The spurious correlation between concentration and creatinine-corrected concentration in urine

Simon Brown, Delwyn G. Cooke, Leonard F. Blackwell and David C. Simcock

***Abstract*—The use of urinary analytes to monitor physiological processes relies on making the correct measurement. Three alternatives are commonly contemplated: concentration, creatinine-corrected concentration and excretion rate. Of these, the latter is the most reliable, but is perceived by some to be difficult to measure. This has led to the more frequent reliance on concentration and one of the justifications for this is the reported linear relationship between the concentration and the creatinine-corrected concentration. We show that this correlation is spurious in that the magnitude of the correlation coefficient depends on the ratio of the standard deviations of the creatinine and analyte concentrations. As an example urinary analyte we use pregnanediol (Pd) which is an important tool for women wishing to monitor their own fertility. Urinary Pd concentration is not a reliable substitute for creatinine-corrected Pd concentration or the Pd excretion rate.**

***Keywords*—creatinine correction, menstrual cycle, spurious correlation, urinary analyte concentration.**

I. Introduction

It is fundamental to the meaningful use of any data that the measurement on which they are based is reliable, appropriate and free from confounding factors. However, there are instances where data quantity is taken to be a reasonable substitute for data quality. Moreover, the continued use of a measurement known to be defective is sometimes justified by an argument that it is 'difficult' or 'inconvenient' to do a better measurement. Problems of this sort are widespread, but are especially common in measurements of urinary analytes, including those involved in the measurement of reproductive hormones in urine by women monitoring their own fertility.

The quantity of an analyte (A) in a urine sample has been expressed in many ways, including (i) concentration ([A]), (ii) [A] normalised by the creatinine (Cr) concentration ([A]/[Cr]) and (iii) the excretion rate (J_A). We have shown that J_A can be related to the rate of production of A and that [A] is, at best, a poor estimate of J_A [1]. This is because the variability of both the volume of urine accumulated (V in mL) and the time between voids (Δt in h) means that [A] changes between voids. Variation of this sort results from environmental and lifestyle factors. The most direct measure of the physiological urinary output of an analyte is its excretion rate (J_A, in g h^{-1} or mol h^{-1}) which, as we have outlined previously [2], is the product of [A] and the urine production rate (J_V in mL h^{-1})

$$J_A = [A]J_V = \frac{q_A}{V}\frac{V}{\Delta t} = \frac{q_A}{\Delta t}, \quad (1)$$

where q_A is the quantity (in mol or g) of A in the void. An alternative measure that is often used is the ratio of [A] to the concentration of creatinine (Cr). It is widely assumed that Cr is excreted at a constant rate [3-5]. This approach follows from (1): if $J_{Cr} = [Cr]J_V$ is constant, then $J_V \propto 1/[Cr]$ and

$$J_A \propto \frac{[A]}{[Cr]}, \quad (2)$$

which is the basis of the widespread use of [Cr] to 'correct' for J_V.

However, the perception that it is difficult to measure J_V and the desire to avoid determining [Cr] have motivated many to assume that concentration ([A]) is a reasonable means of monitoring a urinary analyte. Two recent 'justifications' for this are that plots of (a) ln([A]) versus ln(J_A) [6] and (b) ln([A]) versus ln([A]/[Cr]) [7] are 'linear'. In both of these cases [6, 7], the urinary analyte (A) is pregnanediol-3-glucuronide (PdG) which is a metabolite of the reproductive hormone progesterone, although Roos *et al.* [7] also applied this analysis to oestrone-3-glucuronide (E1G) which is a metabolite of the reproductive hormone oestradiol. The combination of J_{PdG} and J_{E1G} provides a powerful means of monitoring the menstrual cycle and fertility [8, 9]. However, there is a recent trend, based in part on these 'linear' plots, towards a reliance on [PdG] and [E1G] [7, 10-14], despite the very substantial literature based on excretion rates [15-43].

The notion that this sort of analysis provides some support for the idea that [PdG] might be a reasonable substitute for J_{PdG} [6] or even [PdG]/[Cr] [7] has prompted us to examine the evidence. We do so using some numerical experiments and also using measurements of the urinary concentration of pregnanediol (Pd, which is obtained by hydrolysis of PdG), [Cr] and J_V.

II. Background

To examine the 'linearity' of ln(y) *versus* ln(y/x) and ln(y)

Manuscript received 30 October 2018.

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versus ln(*xy*) we summarise both by writing them as ln(*y*) *versus* ln(g(*x*, *y*)), where g(*x*, *y*) = $x^{\gamma}y$ and $\gamma = \pm 1$, although the analysis is not restricted to these values of γ. A linear relationship of this type would imply

$$\ln(y) = \beta_0 + \beta_1 \ln(\mathrm{g}(x,y)) = \beta_0 + \beta_1 \ln(y) + \gamma\beta_1 \ln(x), \quad (3)$$

from which it is clear that if $x = 1$, then $\beta_0 = 0$ and $\beta_1 = 1$. The ordinary least squares (OLS) estimates of β_0 and β_1 are

$$\hat{\beta}_0 = \langle \ln(y) \rangle - \hat{\beta}_1 \langle \ln(\mathrm{g}(x,y)) \rangle \text{ and } \hat{\beta}_1 = R_0 \frac{s_{\ln(y)}}{s_{\ln(\mathrm{g}(x,y))}}, \quad (4)$$

where <*z*> and s_z are the sample mean and sample standard deviation of *z*, respectively [44]. In (4) R_0 is the correlation coefficient between ln(*y*) and ln(g(*x*, *y*))

$$R_0 = \frac{\mathrm{cov}(\ln(y), \ln(\mathrm{g}(x,y)))}{s_{\ln(y)} s_{\ln(\mathrm{g}(x,y))}} \quad (5)$$

where cov(*w*, *z*) is the covariance of *w* and *z*. The mean and standard deviation of ln(g(*x*, *y*)) are

$$\langle \ln(\mathrm{g}(x,y)) \rangle = \langle \ln(y) \rangle + \gamma \langle \ln(x) \rangle \quad (6)$$

and

$$s^2_{\ln(\mathrm{g}(x,y))} = \gamma^2 s^2_{\ln(x)} + s^2_{\ln(y)} + 2\gamma \,\mathrm{cov}(\ln(x), \ln(y)), \quad (7)$$

respectively, and

$$\mathrm{cov}(\ln(y), \ln(\mathrm{g}(x,y))) = s^2_{\ln(y)} + \gamma \,\mathrm{cov}(\ln(x), \ln(y)). \quad (8)$$

