A Practical Method for Remedying Some Biased Data Sets: Looking for Fractal Traces

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Abstract

Background and aim. Biases are largely diffused in medical studies. Methods for remedying biases in medical literature would be advisable. Here we propose a simple tool for correcting some biased data by calculating the proportion of non-random biases embedded in the variance. Method. Starting from a variable in a given series, the proportion of variability due to fractal behavior and the proportion of variability due to stochastic distribution can be calculated. Thus, the ratio among proportions can provide the amount of variance due to non-random biases. This proportion is used for re-calculating standard errors and confidence intervals. The method is applied to 2018 rates of in-hospital births in the Umbria region of Italy and to a set of effect sizes re-calculated from already published systematic reviews and meta-analyses on intrahepatic cholestasis of pregnancy. Those topics have been chosen because they have been already acknowledged as heterogeneous. Results. Proofs demonstrated that corrected standard errors work better than usual standard errors in heterogeneous data syntheses. Conclusion. By combining fractal behavior and stochastic distribution characteristics to data sets, some non-random biases can be corrected.

Keywords: Bias, fractal, confidence intervals, Cesarean section, birth, intrahepatic cholestasis of pregnancy.

Introduction

Evidence-based medicine is littered with biases [1]. In an instructive article, Delgado-Rodríguez and Llorca [1] illustrated how many biases can be observed in medical studies, leading readers to perceive that evidence-based medicine is rather a bias-based medicine. Moreover, in the medical literature, concerns have been reported for interpreting biased studies and how to correct biases [2-7].

Lots of biases in medical studies would fall in the chaotic behavior of the natural processes, thereby describing a Gauss' bell of stochastic events in a given population. Therefore, in two samples of a given population, the bell shape would describe the behavior of a biased phenomenon and would allow comparisons with another biased phenomenon if same biases (qualitatively and quantitatively) have occurred. Ideally, it would be advisable to improve quality of data and methodologies of studies in medical literature. However, from a practical point of view, the main concern of the medical literature is to know how much and how many biases have occurred in studies on a single event. Therefore, in the vast medical literature, one would assume that the diffusion of biases approximates best a stochastic shape if a highest number of articles assess the same phenomenon in the same way (the key concept of meta-analyses). Unfortunately, scientific journals reject studies assessing already published phenomena, as studies with the same characteristics of already published articles lack originality.

In the current article, we propose a simple calculation for assessing and remedying some biases of data sets. Such analysis can be used to better interpret the poor data spread of medical literature.

Simulation

Let set a random sequence of 12 numbers (OpenEpi 3.01, wwww.openepi.com/Random/Random.htm, last accessed 11-Jan-2022), from 3 to 13. This set of numbers can be imagined as an outcome measure in a medical study, expressed as integer. Random numbers are listed as Set A and are reported in Table 1. Set B to E (Table 1) are transformations of Set A as following:

Set B: to Set A numbers, it has been added or subtracted *non-randomly* a *random* sequence of numbers from 1 to 3 (OpenEpi 3.01, wwww.openepi.com/Random/Random.htm, last accessed 11-Jan-2022).

Set C: to Set A numbers, it has been added or subtracted *randomly* same *random* sequence of numbers added in Set B.

Set D: to Set A numbers, it has been added or subtracted *non-randomly* a *non-random* sequence of numbers from 1 to 3.

Set E: to Set A numbers, it has been added or subtracted *randomly* same *non-random* sequence of numbers added in Set D.

Finally, set F is a sequence of *non-random* numbers from 3 to 13.

Table 1. Data Sets for simulation.

	Set A	**Set B**	**Set C**	**Set D**	**Set E**	**Set F**
1st	5	3	7	3	8	13
2nd	10	13	13	12	12	3
3rd	6	4	8	5	7	5
4th	6	7	7	7	7	5
5th	9	11	11	12	12	7
6th	10	12	8	13	7	9
7th	10	11	9	13	7	11
8th	5	8	8	6	6	12
9th	13	12	15	12	14	13
10th	4	6	2	7	1	13
11th	12	13	11	15	9	4
12th	5	6	6	7	7	6
Mean	7.92	8.83	8.75	9.33	8.08	8.42
Uncorrected standard error	0.892	1.036	0.986	1.124	0.981	1.111
Corrected standard error	0.892	1.036	0.986	0.969	0.824	0.956
Percentage of correction	0	0	0	13.8%↓	18.0%↓	4.0%↓

-Set A: *random* data from 3 to 13.
-Set B: to Set A, added or subtracted *non-randomly* a *random* sequence of numbers from 1 to 3.
-Set C: to Set A, added or subtracted *randomly* same *random* sequence of numbers added in Set B.
-Set D: to Set A, added or subtracted *non-randomly* a *non-random* sequence of numbers from 1 to 3.
-Set E: to Set A, added or subtracted *randomly* same *non-random* sequence of numbers added in Set D.
-Set F: *non-random* sequence of numbers to 3 from 13.

Table 1. Data sets built for simulation. The method for correcting standard errors is reported in the text.

