for every approach. The apparently superior performance of Bland's method in Scenario 5 should not be interpreted as genuine robustness, but rather as a coincidence. Because Bland's estimator gives direct weight to the extreme values, the unusually high maximum in this dataset pulled its estimate closer to the true mean. Model-based approaches such as McGrath's and Cai's, which attempt to reconstruct the underlying distribution, can misfire when the assumed shape does not perfectly match the data. This case illustrates that simple heuristics may sometimes look "right for the wrong reasons," a useful reminder that accuracy in a single skewed scenario does not imply general reliability.
- **Scenario 6 (Moderate sample, range only with outliers, n=42):** Extreme values caused catastrophic failures of range-based estimators, with Hozo and Wan overestimating the SD by 30% and 19%, respectively, and producing biased means. Even McGrath exaggerated dispersion in this contaminated setting. Luo's estimate was the least distorted, but overall, all methods performed poorly, confirming that range-based approaches are unreliable in the presence of outliers.

The calculation of values for Hozo, Bland, and Wan can be replicated using the supplementary file provided by Wan et al., [5]. At the same time, estimates for Luo and Shi can be obtained through the above-referenced web tool. Sample R code demonstrating the use of the *estmeansd* package to derive estimates with McGrath's quantile estimation (QE) and Cai's (MLN) methods is available in Supplementary File 2.

Special Situations

In practice, certain reporting patterns pose particular challenges for conversion methods. Extremely narrow IQRs (e.g., 5 [5–5.5]) may reflect genuine low variability, but can also indicate rounding or reporting errors, yielding artificially small SDs and inflating a study's weight in meta-analysis. Conversely, implausibly wide ranges (e.g., 0–1000 for a biomarker usually <100) typically signal outliers, mis-specified units, or transcription errors, and lead to grossly inflated SDs when range-based methods are applied. Asymmetric IQRs (e.g., 20 [5–100]) are a clear marker of skewness, for which no conversion fully corrects the distortion; in such cases sensitivity analyses or contacting study authors are preferable. Situations where quartiles coincide with extremes (e.g., min = Q1 = median = 5) suggest highly clustered or categorical data, which again undermine the assumptions of continuous-distribution conversions. Finally, studies reporting only a median without dispersion cannot be converted at all, except by borrowing an SD from external sources—an approach that must be explicitly labeled as low-confidence imputation.

Best Practices in Conversion

When continuous data are reported as medians with ranges or IQRs, careful conversion to means and SDs can allow their inclusion in meta-analysis. However, these conversions are not a neutral operation: they rely on assumptions about distributional shape, sample size, and completeness of reported statistics. Best practice is to apply modern methods (e.g., Luo, Wan, McGrath, Cai) that incorporate all available information and provide greater accuracy than earlier rule-based approaches. Conversion should always be reported transparently, specifying the exact method used and the input statistics, so that readers can assess the robustness of the synthesis.

Equally important is to acknowledge the inferential limitations of converted estimates. Conversion formulas cannot correct for heavy skewness or the influence of extreme outliers, and their validity decreases as these conditions intensify. Converted means and SDs should therefore be treated as approximations, suitable for sensitivity analyses or for complementing, but not replacing, directly reported values. Analysts should avoid excessive reliance on imputed data, and whenever possible, contact study authors for original statistics.

A practical decision pathway can help researchers structure this choice: (1) assess skewness using available summary statistics (e.g., Shi’s test); (2) if marked skewness is present, prioritize a meta-analysis of medians using dedicated tools (e.g., the R package *metamedian*), as this preserves the original data structure; (3) if a median-based synthesis is not feasible, then conversion to mean/SD may be considered as a secondary or sensitivity strategy, guided by the simulation evidence of method performance.

To provide practical guidance, Table 2 summarizes the main “Dos and Don’ts” of converting medians and ranges for meta-analysis, offering clinicians and researchers a concise reference for appropriate application and transparent reporting.

Table 2. Dos and don’ts for converting medians and ranges in meta-analysis.

Dos	Don’ts
Double-check the original article carefully for units and reporting format. Distinguish clearly whether values correspond to a range, an interquartile range, or even a 95% confidence interval; in cases of doubt, contacting the study authors is the safest approach.	Do not misclassify summary statistics. Verify whether (X-Y) represents a range, IQR, or confidence interval. Misclassification invalidates the conversion.
Use validated conversion methods (Wan, Luo, McGrath, Cai) instead of discarding studies.	Do not assume the median equals the mean unless the distribution is symmetric.
Prefer conversions based on quartiles (IQR, five-number summary) for more accurate estimates.	Avoid relying only on outdated methods (e.g., Hozo), which are unstable and outlier-sensitive.
Mandate a pre-specified skewness check (e.g., Shi et al.). If the test is positive, treat converted estimates with extreme caution.	Do not assume conversion “solves” skewness. The mean is often not a meaningful summary for skewed data. If data are significantly skewed, prioritize a medians-only meta-analysis.
Perform mandatory sensitivity analyses: (1) exclude converted studies; (2) vary the conversion method; (3) compare results to a medians-only analysis if applicable.	Do not pool studies reported on incomparable scales (e.g., different transformations or outcome definitions) without appropriate adjustment.
Report transparently: specify the exact method, software, and version used for each conversion, and explicitly state the limitations of this approach in the methods section.	Do not impute means or SDs for a substantial proportion (>20–25%) of the total sample size. If extensive conversion is needed, the validity of the meta-analysis is questionable.
Prioritize obtaining the five-number summary (min, Q1, median, Q3, max). This contains the maximum information for accurate conversion.	Do not use range-only estimators (e.g., Hozo et al.) if outliers are suspected. They are extremely fragile and will produce biased SD estimates.
Use modern, validated conversion methods (McGrath, Cai, Shi, Luo) whenever the necessary inputs are available.	Do not rely on outdated or overly simple methods (e.g., Hozo). Their performance is demonstrably inferior.

Conclusions

The conversion of medians, ranges, and IQRs into means and SDs has evolved substantially, from the crude early rules of Hozo et al. to the more refined approaches of Wan et al., Luo et al., Shi et al., McGrath et al., and Cai et al. While modern methods offer greater accuracy and stability, especially when quartile information is available, none fully overcome the challenges of heavy skewness, extreme outliers, or incomplete reporting—as starkly illustrated in Scenario 5, where even methods explicitly designed for skewed data produced biased estimates, whereas Bland’s simpler approach performed unexpectedly well. This paradox highlights that method choice is not a linear progression from “old/bad” to “new/good,” but a context-dependent decision. Conversion can expand the pool of eligible studies, yet it should be applied cautiously, reserved for sensitivity or secondary analyses, and always reported transparently. The primary safeguard against bias remains improved primary reporting practices—ensuring that both means and SDs are provided alongside medians and IQRs—until such standards become universal.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. **Supplementary File 1.** Simulated dataset of six studies, including the application of all methods described in the manuscript for converting medians and ranges/interquartile ranges into means and standard deviations. **Supplementary File 2.** Sample R code demonstrating the use of the *estmeansd* package to obtain mean and standard deviation estimates from summary statistics. Both McGrath’s quantile estimation (QE) and Cai’s (MLN) methods are illustrated.

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Informed Consent: N/A.

Data Availability Statement: The dataset used in this study is simulated and has been provided as supplementary material (Supplementary File 1).

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Ethical Statement: This study did not involve human subjects or animals. As only simulated data were used, no ethical approval or informed consent was required.

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