Substituting (7) and (8) into (5) yields

$$R_0 = \frac{1 + \gamma R_1 \lambda}{\sqrt{\gamma^2\lambda^2 + 2\gamma R_1 \lambda + 1}}, \quad (9)$$

where $\lambda = s_{\ln(x)}/s_{\ln(y)} > 0$ and we have written the correlation coefficient between ln(*x*) and ln(*y*) as $R_1 = \mathrm{cov}(\ln(x), \ln(y)) / s_{\ln(x)} s_{\ln(y)}$. Substituting (6) into (4) yields

$$\hat{\beta}_0 = (1 - \hat{\beta}_1)\langle \ln(y) \rangle - \gamma\hat{\beta}_1 \langle \ln(x) \rangle \quad (10)$$

and, using (4), (5), (7) and (8) gives

$$\hat{\beta}_1 = \frac{\gamma R_1 \lambda + 1}{\gamma^2\lambda^2 + 2\gamma R_1 \lambda + 1}. \quad (11)$$

In general (i) $\hat{\beta}_1$ tends to decline with increasing λ, although the behaviour is more complex for $\gamma = -1$ if R_1 is large (Figure 1A), (ii) if λ is small $\hat{\beta}_1 \approx 1$ and if λ is large $\hat{\beta}_1 \approx 0$ (Figure 1A), (iii) if λ is small $R_0 \approx 1$ and if λ is large R_0 is smaller and can be negative depending on γ and R_1 (Figure 1B) and (iv) neither R_0 nor $\hat{\beta}_1$ depends systematically on <ln(*x*)> or <ln(*y*)>. The corollaries are that (i) if λ is small $\hat{\beta}_0$ approaches -γ<ln(*x*)> and (ii) as λ increases $\hat{\beta}_0$ approaches <ln(*y*)>.

III. Methods

Measurements of urinary concentration of pregnanediol (Pd), which is quantitatively derived from PdG [45], and Cr, and of J_V were obtained from the DIY trial carried out in the late 1980s in Melbourne. The data we analyse here are a subset of these and comprise periovulatory measurements of Pd and Cr for 26 menstrual cycles from 12 subjects, yielding a total of $n = 190$ complete records.

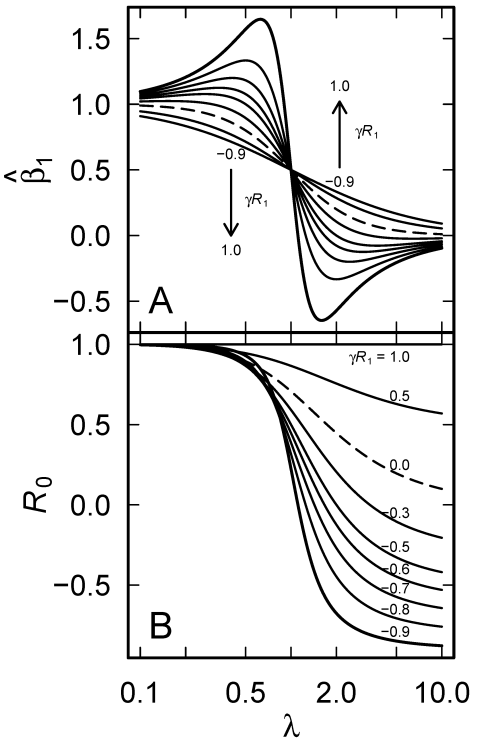

Figure 1. Relationship between λ and $\hat{\beta}_1$ (A) and R_0 (B) for γR_1 = {-0.9, -0.8, -0.7, -0.6, -0.5, -0.3, 0.0, 0.5, 1.0} using (11) and (9), respectively. In each panel the dashed curve corresponds to $\gamma R_1 = 0$.

In the numerical experiments described we chose to use lognormally distributed random variables (*x* and *y*), but trials based on other distributions yielded similar results. This choice of distribution was based on the fact that it provides a better approximation to the distribution of the observed urinary concentrations of Pd (Figure 2A) and of Cr (Figure 2B) based on the Akaike information criterion as described previously [46]. The quantile-quantile (QQ) plots shown in Figure 2 confirm that the lognormal distribution is a reasonal representation of the data for each analyte. Lognormally distributed random variables were generated using the rlnorm function in R in which μ and σ are the mean and standard deviation, respectively, of ln(*x*) and, to avoid ambiguity, the probability density of *x* is

$$LN(x;\mu,\sigma) = \frac{1}{\sqrt{2\pi}\sigma x} \exp\left(-\frac{(\ln(x) - \mu)^2}{2\sigma^2} \right). \quad (12)$$

The values of μ and σ were uniformly distributed random variables to ensure an even distribution across the chosen range. Other details of the simulations are given below.