Figure 1

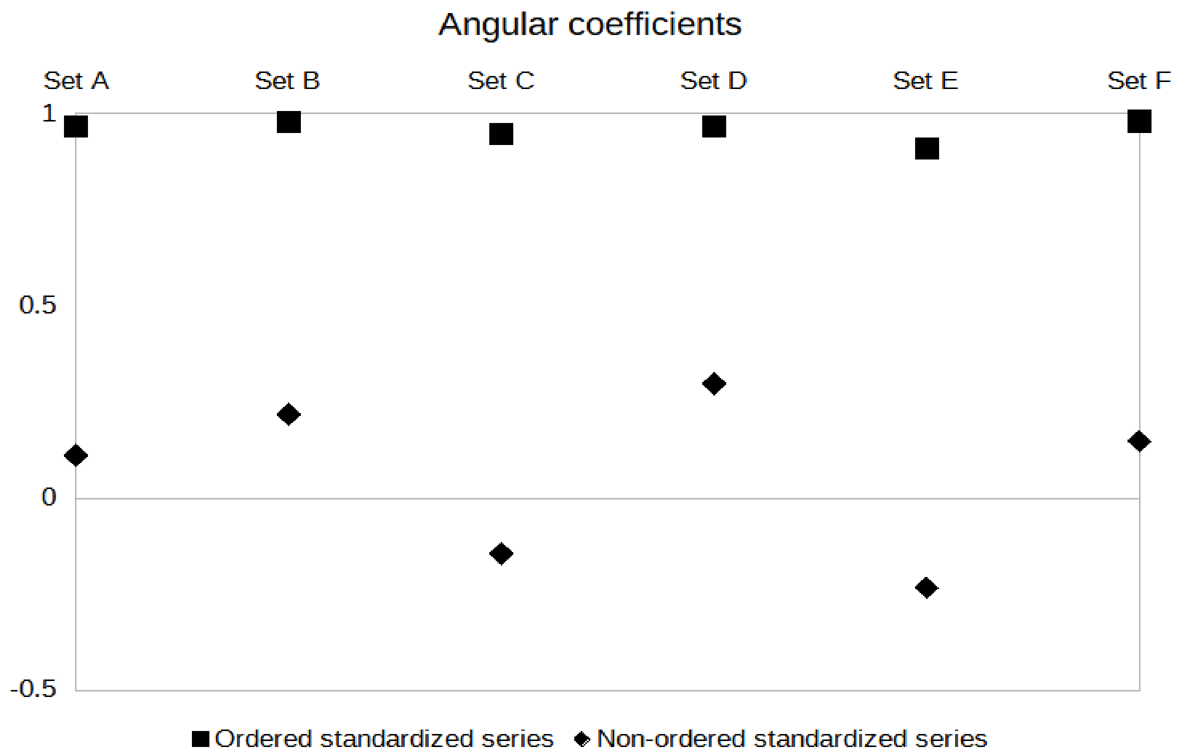


Figure 1. Angular coefficients of ordered and non-ordered standardized series reported in Table 1. Regression lines were built versus ordinal numbers from 1^{st} to 12^{th}.

Numbers from 1 to 3 added or subtracted in Set B, C, D, E can be imagined as a confounding variable of the outcome measure, strongly linked to the outcome measure reported in Set A (endogeneity bias), while non-random processes would add more biases to the data Sets. All series fail the Shapiro-Wilk test for normality. This is due to the low sample size (all Sets share the low-sample size bias). However, random numbers should fluctuate more homogenously around their mean, so better quality data should be supposed in Set A and C. To test this hypothesis, regression lines can be constructed among standardized values of each Set versus ordinal place from 1^{st} to 12^{th} of observed value. In ordered series from the lower to the higher value, the "best" series would have its angular coefficient of regression line closer to 1, and, in non ordered series, closer to 0. Figure 1 illustrates these coefficients. As expected, Set A and C have angular coefficients closer to 1 and 0 in ordered and non-ordered correlations. Even Set F seems having good fit, in spite of its not random genesis.

Can be hypothesized that non-random changes (Set B, D, E) and non-random numbers (Set F) have any ordered, non-stochastic, fluctuations across their means before becoming chaotic and falling into the Gauss' shape of the chaotic events?

As reported in the introduction section, stochastic events are best described by the Gauss' bell shape. Also, multiple biases produce a Gauss' bell shape. So, in multiple repeated observations of the same biased event, the equation of the normal distribution of biases is the same as the one of a biased event:

$$\frac{1}{\sigma\sqrt{2\pi}}e^{-\frac{(x-\mu)^2}{2\sigma^2}}biases \cong \frac{1}{\sigma\sqrt{2\pi}}e^{-\frac{(x-\mu)^2}{2\sigma^2}}biased-event$$

(1)

The chaos provoked by biases impedes efforts to distinguish the behavior of the event.

Now, let's remember that nature can arrange itself in ordered shapes, regardless of spatial and time dimensions [8]. This behavior is called self-organized criticality, being able to deliver shapes from chaos in relation to the characteristics of natural phenomena [9-13]. Therefore, the above mentioned (1) can be re-written as:

$$\frac{1}{\sigma\sqrt{2\pi}}e^{-\frac{(x-\mu)^2}{2\sigma^2}}biases \cong \frac{1}{\sigma\sqrt{2\pi}}e^{-\frac{(x-\mu)^2}{2\sigma^2}}biased-event+\Phi$$

(2)

where Φ would be a measure of a vanish fractal entity that can emerge from the chaos of the biased data.

The fractal shape (Φ) is a function of the space and of a proper measure D: the so-called fractal dimension. There are some practical difficulties in addressing the fractal dimensions, partly due to the definition of space and partly due to the measure-unit of that space [14].

In the present work, we refer to the two-dimension Euclidean space and estimate the fractal dimension D as 2-H, where H is the Hurst' exponent, according to what was reported by Jahn and Truckenbrodt [15]. Jahn and Truckenbrodt [15] developed a simple formula to estimate the variance of a surface by combining Brownian motion with the fractal perturbation (roughness) of a surface. This is

$$\sigma^2=\sqrt{(2/\pi)}\sigma(\Delta x/1mm)^{(2-D)}$$

(3)

The formula composes the stochastic portion with the fractal portion of the roughness of a surface, thereby linking D to standard deviation σ. The authors also highlights that the measure-unit is not arbitrary and that the formula can work best with medium size fractals (D≈1.5). So, for medium size fractals, the fractal component $(\Delta x/1mm)^{(2-D)}$ can be easily detected by measuring point-by-point space in manufactured objects.

