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Letter to the Editor

Between-subject variation of the within-subject biological variation

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Recently, the European Federation of Clinical Chemistry Laboratory Medicine (1), within the frame of its Science Committee, has created a working group (WG) on biological variation. In its website (2), this WG describes its structure and its purpose ("Terms for reference"). Some members of this WG and other authors published a very interesting systematic review of data on biological variation for the catalytic concentrations of three enzymes in serum (3). Among other conclusions, the authors stated that published biological variation data for the three enzymes studies demonstrate a wide range of values derived from inconsistent protocols, and also stated that the findings in their review raise concerns around the utility of the data currently available. Examples of publications with these biological variation data are given in references (4) and (5).

I agree absolutely with the conclusions raised by the authors of the systematic review. Nevertheless, may I add some opinion and some objective data that can reinforce the information given by the authors of the systematic review.

In my opinion, the main factor that hampers the use of data of within-subject biological variation for the proposed (by the review's authors) purposes is the between-subject variation affecting these kind of data. And consequently, a doubt must be cast upon the general application of the usual point estimations of within-subject biological variation, usually expressed as a single value of coefficient of variation.

This opinion is based in my own experience. Some years ago I was doctoral supervisor (dissertation director), working on within-subject biological variation observed during one year (6, 9). These dissertations generated seven articles of different types published in well recognized international scientific journals (10-16). The information shown in Table 1 comes from these dissertations and articles.

Table 1 shows the number of healthy adult volunteers involved in each study. In all these studies, blood was collected once a month for one year, and only one measurement per sample was performed. Measurements were done the same day of blood collection. For each volunteer, no outliers were detected (simply Dixon statistical test) after pooling the twelve measured values. For each biological quantity, variance corresponding to day-to-day imprecision of the corresponding measuring system, used according a given measurement procedure, was subtracted to the total within-subject variance to obtain the within-subject biological variance (plus the pre-metrological variance, when it is not zero).

Bearing in mind that in each study all the volunteers were treated in the same way, lowest and highest individual coefficients of variation corresponding to the within-subject biological variances shown in Table 1 indicate that standardization of all processes concerned with the estimation on the within-subject biological variance is not sufficient to obtain point estimates (single values) of within-subject biological coefficients of variation which could be useful for the purposes proposed elsewhere. Furthermore, for each biological quantity, when the highest coefficient of variation is greater than 33 %, we can admit that the probability distribution function of the individual coefficients of variation is asymmetric.

Table 1
Biological quantities and references, number of volunteers involved in each study (n), median, lowest and highest values of the coefficients of variation corresponding to the within-subject biological variation (CVBw) (6-9, 10-16). [Biological quantities are described according to the IFCC and IUPAC recommendations (17)]

Biological quantity (and references)	n	Median of CV_{Bw}	Lowest CV_{Bw}	Highest CV_{Bw}
P—Alanine aminotransferase; cat.c. (6)	20	27.7	< 0.1	68.8
Prot.(S)—Albumin; mass fr. (6, 10)	20	4.1	< 0.1	6.9
P—Alkaline phosphatase; c.con. (6)	20	8.2	2.5	24.1
P—α-Amylase; cat.c. (6)	20	8.4	< 0.1	17.0
P—Aspartate aminotransferase; cat.c. (6)	20	16.0	< 0.1	31.6
P—Bilirubin; subst.c. (6)	20	28.9	8.7	43.9
P—Calcium(II); subst.c. (6)	20	2.0	< 0.1	4.1
P—Chloride; subst.c. (6)	20	1.6	< 0.1	3.6
P—Creatine kinase; cat.c. (6)	20	20.0	12.0	49.6
P—Creatininium; subst.c. (6)	20	6.7	1.5	15.7
Prot.(S)—α1-Globulin; mass fr. (6, 10)	20	9.6	< 0.1	35.4
Prot.(S)—α2-Globulin; mass fr. (6, 10)	20	10.4	3.4	17.2
Prot.(S)—β-Globulin; mass fr. (6, 10)	20	9.6	5.3	19.9
Prot.(S)—γ-Globulin; mass fr. (6, 10)	20	11.2	< 0.1	28.3
P—Glucose; subst.c. (6)	20	5.0	2.1	7.0
P—γ-Glutamyltransferase; cat.c. (6)	20	30.1	11.7	63.4
P—Iron(II+III); subst.c. (6)	20	21.6	13.5	36.6
P—Lactate dehydrogenase; cat.c. (6)	20		< 0.1	11.3
P—Phosphate(inorganic); subst.c. (6)	20	8.6	19.3	1.3
P—Potassium ion; subst.c. (6)	20	5.0	1.0	7.7
P—Protein; mass c. (6)	20	3.1	1.6	8.0
P—Sodium ion; subst.c. (6)	20	0.1	< 0.1	1.6
P—Thyrotropin; arb.subst.c. (6)	20	29.6	9.9	46.9
P—Thyroxine; subst.c. (6, 11)	20	8.2	< 0.1	14.4
P—Triiodothyronine; subst.c. (6, 11)	20	9.8	< 0.1	16.6
P—Urate; subst.c. (6)	20	10.2	6.4	23.8
P—Urea; subst.c. (6)	20	13.5	5.0	22.7
P—Cholesterol; subst.c. (7, 15)	40	6.9	2.2	11.0
P—HDL-Cholesterol; subst.c. (7, 15)	40	7.1	3.1	13.5
P—LDL-Cholesterol; subst.c. (7, 15)	40	13.3	6.7	29.0
P—Triglyceride; subst.c. (7, 15)	40	16.7	9.9	36.3
P—Apolipoprotein A-I; mass c. (7, 15)	40	6.4	< 0.1	22.9
P—Apolipoprotein B; mass c. (7, 15)	40	13.5	6.0	27.3
P—Coagulation, tissue factor-induced; rel.time (8, 12)	39	1.7	< 0.1	11.7
P—Coagulation, surface-induced; rel.time (8, 12)	39	< 0.1	< 0.1	8.4
B—Erythrocytes; entitic vol. (8, 13)	39	1.1	0.2	1.8
B—Erythrocytes; num.c. (8, 13)	39	2.8	1.6	5.7
B—Erythrocytes; vol.fr. (8, 13)	39	2.7	1.3	6.0
B—Haemoglobin; mass c. (8, 13)	39	2.7	1.2	5.5
B—Leukocytes; num.c. (8, 13)	39	12.2	3.5	32.3
Lkcs(B)—Lymphocytes; num.fr. (8, 14)	39	< 0.1	< 0.1	23.1
Lkcs(B)—Neutrophils; num.fr. (8, 14)	39	8.6	< 0.1	24.6
B—Thrombocytes; num.c. (8, 13)	39	7.5	< 0.1	16.7
P—Follitropin; arb.subst.c. (9, 16)	20	17.3	6.1	42.9
P—Lutropin; arb.subst.c. (9, 16)	20	24.0	8.9	47.3
P—Testosterone; subst.c. (9, 16)	20	10.9	0.0	21.8

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