IV. Results

A. An example

The relationship between ln([Pd]) and ln([Pd]/[Cr]) is approximately linear (Figure 3A) and OLS regression yields $\hat{\beta}_0$ = -0.04 ± 0.09 [95% CI] and $\hat{\beta}_1$ = 0.94 ± 0.08 [95% CI] (R_0 = 0.855 [95% CI: 0.811, 0.889], $p < 0.001$). As the independent variable is uncertain, Deming regression might be a more appropriate approach but it yields similar

estimates of the intercept (0.06 ± 0.09 [95% CI]) and slope (1.11 ± 0.09 [95% CI]) assuming a precision ratio of one. In neither case is the slope significantly different from one ($p \geq 0.891$).

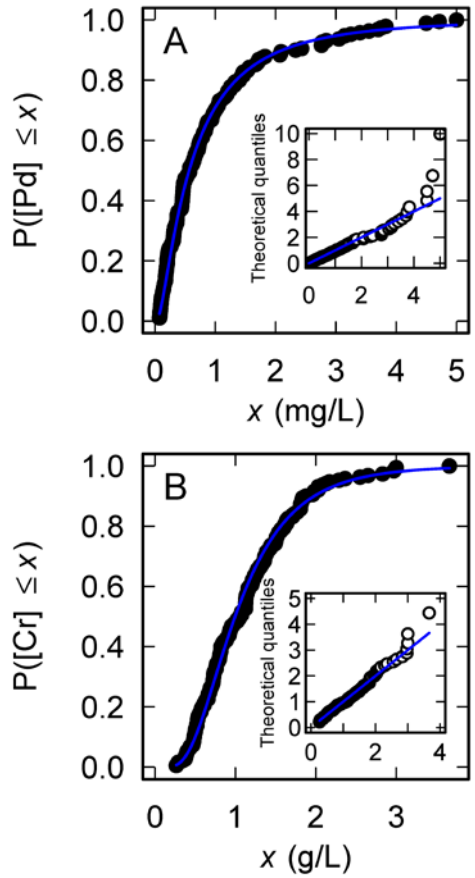

Figure 2. Distribution of urinary Pd (A: <ln([Pd])> = -0.57 ± 0.07 (SD), $s_{\ln([Pd])}$ = 1.03 ± 0.05 (SD)) and Cr (B: <ln([Cr])> = 0.00 ± 0.04 (SD), $s_{\ln([Cr])}$ = 0.54 ± 0.03 (SD)) concentration (n = 190). In each panel the curve is the lognormal cumulative distribution function fitted to the data by maximum likelihood. The insets show the corresponding QQ plot in which the straight line indicates equality between the theoretical lognormal and observed quantiles.

For these data, $s_{\ln([Pd])}$ = 1.03 (Figure 2A), $s_{\ln([Cr])}$ = 0.54 (Figure 2B), R_1 = 0.424 and cov(ln([Pd]), ln([Cr])) = 0.23, so $\lambda = s_{\ln([Cr])}/s_{\ln([Pd])} = 0.52$ is small and it follows from (9) that no matter the value of R_1 the correlation between ln([Pd]) and ln([Pd]/[Cr]) is likely to be high (Figure 1B), which is the case (R_0 = 0.855). To examine this point, we randomly sampled the [Cr] data without replacement using the sample function in R, so that each [PdG] was 'corrected' (2) by a random [Cr] but n, $s_{\ln([Pd])}$, $s_{\ln([Cr])}$ and λ were identical for each iteration. For each of 1000 iterations R_0 was calculated and the distribution of these values is shown in Figure 3B. While R_0 = 0.855 for the data shown in Figure 3A, the randomised [Cr] values yielded R_0 that were all high (Figure 3B, <R_0> = 0.887 ± 0.007 (SD)).

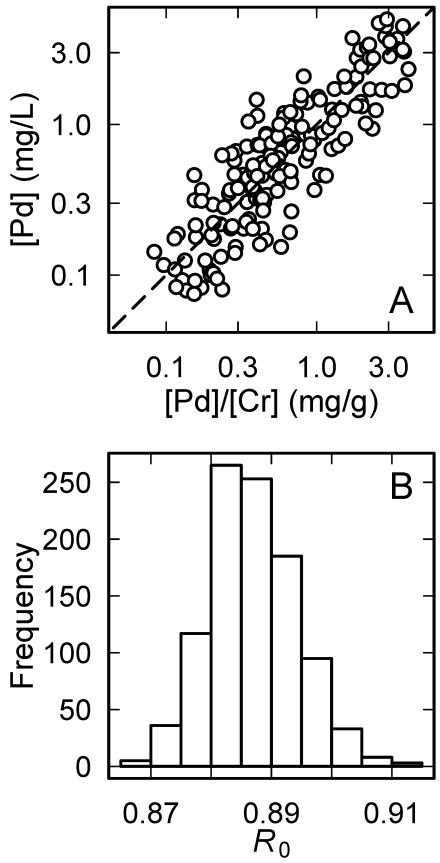

Figure 3. The relationship between [Pd] and [Pd]/[Cr] in n = 190 periovulatory urine samples (A) and the distribution of R_0 obtained by randomising the [Cr] data (B). In (A) the dashed line indicates [Pd] = [Pd]/[Cr]. For each of the 1000 iterations in (B) n, $s_{\ln([Pd])}$, $s_{\ln([Cr])}$ and λ were identical to the original data shown in (A).

B. Numerical experiments

To examine the effect of changes to specific parameters we carried out numerical experiments in which <ln(y)>, $s_{\ln(y)}$, <ln(x)> and $s_{\ln(x)}$ were varied independently. For simplicity, we concentrate on g(x, y) = y/x (so γ = -1), but an analogous treatment can be given for g(x, y) = xy (3). In each case, 1000 random values of each of x and y were generated from the lognormal distribution and (3) was fitted to the values by OLS regression to obtain estimates of $\hat{\beta}_0$ and $\hat{\beta}_1$.