In estimating the point-by-point distance in time spread observations (n_i from *i*=1 to *i*=N), the same event would be affected by stochastic behavior in a non-stochastic way, leading to a fractal perturbation. Most procedures for the determination of fractal parameters are based on power law, such

$$f(x)=a(x)^g$$

(4)

(where g is the rule for calculating D in the Euclidean space). Therefore, the trend of ordered series allows to link the observed trend to a power law, where D is embedded in the observed trend:

$$ax(n) - c = ax(n)^{(2-D)}$$
(5)

If the trend of ordered series has only a stochastic perturbation, it would be equal to the trend observed in non-ordered series, and Equation (5) becomes:

$$ax(n)^{(2-D)} ordered = ax(n)^{(2-D)} non-ordered$$
(6)

Therefore, the (3) Jahn' formula [15] can be re-written as:

$$R = \sigma^2 = \sqrt{(2/\pi)} \cdot (\Delta x fract / Var\, \Delta x fract)^{(2-D)}$$
(7)

assuming that the whole variance σ^2 of a given variable in a series has any fractal perturbation (in a 2-dimension Euclidean space) as R is the roughness of a surface with both stochastic and fractal perturbation. The Δx_{fract} is the mean of the quadratic differences from trend, and $Var\Delta x_{fract}$ is the variance among quadratic differences from trend in the ordered series. $\Delta x_{fract}/Var\Delta x_{fract}$ works as a measure of the space of statistic distribution like Δx/1mm describes the space of a surface of a manufactured object in the Jahn and Truckenbrodt (15) formula [3]. Additionally, let's re-write the Jahn and Truckenbrodt [15] formula (3) as:

$$\sigma^2 = \sqrt{(2/\pi)} \cdot (\Delta x biases / Var\, \Delta x biases)^{(2-D)}$$
(8)

(in the same 2-dimension Euclidean space) hypothesizing that no fractal observation is proven. Again, the Δx_{biases} is the mean of the quadratic differences from trend and $Var\Delta x_{biases}$ is the variance among quadratic differences from the trend in the non-ordered series. From what is reported above,

$$\sigma^2 = \sqrt{(2/\pi)} \cdot (\Delta x biases / Var\, \Delta x biases)^{(2-D)} = \sqrt{(2/\pi)} \cdot (\Delta x fract / Var\, \Delta x fract)^{(2-D)}$$
(9)

if no fractal involvement appears from the data-set, and all biases are absorbed in the stochastic behavior of Gauss' shape.

If

$$\sqrt{(2/\pi)} \cdot (\Delta x biases / Var\, \Delta x biases)^{(2-D)} - \sqrt{(2/\pi)} \cdot (\Delta x fract / Var\, \Delta x fract)^{(2-D)} > 0$$
(10)

chaotic behavior is perturbed by something of non chaotic, that can be interpreted as the action of one or more non-random biases, leading to overestimating the variance of:

$$1 - (\sqrt{(2/\pi)} \cdot (\Delta x fract / Var\, \Delta x fract)^{(2-D)} / \sqrt{(2/\pi)} \cdot (\Delta x biases / Var\, \Delta x biases)^{(2-D)}) = k$$
(11)

Observed variance can be corrected as $\sigma^2 - \sigma^2 k$. The standard error can be therefore corrected as:

$$\sqrt{(\sigma^2-\sigma^2 k)}/\sqrt{(n)}$$
(12)

If

$$\sqrt{(2/\square)}\,\square(\square x\,biases/Var\,\square x\,biases)^{(2-D)}-\sqrt{(2/\square)}\,\square(\square x\,fract/Var\,\square x\,fract)^{(2-D)}<0$$
(13)

chaotic behavior due to non-random biases has underestimated the variance of:

$$1-(\sqrt{(2/\square)}\,\square(\square x\,biases/Var\,\square x\,biases)^{(2-D)}/\sqrt{(2/\square)}\,\square(\square x\,fract/Var\,\square x\,fract)^{(2-D)})=y$$
(14)

Observed variance can be corrected as $\sigma^2+\sigma^2 y$. The standard error can be therefore corrected as:

$$\sqrt{(\sigma^2+\sigma^2 y)}/\sqrt{(n)}$$
(15)

In the above reported data Sets (Table 1), we applied the proposed hypothesis of rule (2), aiming to check if the hypothetical fractal perturbation of non-random data Sets would have $\Phi\neq 0$, while better quality data Sets would have $\Phi=0$.

As a corollary, better quality data Sets (Set A and C) should not have any correction of their variance, while poor quality data Sets should have a correction of their variance. Therefore, standard errors should not be changed in good quality series and should be changed in poor quality series. By applying the rules from (9) to (12) we can prove that Sets A, B, and C does not have any standard errors correction, while Sets D, E, F have a standard error reduction (Table 1) of 13.8% (Set D), 18.0% (Set E), 4.0% (Set F). Rules from (13) to (15) have not be applied because Φ was not found <0, leading to suppose that non-stochastic fluctuations around mean would more likely increase than reduce standard errors of data distributions. Finally, it should be noticed that Set B does not have any standard error correction, leading to conclude that its fluctuation of data around its mean has been stochastic. Therefore the non-random addition of subtraction of random sets of numbers from 1 to 3 does not have disrupted the homogeneity of fluctuations of the random data distribution in the Set B.

Real world applications

-Administrative data

Administrative data on birth in the Italian region of Umbria in 2018 has been provided by the regional Government (CeDAP 2018). These are reported in Table 2 at the aggregate level. Data had been provided according to Umbria hospitals for each month. We already know that data on birth in Italy is largely heterogeneous, as previously reported by authors. This is acknowledged even for the Umbria region [16, 17]. Causes of such heterogeneity are related to the level of assistance and several cultural beliefs and criticality in Italy [18-20]. Therefore, it is difficult to compare data on mode of birth and hospital care among Italian hospitals, among Italian regions, and across the whole of Italy. Heterogeneity and biases can also be presumed by reading Table 2 concerning the wording “other kind of birth” and their relative distribution among hospitals. We cannot clarify what “other kind of birth” wording means, but we strongly suspect misclassification among hospitals.

