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Application of multivariate analysis to height-weight comparisons of normal children and children with cystic fibrosis

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With 2 tables

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Recently, WEIHOFEN and PRINGLE (1) compared the heights and weights of 36 children with cystic fibrosis with the heights and weights of 30 normal children, by means of Z-scores (2), which theoretically remove the effect of sex and age of each child. The W-P paper showed that the CF children are both significantly shorter and significantly lighter than the normal children at a high level of significance. However, it is generally regarded that heights and weights of CF children are below those of normal children. In particular, SPROUL and HUANG (3) found significant retardation of physical growth in all age periods.

In fact, it would be expected that chronically sick children have both height and weight significantly less than normal children. The problem we believe of interest is whether or not the CF children have had their height-weight growth distorted, and we will mathematically define exactly what we mean by distortion. We believe that any chronically ill children probably will have their height-weight growth retarded, and that any ill child could possibly recover what he has lost more readily if his growth is uniformly retarded, as a prematurely born infant can reach full height-weight proportions.

In our discussion, we correct several calculation errors of the W-P paper, and make several comments about their analyses. Also, we comment on the inability to obtain raw data referred to in their article.

Methods

Since it would be expected that heights-H and weights-W of children be highly correlated, then it is clear that any analysis involving them could have greatly improved accuracy, by taking advantage of this correlation. We would similarly expect the Z-scores for heights and weights also to be highly correlated. Using subscripts CF and N to denote children with cystic fibrosis and normal children, respectively, we have the following notation.

$Z_{H,\,CF}$: the mean Z-score for the height of a child with cystic fibrosis.

$Z_{W,\,CF}$: the mean Z-score for the weight of a child with cystic fibrosis.

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$Z_{H,\,N}$: the mean Z-score for the height of a normal child.
$Z_{W,N}$: the mean Z-score for the weight of a normal child.

We would ask how does the pair ($Z_{H,\,CF}$, $Z_{W,\,CF}$) for CF children compare with the pair ($Z_{H,\,N}$, $Z_{W,\,N}$) for normal children. It was shown by WEIHOFEN and PRINGLE (see our comment (4)) that the tests

of $H_0: Z_{H,\,CF} = Z_{H,\,N}$ versus $H_1: Z_{H,\,CF} < Z_{H,\,N}$

and $H_0: Z_{W,\,CF} = Z_{W,\,N}$ versus $H_1: Z_{W,\,CF} < Z_{W,\,N}$

both resulted in rejecting H_0 at high levels of significance. However, as we have pointed out, it would be expected that most any chronically ill children be shorter and lighter than healthy (normal) children.

Let us define now what we mean by distortion. If the Z-scores of heights and weights of CF children could be shifted in some uniform way, then we would say that their growth has not been warped, only retarded symmetrically. Hence, we will say that distortion has not occurred if there exists some number d such that if d is added to both the Z-scores for height and weight of CF children, the results equal the Z-scores for height and weight of normal children. In other words, retardation has been symmetric if the CF children's Z-scores be shifted below the normals' by an amount d. Therefore, the appropriate statistical test to be made would be as follows.

$$H_0: Z_{H,\,CF} + d = Z_{H,\,N} \text{ and } Z_{W,\,CF} + d = Z_{W,\,N}$$

versus

H_1: all possible alternatives to H_0.

The above hypotheses involve a multivariate statistical procedure based on the multivariate normal distribution. The appropriate statistic for testing this H_0 versus H_1 will be derived from the likelihood ratio criterion. The shift parameter d will be estimated by d*, determined from the method of maximum likelihood, and the asymptotic (approximating) distribution of d* presented. These theoretical procedures are standardized in ANDERSON (4), and the applied derivations are presented in the following section.

The multivariate test of H_0 resulted in an observed chi-square statistic with one degree of freedom equal to 0.0569 which is not significant at the 95% level of significance. Therefore, the observed heights and weights of CF children appear not to be significantly distorted from heights and weights of normal children. We therefore accept the hypothesis H_0.