These experiments indicate that <ln(x)> and <ln(y)> merely move the value of $\hat{\beta}_0$ in the ln(y)-ln(y/x) plane (data not shown), as would be expected from (10). In contrast, increasing $s_{\ln(x)}$ or $s_{\ln(y)}$ increases the deviation from the regression line and also rotates the values clockwise around (<ln(y/x)>, <ln(y)>) thereby changing $\hat{\beta}_1$, consistent with (11). For example, increasing $s_{\ln(x)}$ from about 0.1 to 1.0 to 2.0 (Figure 4) results in a decline in $\hat{\beta}_1$, from 0.941 to 0.036, and in R_1 (from 0.969 to 0.185) (Table 1). The covariance of ln(y) and ln(y/x) (= $R_1 s_{\ln(y)} s_{\ln(y/x)}$) is about 0.16 and $\hat{\beta}_0$ is about 4.61 over this range (Table 1). Given that $R_1 \leq 0.011$ for these simulations, (9) and (11) are

$$R_0 \approx \left(\lambda^2 + 1\right)^{-1/2} \text{ and } \hat{\beta}_1 \approx \left(\lambda^2 + 1\right)^{-1}, \quad (13)$$

respectively, so the correlation between ln(y) and ln(y/x) depends on λ alone.

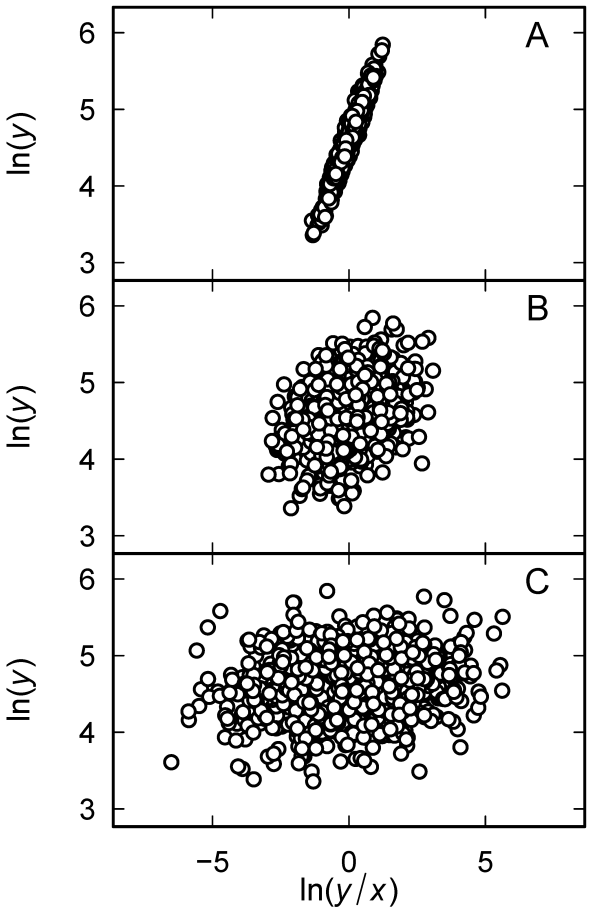

Figure 4. Relationship between ln(y) and ln(y/x) for $s_{\ln(x)}$ = 0.103 (A), 0.997 (B) and 2.037 (C) and, for each, $s_{\ln(y)}$ = 0.407. In each case 1000 lognormally distributed random values were generated for x and y. Further details of the simulations are given in Table 1.

Table 1. Details of the simulations shown in Figure 4. In each case <ln(y)> = 4.615 and $s_{\ln(y)}$ = 0.407.

	Figure 4A	Figure 4B	Figure 4C
<ln(x)>	4.607	4.620	4.637
$s_{\ln(x)}$	0.103	0.997	2.037
<ln(y/x)>	0.008	-0.004	-0.021
$s_{\ln(y/x)}$	0.419	1.076	2.073
cov(ln(y), ln(y/x))	0.1653	0.1643	0.1561
cov(ln(x), ln(y))	0.0003	0.0013	0.0095
$\lambda = s_{\ln(x)}/s_{\ln(y)}$	0.254	2.450	5.007
$\hat{\beta}_0$	4.608	4.616	4.616
$\hat{\beta}_1$	0.941	0.142	0.036
R_0	0.969	0.375	0.185
R_1	0.007	0.003	0.011

To examine this further, the same approach was used to generate lognormally distributed x and y except that uniformly distributed values of μ and σ were used to ensure an even distribution of <ln(x)> and $s_{\ln(x)}$ (Figure 5A). For each iteration the OLS regression coefficients and R_0 were determined (Figures 5, B and C). As shown in Figure 1, (9) and (11) indicate that both R_0 and $\hat{\beta}_1$ decline with increasing λ (13), as is shown in Figure 5C. Consistent with (10), when λ is large, so that $\hat{\beta}_1$ is small (11), $\hat{\beta}_0 \approx$ <ln(y)> and when λ is small, so that $\hat{\beta}_1 \approx 1$ (11), $\hat{\beta}_0 \approx -\gamma$<ln($x$)> (Figure 5B).