Table 2. Distribution of births among Umbria hospitals in 2018.

	Spontaneous vaginal birth	Planned Cesarean section	Ceasrean section during labor	Operative vaginal birth	Urgent cesarean section	Other kind of birth†	TOTAL
Città di Castello	408	67	57	40	12	0	584
Pantalla	166	45	20	4	10	0	245
Spoleto	374	56	19	22	26	3	500
Orvieto	287	54	31	10	31	0	423
Foligno	711	136	56	35	62	16	1016
Branca	228	54	46	11	16	9	364
Perugia	1314	220	161	66	43	2	1806
Terni	745	162	155	18	36	0	1133
TOTAL	4233	794	545	206	236	30	6071

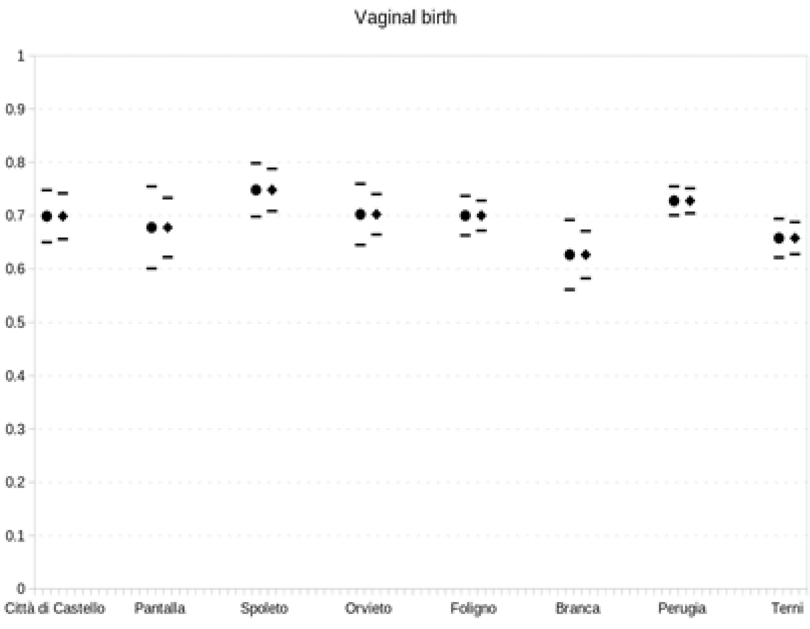
† It's unclear what "other kind of birth" means.

Table 2. Raw numbers are reported for all 2018 Umbria hospitals, according to kind of birth.

We aim to clean up the administrative data reported in Tables 2 on birth rates from non-random biases. According to all categories of birth, rates were calculated monthly for all hospitals and all of 2018 (except for the category "other kind of birth"). Mean rates were calculated. Then, trends of ordered and non-ordered series were calculated. The squared differences among observed rates and trends for ordered and non-ordered series were averaged, and variances were calculated. Then, the rules above were applied (11 and 14), and the variances were corrected for having the corrected standard errors (by applying rules (12) and (15)). From the corrected standard errors, the 99.9% confidence intervals (CI) were calculated. In this paper, the Hurst coefficient (H) has been calculated according to Glattre and Nygård [21]: H=(Hurst' fluctuation/2)$^{0.73}$σ.

Figure 2 to 4 reports results. Diamonds represent mean rates included in the corrected 99.9% CI, while circles represent mean rates included in uncorrected 99.9% CI. Table 3 reports the percentage of correction of the variance, also clarifying in which direction biases have acted.

Figure 2



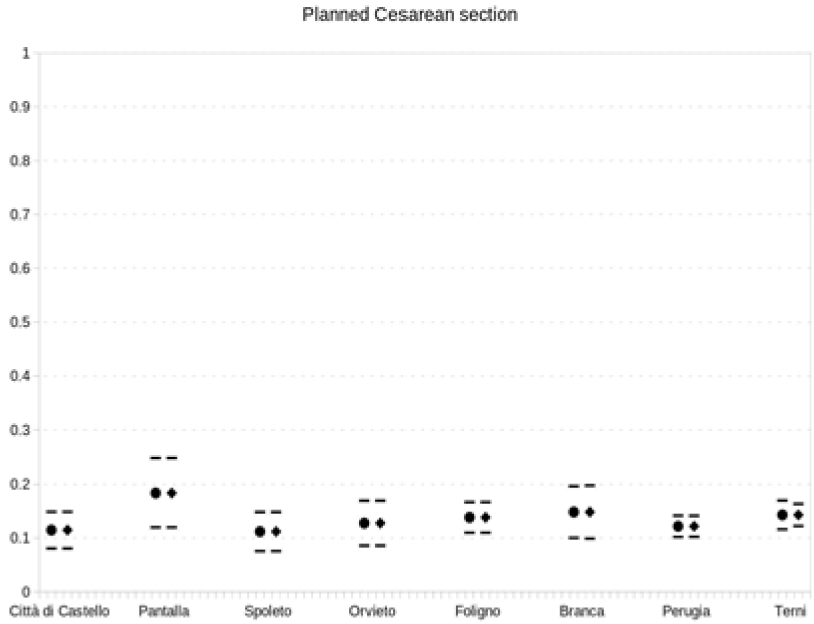
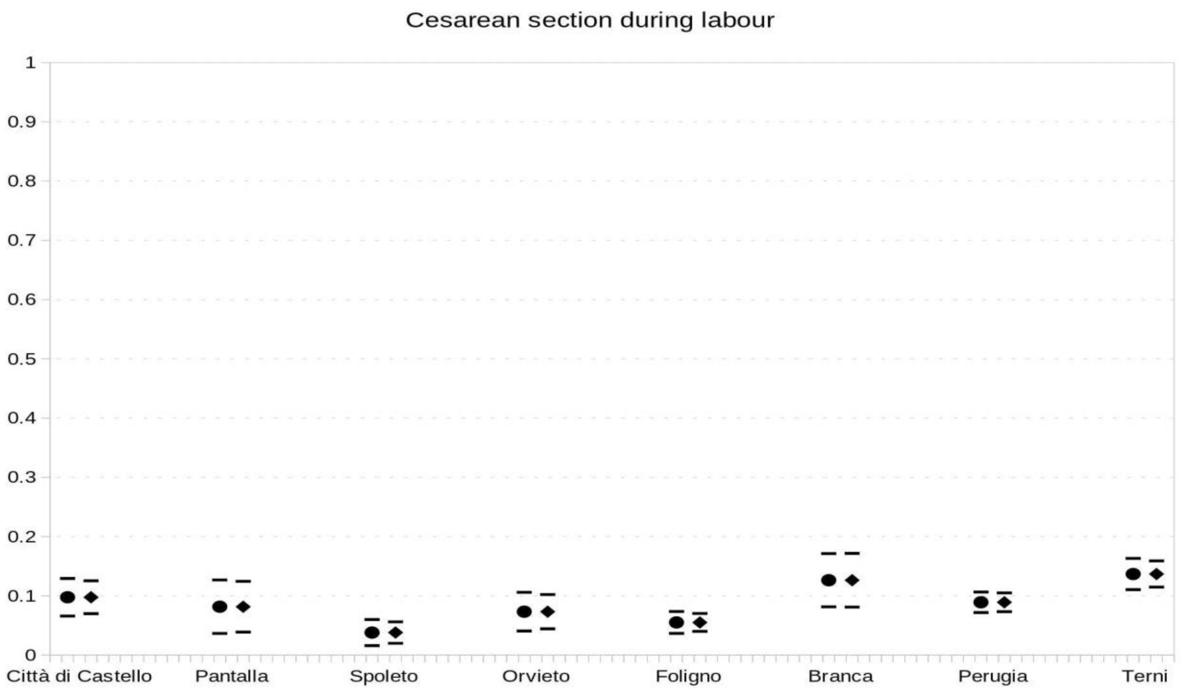