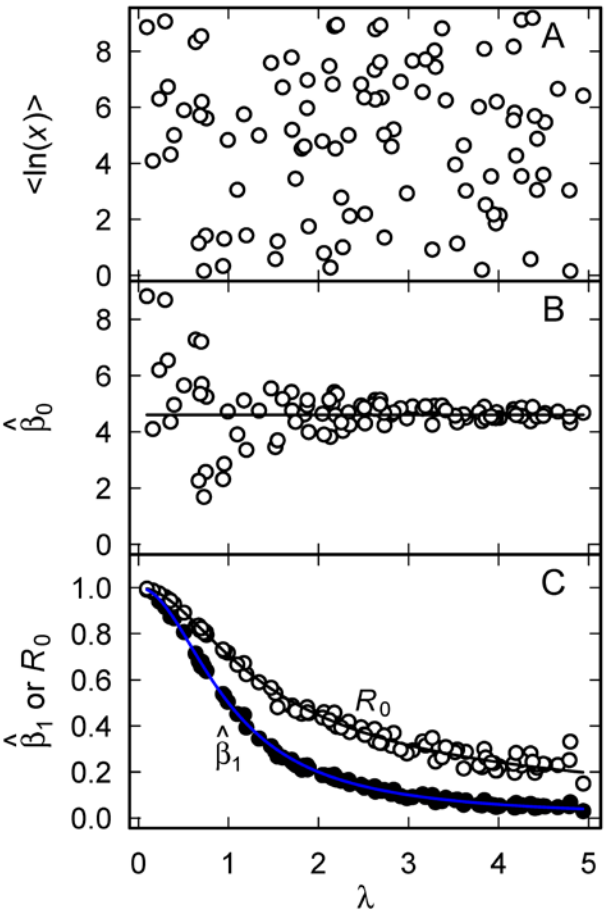

Figure 5. Relationship between λ and (A) <ln(x)>, (B) $\hat{\beta}_0$ and (C) $\hat{\beta}_1$ and R_0. Random values of μ and σ were generated from the uniform distribution to ensure even representation (A). For each value of λ 1000 lognormally distributed random values were generated for x and y. In (B) the horizontal line represents <ln(y)> and in (C) the curves are given by (13). The values of $s_{\ln(x)}$ range from 0 to 2.

V. Discussion

We have shown that the correlation (R_0) between ln(y) and ln($x^{\gamma}y$) is determined largely by the relative magnitude of $\lambda = s_{\ln(x)}/s_{\ln(y)}$ (Figure 1B). If λ is small it is inevitable that R_0 is high (it can not be low), but even if λ is larger it may be that R_0 is significant depending on γR_1 (Figure 1B). Based on this analysis, the correlation between ln([PdG]) and ln([PdG]/[Cr]) shown in Figure 3A must be high simply because $s_{\ln(Cr)}$ is small. Given this, the relationship shown in Figure 3A, which is similar to that of Roos *et al.* [7], can provide no convincing support for the idea that [PdG] is 'equivalent to' [PdG]/[Cr]. Most importantly, this relationship can *only* be strong (Figure 1B), so the fact that this is the case (R_0 = 0.855 for the data in Figure 3A) conveys no significant information: it has no bearing on the equivalence or otherwise of the two measurements of urinary PdG.

Karl Pearson [47] pointed out that correlations of the form *y versus y/x* or *y/x versus w/x*, among others, tend to be spurious and his point has been reinforced regularly ever since [48-53]. One of the best known examples of this is the correlation between the number of storks and the birth rate in a particular region which has been reported several times [54: 144-147, 55-57]. Despite the problem being well known, such analyses continue to be common [50, 51]. The relationship between ln([PdG]) and ln([PdG]/[Cr]) [7] is another example of a spurious correlation.

In essence the logarithmic transformation considered here (3) renders the correlation between y and $x^n y$ even more apparent. It is clear from (3) that the underlying relationship is just ln(y) = ln(y), but where λ is small (say $\lambda \leq 0.5$ or higher depending on γR_1, Figure 1B), it is inevitable that R_0 is high (Figures 4A and 5C), but even if λ is somewhat larger R_0 can be significant (Figures 4B and 5C). However, if λ is large R_0 tends to be small (Figures 4C and 5C). Equation (9) indicates that it is not possible to observe a low R_0 for (3) if λ is small (Figure 1B) and so it is incorrect to infer from data such as those shown in Figure 3A that [PdG] is a reasonable substitute for [PdG]/[Cr] [7]. To draw this inference is to ignore the spuriousness of the correlation. While [PdG] may be a useful measurement in some circumstances, the apparent correlation between ln([PdG]) and ln([PdG]/[Cr]) [7] does not provide any significant support for the assertion.

Our general treatment of ln(y) *versus* ln(g(x, y)) (3), as expressed in (9), includes as a particular case (γ = 1) the spurious correlation between ln([PdG]) and ln(J_{PdG}) reported by Alliende *et al.* [6]. We defer to a later date consideration of the specific relationship between J_{PdG} and [PdG]/[Cr] which has not yet been treated systematically despite the implicit assumption that they are equivalent [6, 7, 13].

VI. Conclusions

No matter how well data are analysed, if those data are flawed the analysis is also flawed. This is the case for what Pearson [47] called a “spurious” correlation. We have shown that the relationship between two measures of urinary PdG, the concentration (ln([PdG])) and the creatinine-corrected concentration (ln([PdG]/[Cr])) depends almost entirely on λ, the ratio of the standard deviations of ln([Cr]) and ln([PdG]) (9, 11). In practice, because $s_{\ln([Cr])}$is small, these two measures can *only* be highly correlated (Figure 1B) and so the fact that R_0 is high signifies nothing. Certainly, it can not be concluded from this relationship that [PdG] is as good a measure of urinary PdG as [PdG]/[Cr]. This is just one example of this class of spurious correlation, but it is a good reminder that a high correlation coefficient does not abrogate one’s responsibility to examine the data carefully.

References

[1] S. Brown, D. G. Cooke, and L. F. Blackwell, "Monitoring the menstrual cycle using urine oestrone glucuronide: the relationship between excretion rate and concentration," *International Journal of Basic Medical Sciences and Pharmacy*, submitted, 2018.