Figure 2. Rates and 99.9% CI for uncorrected (●) and corrected (♦) rates for vaginal births and planned Cesarean sections.

Figure 3



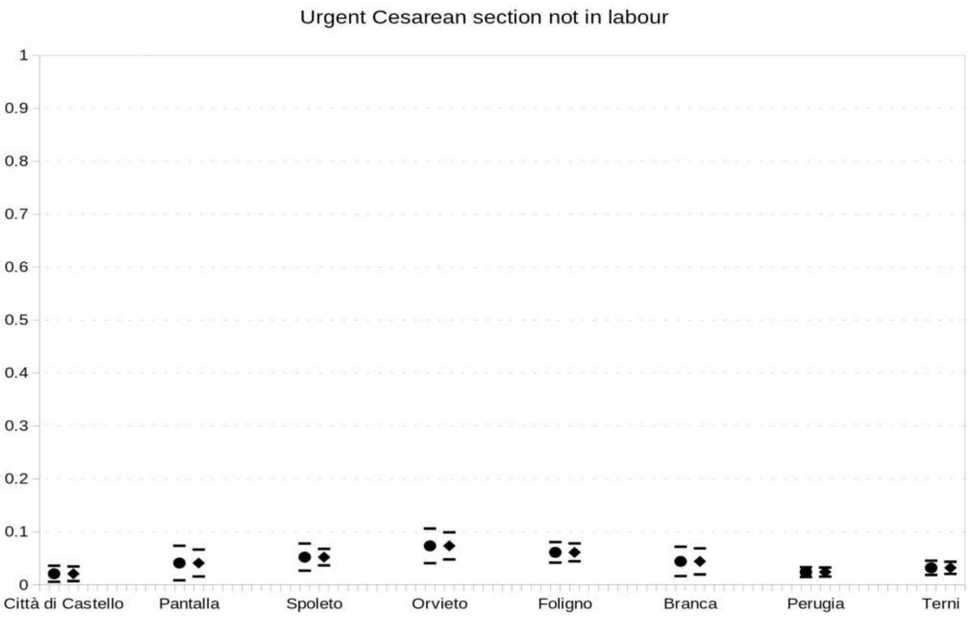


Figure 3. Rates and 99.9% CI for uncorrected (●) and corrected (♦) rates for Cesarean sections during labor and urgent Cesarean sections not in labor.

Figure 4

Figure 4. Rates and 99.9% CI for uncorrected (●) and corrected (♦) rates for operative vaginal births.

Table 3. Percentage of correction of variance.

	Vaginal birth	Planned Cesarean section	Cesarean section in labor	Urgent Cesarean section not in labor	Operative vaginal birth
Città di Castello	23.2% ↓	≈0% ↑	23.4% ↓	17.2% ↓	81.1% ↑
Pantalla	47.7% ↓	≈0% ↑	9.9% ↓	39.3% ↓	76.4% ↑

Spoleto	37.3% ↓	≈0% ↑	33.2% ↓	62.8% ↓	78.3% ↑
Orvieto	56.2% ↓	≈0% ↓	21.8% ↓	38.6% ↓	73.6% ↑
Foligno	42.5% ↓	≈0% ↓	32.8% ↓	24.4% ↓	67.1% ↑
Branca	54.1% ↓	5.3% ↑	1.8% ↑	20.8% ↓	80.2% ↑
Perugia	25.2% ↓	2.6%↓	15.7% ↓	15.0% ↓	72.9% ↑
Terni	31.3% ↓	41.3%↓	29.6% ↓	27.5% ↓	37.8% ↑

Table 3. ↓ means that variance has been decreased because chaos has increased the observed variance value; ↑ means that variance has been increased because chaos has decreased the observed variance value.

Table 4 reports the overall rate of each kind of birth for Umbria. These rates, along with 99.9% CI, have been calculated, weighing the rates for the inverse of variances (random effect models always used) as is usually done for meta-analyses. The corrected standard errors clean up the overall rates from non random biases (while random effect model would clean up the random biases), providing overall estimated rates slightly different from usual weighted data syntheses. P-values reported in Table 4 refer to comparisons of means of uncorrected and corrected standard errors.

Table 4. Overall proportions with CI – Administrative data.

DATA ON BIRTH MODE IN UMBRIA, 2018 – Rates		Uncorrected standard error	Corrected standard error	p†
	Lower 99.9% CI	0.6905516	0.6901429	
-Vaginal birth		0.6923549	0.6925201	0.003*
	Upper 99.9% CI	0.6941524	0.6948871	
	Lower 99.9% CI	0.1330681	0.1331729	
-Planned Cesarean section		0.1344394	0.1344417	n.s.
	Upper 99.9% CI	0.1358237	0.1357207	
	Lower 99.9% CI	0.0798727	0.0812213	
-Cesarean section in labor		0.0809823	0.0819153	0.044*
	Upper 99.9% CI	0.0821060	0.0826147	
	Lower 99.9% CI	0.0389827	0.0398118	
-Urgent Cesarean section not in labor		0.0397563	0.0401002	0.018*
	Upper 99.9% CI	0.0405446	0.0403905	
	Lower 99.9% CI	0.0291036	0.0301858	

-Operative vaginal birth		0.0298074	0.0304518	0.001*
	Upper 99.9% CI	0.0305278	0.0307201	

† Comparisons among uncorrected standard errors and corrected standard errors. Testing the null hypothesis that means of corrected standard errors are not lower or higher than means of uncorrected standard errors. t-test for paired data (two tiled).

Figure 5 reports the mean percentage of correction plotted versus the numerosity of the samples. As expected, the higher the numerosity of the sample, the lower the mean percentage of correction.

Figure 5

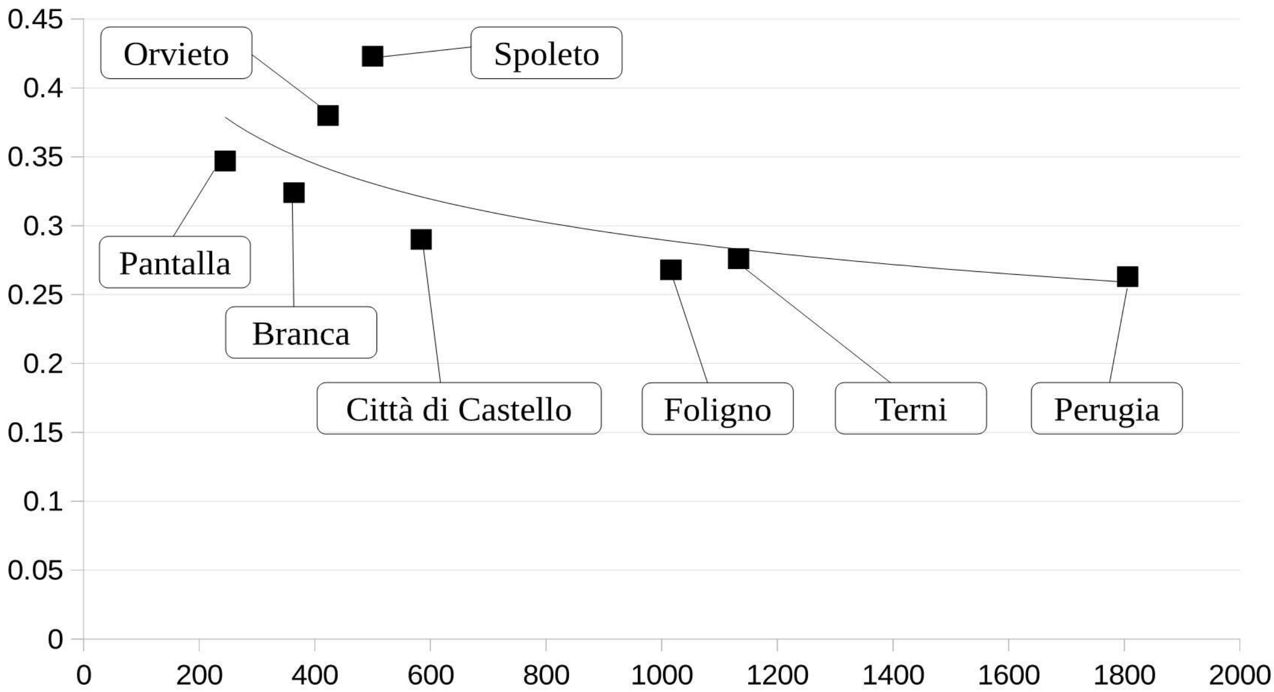


Figure 5. Mean percentage of correction (y-axis) plotted according to number of births (x-axis). The higher number of births, the lower the percentage of correction.

-Meta-analysis

In line with the aim of this article, we have chosen to re-make some recent meta-analyses about intrahepatic cholestasis of pregnancy by applying the standard error corrections. We clarify we do not aim to improve the results of the already published studies.

Intrahepatic cholestasis of pregnancy is uncommon and very heterogeneous pregnancy disorder thereby providing biased data at aggregate level. Finding several reviews and meta-analyses on intrahepatic cholestasis of pregnancy in recent literature suggests that data on the diseases would be heterogeneous and still under debate [22].