[2] S. Brown, L. F. Blackwell, and D. G. Cooke, "Online fertility monitoring: some of the issues," *International Journal of Open Information Technologies*, vol. 5, pp. 85-91, 2017. http://injoit.org/index.php/j1/article/view/414

[3] R. D. Perrone, N. E. Madias, and A. S. Levey, "Serum creatinine as an index of renal function: new insights into old concepts," *Clinical Chemistry*, vol. 38, pp. 1933-1953, 1992. http://clinchem.aaccjnls.org/content/38/10/1933

[4] T. Remer, A. Neubert, and C. Maser-Gluth, "Anthropometry-based reference values for 24-h urinary creatinine excretion during growth and their use in endocrine and nutritional research," *American Journal of Clinical Nutrition*, vol. 75, pp. 561-569, 2002. http://dx.doi.org/10.1093/ajcn/75.3.561

[5] D. B. Barr, L. C. Wilder, S. P. Caudill, A. J. Gonzalez, L. L. Needham, and J. L. Pirkle, "Urinary creatinine concentrations in the U. S. population: implications for urinary biologic monitoring measurements," *Environmental Health Perspectives*, vol. 113, pp. 192-200, 2005. http://dx.doi.org/10.1289/ehp.7337

[6] M. E. Alliende, J. A. Arraztoa, U. Guajardo, and F. Mellado, "Towards the clinical evaluation of the luteal phase in fertile women: a preliminary study of normative urinary hormone profiles," *Frontiers in Public Health*, vol. 6, pp. 147, 2018. http://dx.doi.org/10.3389/fpubh.2018.00147

[7] J. Roos, S. Johnson, S. Weddell, E. Godehardt, J. Schiffner, G. Freundl, and C. Gnoth, "Monitoring the menstrual cycle: comparison of urinary and serum reproductive hormones referenced to true ovulation," *European Journal of Contraception and Reproductive Health Care*, vol. 20, pp. 438-450, 2015. http://dx.doi.org/10.3109/13625187.2015.1048331

[8] L. F. Blackwell, D. G. Cooke, and S. Brown, "The use of estrone-3-glucuronide and pregnanediol-3-glucuronide excretion rates to navigate the continuum of ovarian activity," *Frontiers in Public Health*, vol. 6, pp. 153, 2018. http://dx.doi.org/10.3389/fpubh.2018.00153

[9] L. Blackwell, D. Cooke, and S. Brown, "Self-monitoring of fertility hormones: a new era for natural family planning?," *Linacre Quarterly*, vol. 85, pp. 26-34, 2018. http://dx.doi.org/10.1080/00243639.2017.1343222

[10] R. Ecochard and A. Gougeon, "Side of ovulation and cycle characteristics in normally fertile women," *Human Reproduction*, vol. 15, pp. 752-755, 2000. http://dx.doi.org/10.1093/humrep/15.4.752

[11] M. Desai, U. M. Donde, and M. I. Khatkhatay, "Feasibility of determination of fertile period in Indian women based on urinary hormone estimations," *Indian Journal of Clinical Biochemistry*, vol. 16, pp. 127-131, 2001. http://dx.doi.org/10.1007/BF02867582

[12] R. Ecochard, R. Leiva, T. Bouchard, H. Boehringer, A. Direito, A. Mariani, and R. Fehring, "Use of urinary pregnanediol 3-glucuronide to confirm ovulation," *Steroids*, vol. 78, pp. 1035-1040, 2013. http://dx.doi.org/10.1016/j.steroids.2013.06.006

[13] S. Johnson, S. Weddell, S. Godbert, G. Freundl, J. Roos, and C. Gnoth, "Development of the first urinary reproductive hormone ranges referenced to independently determined ovulation day," *Clinical Chemistry and Laboratory Medicine*, vol. 53, pp. 1099-1108, 2015. http://dx.doi.org/10.1515/cclm-2014-1087

[14] H. C. M. Allaway, N. I. Williams, R. J. Mallinson, K. Koehler, and M. J. de Souta, "Reductions in urinary collection frequency for assessment of reproductive hormones provide physiologically representative exposure and mean concentrations when compared with daily collection," *American Journal of Human Biology*, vol. 27, pp. 358-371, 2015. http://dx.doi.org/10.1002/ajhb.22649

[15] A. D. Papanicolaou, D. A. Adamopoulos, J. A. Loraine, and S. F. Lunn, "Studies on the urinary excretion of gonadotrophins during the normal menstrual cycle in young women," *Journal of Obstetrics and Gynaecology of the British Commonwealth*, vol. 77, pp. 961-966, 1970. http://dx.doi.org/10.1111/j.1471-0528.1970.tb03438.x

[16] A. D. Papanicolaou, J. A. Loraine, G. A. Dove, and N. B. Loudon, "Hormone excretion patterns in perimenopausal women," *Journal of Obstetrics and Gynaecology of the British Commonwealth*, vol. 76, pp. 308-316, 1969. http://dx.doi.org/10.1111/j.1471-0528.1969.tb05838.x

[17] J. Rock, G. Pincus, and C. R. Garcia, "Effects of certain 19-nor steriods on the normal human menstrual cycle," *Science*, vol. 124, pp. 891-893, 1956. http://dx.doi.org/10.1126/science.124.3227.891

[18] D. Bernstein, H. B. Frishman, S. Levin, and S. Schwartz, "The value of urinary pregnanediol estimation for monitoring early pregnancies," *Fertility and Sterility*, vol. 29, pp. 141-143, 1978. http://dx.doi.org/10.1016/S0015-0282(16)43089-X

[19] M. G. Brush, R. W. Taylor, and R. Maxwell, "Gas chromatographic determination of urinary pregnanediol in toxaemia of pregnancy and suspected dysmaturity," *Journal of Obstetrics and Gynaecology of*

the British Commonwealth, vol. 73, pp. 954-960, 1966. http://dx.doi.org/10.1111/j.1471-0528.1966.tb06119.x

[20] J. M. Cruickshank, R. Morris, W. R. Butt, and C. S. Corker, "Inter-relationships between levels of plasma oestradiol, urinary total oestrogens and blood haemoglobin and neutrophil counts," *Journal of Obstetrics and Gynaecology of the British Commonwealth*, vol. 79, pp. 450-454, 1972. http://dx.doi.org/10.1111/j.1471-0528.1972.tb14183.x

[21] O. A. Dada and B. Kwaku Adadevoh, "Total urinary oestrogen excretion during normal menstrual cycle and normal pregnancy in Nigerians," *British Journal of Obstetrics and Gynaecology*, vol. 82, pp. 40-43, 1975. http://dx.doi.org/10.1111/j.1471-0528.1975.tb00561.x

[22] W. P. Dmowski, R. Rao, and A. Scommegna, "The luteinized unruptured follicle syndrome and endometriosis," *Fertility and Sterility*, vol. 33, pp. 30-34, 1980. http://dx.doi.org/10.1016/S0015-0282(16)44473-0

[23] C. B. Coulam, L. M. Hill, and R. Breckle, "Ultrasonic assessment of subsequent unexplained infertility after ovulation induction," *British Journal of Obstetrics and Gynaecology*, vol. 90, pp. 460-467, 1983. http://dx.doi.org/10.1111/j.1471-0528.1983.tb08945.x

[24] H. Adlercreutz, O. Jänne, T. Laatikainen, B. Lindstrom, T. Luukkainen, and R. Vihko, "Studies on conjugated mono- and dihydroxy metabolites of progesterone in plasma, bile and urine in a human subject," *Bulletin der Schweizerischen Akademie der Medizinischen*, vol. 25, pp. 328-336, 1969. http://dx.doi.org/10.5169/seals-307774

[25] L. F. Blackwell, P. Vigil, M. E. Alliende, S. Brown, M. Festin, and D. G. Cooke, "Monitoring of ovarian activity by measurement of urinary excretion rates using the Ovarian Monitor, part IV: the relationship of the pregnanediol glucuronide threshold, basal body temperature and cervical mucus as markers for the beginning of the post-ovulatory infertile period," *Human Reproduction*, vol. 31, pp. 445-453, 2016. http://dx.doi.org/10.1093/humrep/dev303

[26] T. S. Baker, K. Jennison, and A. E. Kellie, "A possible method for the detection of ovulation and the determination of the duration of the fertile period," *Journal of Steroid Biochemistry*, vol. 12, pp. 411-415, 1980. http://dx.doi.org/10.1016/0022-4731(80)90300-3

[27] B. R. Goldin, H. Adlercreutz, S. L. Gorbach, M. N. Woods, J. T. Dwyer, T. Conlon, E. Bohn, and S. N. Gershoff, "The relationship between estrogen levels and diets of Caucasian American and Oriental immigrant women," *American Journal of Clinical Nutrition*, vol. 44, pp. 945-953, 1986. http://dx.doi.org/10.1093/ajcn/44.6.945

[28] R. D. Bulbrook, M. C. Swain, D. Y. Wang, J. L. Hayward, S. Kumaoka, O. Takatani, O. Abe, and J. Utsunomiya, "Breast cancer in Britain and Japan: plasma, oestradiol-17β, oestrone and progesterone, and their urinary metabolites in normal British and Japanese women," *European Journal of Cancer*, vol. 12, pp. 725-735, 1976. http://dx.doi.org/10.1016/0014-2964(76)90023-2

[29] M.-F. Jayle, "Excrétion des stéroïdes urinaires après administration de gonadotrophines chorioniques au cours du cycle menstruel," *Comptes rendus des séances de la Société de biologie et de ses filiales*, vol. 150, pp. 1351-1355, 1956.

[30] R. Borth, B. Lunenfeld, and H. de Watteville, "Day-to-day variation in urinary gonadotrophin and steroid levels during the normal menstrual cycle," *Fertility and Sterility*, vol. 8, pp. 233-254, 1957. http://dx.doi.org/10.1016/S0015-0282(16)61356-0

[31] D. Stern, "Pregnanediol estimation: a rapid pregnancy test suitable for routine use," *Journal of Obstetrics and Gynaecology of the British Empire*, vol. 58, pp. 821-825, 1951. http://dx.doi.org/10.1111/j.1471-0528.1951.tb04062.x

[32] M. G. Coyle, F. L. Mitchell, and C. S. Russell, "A report on the chromatographic assay of urinary pregnanediol in pregnancy," *Journal of Obstetrics and Gynaecology of the British Empire*, vol. 63, pp. 560-566, 1956. http://dx.doi.org/10.1111/j.1471-0528.1956.tb05532.x

[33] P. M. Wray and C. Scott Russell, "An investigation into the reliability of short specimens of urine for estimating daily pregnanediol excretion," *Journal of Obstetrics and Gynaecology of the British Empire*, vol. 64, pp. 526-530, 1957. http://dx.doi.org/10.1111/j.1471-0528.1957.tb06282.x

[34] J. B. Brown, R. Kellar, and G. D. Matthew, "Preliminary observations on urinary oestrogen excretion in certain gynaecological disorders," *Journal of Obstetrics and Gynaecology of the British Empire*, vol. 66, pp. 177-211, 1959. http://dx.doi.org/10.1111/j.1471-0528.1959.tb01999.x

[35] J. B. Brown, P. Harrisson, and M. A. Smith, "Oestrogen and pregnanediol excretion through childhood, menarche and first ovulation," *Journal of Biosocial Science*, vol. 10, pp. 43-62, 1978. http://dx.doi.org/10.1017/S0021932000024068

[36] E. L. G. Beavis, J. B. Brown, and M. A. Smith, "Ovarian function after hysterectomy with conservations of the ovaries in pre-menopausal women," *Journal of Obstetrics and Gynaecology of the British Commonwealth*, vol. 76, pp. 969-978, 1969. http://dx.doi.org/10.1111/j.1471-0528.1969.tb09462.x