Intrahepatic cholestasis of pregnancy data were extracted from references [23-28] at aggregate level. The Di Mascio et al [28] systematic review assesses some pregnancy outcomes according with bile acid levels. Rates of some outcomes reported in that article [28] were meta-analyzed independently from bile acid levels. Table 4 reports all results of calculations at aggregate level, performed by re-computing variances and standard errors (rules (11) and (14); rules (12) and (15)). The 95% CI are reported both using uncorrected and corrected standard errors in Table 5. While corrected standard errors do not add more information as usual methods (except for "stillbirth" outcome in the 2019' Ovadia et al [23] meta-analysis: Table 5), it is proven that means of corrected and uncorrected standard errors are significantly different (p=0.02). The corrected standard errors is mainly lower than uncorrected standard error, as non random biases act mainly by increasing the CI of means from mean effect sizes. Additional, the scatter plot provided in Figure 6 (upper and left plot-graph) highlights that the regression slope of corrected standard errors is closer to effect sizes and more horizontal, as compared with regression slope obtained from uncorrected standard errors. This behavior demonstrates more homogeneous estimates.

Table 5. Overall proportions with 95% CI – Meta-analyses

OUTCOMES measures of meta-analyses		Uncorrected standard error	Corrected standard error	p†
Ovadia et al 2021 (24) meta-analysis – Odds Ratio				
	Lower 95.0% CI	0.0866486	0.0977676	
-Stillbirth		0.4422247	0.4422247	
UDCA vs No-UDCA	Upper 95.0% CI	1.0157970	2.0002776	
	Lower 95.0% CI	0.4307221	0.5378428	
-All preterm births		0.5654138	0.5654138	
UDCA vs No-UDCA	Upper 95.0% CI	0.7422252	0.5943981	
	Lower 95.0% CI	0.4332457	0.4457312	
-Spontaneous preterm births		0.6854013	0.6854013	
UDCA vs No-UDCA	Upper 95.0% CI	1.0843152	1.0539424	
Ovadia et al 2019 (23) meta-analysis – Odds Ratio				
	Lower 95.0% CI	0.9486583	1.3350636	
-Stillbirth		1.4742224	1.4742224	
Intrahepatic cholestasis vs Controls	Upper 95.0% CI	2.2909529	1.6278862	
	Lower 95.0% CI	2.3790721	2.3802763	
-Spontaneous preterm birth		2.6604697	2.6604697	
Intrahepatic cholestasis vs Controls	Upper 95.0% CI	2.9751512	2.9736461	
	Lower 95.0% CI	2.5011320	2.5029661	
-Meconium stained amniotic fluid		2.7189302	2.7189302	
Intrahepatic cholestasis vs Controls	Upper 95.0% CI	2.9556941	6.2752684	
Bacq et al 2012 (26) meta-analysis – Odds Ratio				

	Lower 95.0% CI	0.1487357	0.2882822	
-Fetal distress		0.2917217	0.2917217	
UDCA vs Others	Upper 95.0% CI	0.5721665	0.2952023	
	Lower 95.0% CI	0.0986099	0.0986099	
-Fetal distress		0.4038097	0.4038097	
UDCA vs Placebo	Upper 95.0% CI	1.6536109	1.6536109	
	Lower 95.0% CI	0.3115257	0.5957708	
-Spontaneous preterm birth		0.5975086	0.5975086	
UDCA vs Others	Upper 95.0% CI	1.1460261	0.5992515	
	Lower 95.0% CI	0.0223740	0.0223740	0.02*
-Sponteneous preterm birth		0.0682378	0.0682378	
UDCA vs Placebo	Upper 95.0% CI	0.2081168	0.2081168	
Walker et al 2020 (25) meta-analysis – Risk Ratio				
	Lower 95.0% CI	0.0400617	0.2698713	
-Stillbirth		0.2917512	0.2917512	
UDCA vs Placebo	Upper 95.0% CI	2.1246923	0.3161845	
	Lower 95.0% CI	0.3929520	0.7520015	
-Fetal distress		0.7522199	0.7522199	
UDCA vs Placebo	Upper 95.0% CI	1.4399590	0.7524384	
	Lower 95.0% CI	0.4350425	0.5871723	
-Meconium stained amniotic fluid		0.6295085	0.6295085	
UDCA vs Placebo	Upper 95.0% CI	0.9082148	0.6748972	
	Lower 95.0% CI	0.5008686	0.5781672	
-Spontaneous preterm birth		0.7984001	0.7984001	
UDCA vs Placebo	Upper 95.0% CI	1.2726746	1.0252313	
Di Mascio et al 2021 (28) systematic review – Rates				
	Lower 95.0% CI	0.0051082	0.0106199	
-Stillbirth		0.0107466	0.0107466	
	Upper 95.0% CI	0.0844040	0.0108748	

	Lower 95.0% CI	0.0894629	0.0931051
-Meconium stained amniotic fluid		0.1232792	0.1232792
	Upper 95.0% CI	0.1675260	0.1265572
	Lower 95.0% CI	0.0375827	0.0523757
-Spontaneous preterm birth		0.0656379	0.0656380
	Upper 95.0% CI	0.1121950	0.0819681
Kong et al 2016 (27) meta-analysis – Risk Ratio			
	Lower 95.0% CI	0.4394761	0.5607298
-Prematurity		0.5664328	0.5664328
UDCA vs Control	Upper 95.0% CI	0.7300648	0.5721937
	Lower 95.0% CI	0.5536480	0.7758501
-Fetal distress UDCA vs Control		0.7764762	0.7764762
	Upper 95.0% CI	1.0889868	0.7771029

†Comparisons among uncorrected standard errors and corrected standard errors. Testing the null hypothesis that means of corrected standard errors are not lower or higher than means of uncorrected standard errors. t-test for paired data (two tiled).

Table 5. Uncorrected and corrected CI for some outcome measures were reported. They are calculated from already published systematic reviews and meta-analyses already published in literature.