[37] D. G. Campbell, J. B. Brown, D. W. Fortune, R. Pepperell, and N. A. Beischer, "Excretion of oestrogens, pregnanediol and chorionic gonadotrophin in patients with hydatiform mole," *Journal of Obstetrics and Gynaecology of the British Commonwealth*, vol. 77, pp. 410-419, 1970. http://dx.doi.org/10.1111/j.1471-0528.1970.tb03542.x

[38] E. T. Bell, J. B. Brown, K. Fotherby, and J. A. Loraine, "Effect of a derivative of dithiocarbamoylhydrazine on hormone excretion during the menstrual cycle," *Lancet*, vol. 2, pp. 528-530, 1962. http://dx.doi.org/10.1016/S0140-6736(62)90401-4

[39] T. J. A. Key, D. Y. Wang, J. B. Brown, C. Hermon, D. S. Allen, J. W. Moore, R. D. Bulbrook, I. S. Fentiman, and M. C. Pike, "A prospective study of urinary oestrogen excretion and breast cancer risk," *British Journal of Cancer*, vol. 73, pp. 1615-1619, 1996. http://dx.doi.org/10.1038/bjc.1996.304

[40] J. B. Brown, "Types of ovarian activity in women and their significance: the continuum (a reinterpretation of early findings)," *Human Reproduction Update*, vol. 17, pp. 141-158, 2011. http://dx.doi.org/10.1093/humupd/dmq040

[41] L. F. Blackwell, J. B. Brown, P. Vigil, B. Gross, S. Sufi, and C. d'Arcangues, "Hormonal monitoring of ovarian activity using the Ovarian Monitor, part I. Validation of home and laboratory results obtained during ovulatory cycles by comparison with radioimmunoassay," *Steroids*, vol. 68, pp. 465-476, 2003. http://dx.doi.org/10.1016/S0039-128X(03)00049-7

[42] L. F. Blackwell, P. Vigil, D. G. Cooke, C. d'Arcangues, and J. B. Brown, "Monitoring of ovarian activity by daily measurement of urinary excretion rates of estrone glucuronide and pregnandediol glucuronide using the Ovarian Monitor, part III: Variability of normal menstrual cycle profiles," *Human Reproduction*, vol. 28, pp. 3306-3315, 2013. http://dx.doi.org/10.1093/humrep/det389

[43] L. F. Blackwell, P. Vigil, B. Gross, C. d'Arcangues, D. G. Cooke, and J. B. Brown, "Monitoring of ovarian activity by measurement of urinary excretion rates of estrone glucuronide and pregnanediol glucuronide using the ovarian monitor, part II: reliability of home testing," *Human Reproduction*, vol. 27, pp. 550-557, 2012. http://dx.doi.org/10.1093/humrep/der409

[44] E. J. Dudewicz and S. N. Mishra, *Modern mathematical statistics*. New York: John Wiley and Sons, Inc., 1988.

[45] S. A. Barrett and J. B. Brown, "An evaluation of the method of Cox for the rapid analysis of pregnanediol in urine by gas-liquid chromatography," *Journal of Endocrinology*, vol. 47, pp. 471-480, 1970. http://dx.doi.org/10.1677/joe.0.0470471

[46] S. Brown, "The distribution of phoneme inventory and language evolution," *Cultural Anthropology and Ethnosemiotics*, vol. 3, pp. 22-34, 2017. https://researchonline.jcu.edu.au/52485/

[47] K. Pearson, "Mathematical contributions to the theory of evolution. On a form of spurious correlation which may arise when indices are used in the measurement of organs," *Proceedings of the Royal Society of London*, vol. 60, pp. 489-498, 1897. http://dx.doi.org/10.1098/rspl.1896.0076

[48] W. R. Atchley, C. T. Gaskins, and D. Anderson, "Statistical properties of ratios. I. Empirical results," *Systematic Zoology*, vol. 25, pp. 137-148, 1976. http://dx.doi.org/10.2307/2412740

[49] J. A. Berges, "Ratios, regression statistics, and "spurious" correlations," *Limnology and Oceanography*, vol. 42, pp. 1006-1007, 1997. http://dx.doi.org/10.4319/lo.1997.42.5.1006

[50] J. M. Tanner, "Fallacy of per-weight and per-surface area standards and their relation to spurious correlation," *Journal of Applied Physiology*, vol. 2, pp. 1-15, 1949. http://dx.doi.org/10.1152/jappl.1949.2.1.1

[51] R. A. Kronmal, "Spurious correlation and the fallacy of the ratio standard revisited," *Journal of the Royal Statistical Society*, vol. 156A, pp. 379-392, 1993. http://dx.doi.org/10.2307/2983064

[52] M. R. Neifeld, "A study of spurious correlation," *Journal of the American Statistical Association*, vol. 22, pp. 331-338, 1927. http://dx.doi.org/10.1080/01621459.1927.10502965

[53] W. Schlager, D. Marsal, P. A. G. van der Geest, and A. Sprenger, "Sedimentation rates, observation span, and the problem of spurious correlation," *Mathematical Geology*, vol. 30, pp. 547-556, 1998. http://dx.doi.org/10.1023/A:1021742228242

[54] J. Neyman, *Lectures and conferences on mathematical statistics and probability*, 2nd ed. Washington: Graduate School, U S Department of Agriculture, 1952. http://hdl.handle.net/2027/mdp.39015007297982

[55] H. Sies, "A new parameter for sex education," *Nature*, vol. 332, pp. 495, 1988. http://dx.doi.org/10.1038/332495a0

[56] R. Matthews, "Storks deliver babies (*p* = 0.008)," *Teaching Statistics*, vol. 22, pp. 36-38, 2000. http://dx.doi.org/10.1111/1467-9639.00013

[57] T. Höfer, H. Przyrembel, and S. Verleger, "New evidence for the theory of the stork," *Paediatric and Perinatal Epidemiology*, vol. 18, pp. 88-92, 2004. http://dx.doi.org/10.1111/j.1365-3016.2003.00534.x