Figure 6

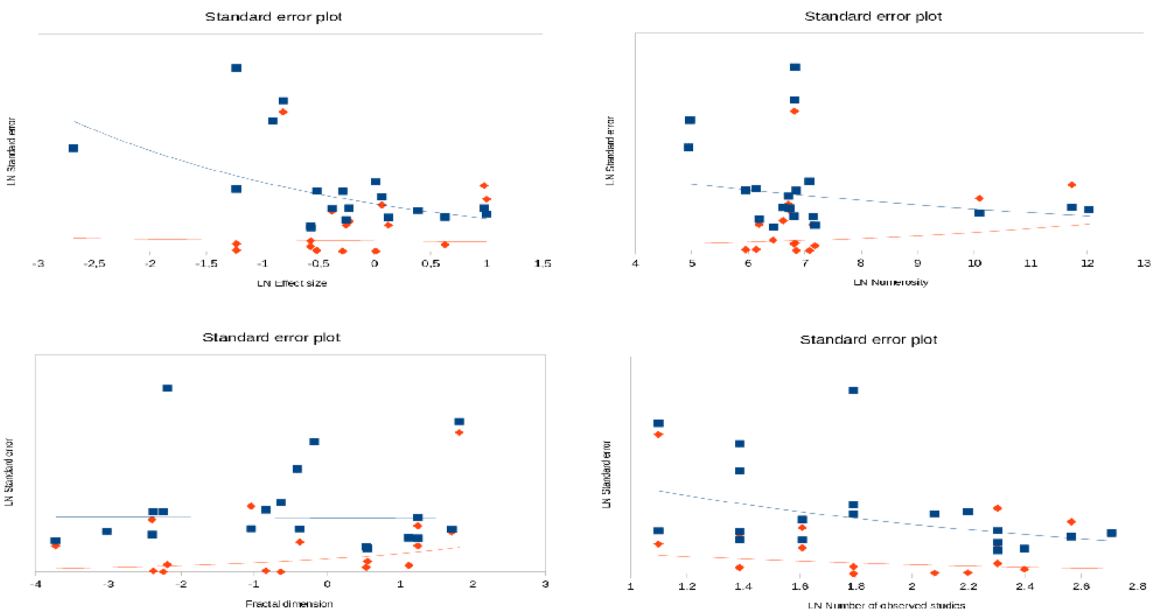


Figure 6. Trends of standard error plotted versus effect size, numerosity, fractal dimension and number of meta-analyzed studies. The blue squares are the uncorrected standard errors. The orange diamonds are the corrected standard errors.

Discussion

We describe a practical method for checking out for non-random biases at a quantitative level in data reporting. Those biases are supposed to be multiple and working non-randomly (Set B, Set D, Set E, Set F). When such behavior of biases can be presumed, oscillations of variance can be corrected by applying the key concept of self-similarities of natural processes. Otherwise, a single bias or a small number of biases are working randomly (Set A and Set C), describing a stochastic perturbation itself or being unable to disrupt the stochastic behavior of the assessed event (Set B).

The method has been applied to rates of births in Umbria, Italy, during 2018. CI for each kind of birth were corrected for Umbria's birth centers. It seems that planned Cesarean sections are more likely to be unbiased in all hospitals, while CI of vaginal birth, Cesarean section during labor, and urgent Cesarean section not in labor are overestimated. Finally, operative vaginal birth CI are largely underestimated. Those findings lead to a better estimate of the true rates of birth in Umbria (Table 4) and are not too different from the usual methods of data synthesis. Perception of chaotic behavior of data can be obtained by plotting the mean percentage of correction of rates for the number of births per hospital (Figure 5). It is expected that the higher the observed sample numerosity, the lower the risk of biases. Contrary, a linear trend is not clearly observed in Figure 5, thereby proving that data variability is not only linked with the sample numerosity. Additionally, Spoleto and Orvieto seem to work out from trend slope, while the trend line lays towards horizontality for a birth/year number of 1000. This phenomenon can be explained for a better distribution of factors conditioning the mode of birth in a stochastic way in the case of a larger number of births, thereby producing a normal distribution shape. As a result, rare events (operative vaginal birth) are more likely to be non-randomly biased, as the conditioning factors are less likely to follow a normal distribution.

In case of meta-analyses, we have proven that standard error corrections result in a mean reduction of CIs, without affecting information drawn by using usual method of data syntheses. It is interesting to observe that the higher the overall effect size, the lower the corrected standard error values, while the higher numerosity and fractal dimension the higher the corrected standard errors values (Figure 6). The behavior suggests that fractal assessment for correcting standard errors with the above formulas provides better estimates in case of lower to medium fractal dimensions (as reported by Jahn and Truckenbrodt [15] in 2004) and with lower numerosity.

Fractal behavior in biological phenomena has been assumed in this paper based on the literature [8]. Authors [21, 29] have reported checking for fractality to distinguish chaotic behavior from non-chaotic behavior. As detrimental fractal analysis has not been performed in this article, the proposed method for remedying non-random biases can be questioned. However, we have reported a calculation for a proportion of the variance to be corrected by dividing the same entity assessed in the same way. Therefore, it is not strictly needed to prove that the trend is fractal. Additionally, vanish fractal shapes are reported but not already proven for Cesarean section trends in a previously published article [16], thereby confirming the premise of self-organized criticality reported in the literature [8].

Conclusion

In conclusion, hypothesizing the Gauss bell as an extremely smoothed (previously rough) fractal object, the roughness of a biased statistic distribution can be assessed from the mean of squared differences from the trend and its variance. The method is easy and can improve data synthesis in meta-analyses. Also, it can allow checking how stochastic administrative data are, thereby helping health managers to assess hospitals' performances in less biased way.

Data availability statements

The author confirms that data generated or analyzed during this study are included in this published article or are reported at aggregate level in the cited references.

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None

Conflict of interest

Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

Author contribution

UI designed the study, made calculations, wrote article.
MC provided 2018 Umbria hospitals data on birth
AF ordered data and contributed to writing articles
SG supervised and coordinated work
All authors gave final approval for publication and agree to be held accountable for the work performed therein.

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