Mathematical derivations

In order to maintain generality, we assume that two populations are to be studied, namely $\underline{X}$ (corresponding to the normal children) and $\underline{Y}$ (corresponding to the children with cystic fibrosis. The $\underline{X}$ and $\underline{Y}$ are vectors, where $\underline{X} = (X_1, X_2 \ldots, X_p)$ and $\underline{Y} = (Y_1, Y_2, \ldots, Y_p)$. We suppose that $\underline{X}$ is normally distributed with mean vector equal to $\underline{a} = (a_1, a_2, \ldots, a_p)$ and variance-covariance matrix $G = (g_{ij})$, where g_{ij} = covariance (X_i, X_j). Similarly, $\underline{Y}$ is normally distributed with mean vector equal to $\underline{b} = (b_1, b_2, \ldots, b_p)$ and the same variance-covariance matrix as $\underline{X}$, namely G. In our particular application, p equals 2, and a_1, b_1 and a_2, b_2 correspond to heights and weights, respectively.

Samples of size m are taken from $\underline{X}$, and size n from $\underline{Y}$. The matrices of observations would be (x_{ij}): $p \times m$ and (y_{ij}): $p \times n$, and define $\underline{\bar{x}} = (\bar{x}_1, \bar{x}_2, \ldots, \bar{x}_p)$, $\underline{\bar{y}} = (\bar{y}_1, \bar{y}_2, \ldots, \bar{y}_p)$ to be the vectors of means, where for example $\bar{x}_1 = m^{-1}(x_{11} + x_{12} + \ldots$

$+ x_{1m}$). Let $A = (A_{ij})$ and $B = (B_{ij})$ be the product moment matrices for $\underline{X}$ and $\underline{Y}$, respectively, where for example,

$$A_{12} = m^{-1} \sum_{i=1} (x_{1i} - \bar{x}_1)(x_{2i} - \bar{x}_2),$$

and let $C = mA + nB$. Then $(\bar{\underline{x}}, \bar{\underline{y}}, C)$ is a sufficient statistic for $(\underline{a}, \underline{b}, G)$, and it follows that the joint density $\bar{\underline{x}}, \bar{\underline{y}}, C$ is

$$f(\bar{\underline{x}}, \bar{\underline{y}}, C; \underline{a}, \underline{b}, J) = k \mid J \mid^{M/2} \exp\left\{ -1/2 \left[m(\bar{\underline{x}} - \underline{a})J(\bar{\underline{x}} - \underline{a})' + n(\bar{\underline{y}} - \underline{b})J(\bar{\underline{y}} - \underline{b})' + \text{trace } (JC)\right] \right\},$$

where $J = G^{-1}$, $M = m + n$, and k is a constant.

It is commonly known that the maximum likelihood estimates for unrestricted $\underline{a}, \underline{b}, J$ are

$$\underline{a}^* = \bar{\underline{x}},\ \underline{b}^* = \bar{\underline{y}},\ J^* = MC^{-1}$$

and that

$$\underset{\underline{a}, \underline{b}, J}{\text{maximum}}\ f(\bar{\underline{x}}, \bar{\underline{y}}, C; \underline{a}, \underline{b}, J) = k \mid MC^{-1} \mid^{M/2} e^{-pM/2}.$$

Then, it can be shown that for $\underline{d} = (d, d, \ldots, d)$ and $\underline{a} = \underline{b} + \underline{d}$, the maximum likelihood estimates for $\underline{b}, \underline{d}, J$ are

$$\underline{b}^* = (m\bar{\underline{x}} + n\bar{\underline{y}} - m\underline{d}^*)/M,\ d^* = IC^{-1}(\bar{\underline{x}} - \bar{\underline{y}})'/IC^{-1}I',\ J^* = MC^{-1}$$

where $I = (1, 1, \ldots, 1)$: $1 \times p$ so that for $Q = C^{-1} - C^{-1}I'IC^{-1}/IC^{-1}I'$,

$$\underset{\underline{b}, \underline{d}, J}{\text{maximum}}\ f(\bar{\underline{x}}, \bar{\underline{y}}, C; \underline{b} + \underline{d}, \underline{b}, J) = k \mid MC^{-1} \mid^{M/2} e^{-pM/2}[1 + mnM^{-1}(\bar{\underline{x}} - \bar{\underline{y}})$$
$$Q(\bar{\underline{x}} - \bar{\underline{y}})']^{-M/2}.$$

Hence, it follows that the likelihood ratio test of $H_o: \underline{a} = \underline{b} + \underline{d}$ is $L^{-2/M} = 1 + mnM^{-1}(\bar{\underline{x}} - \bar{\underline{y}})\, Q\, (\bar{\underline{x}} - \bar{\underline{y}})'$, and rejects H_o if $-2 \log_e L$, being asymptotically chi-square distributed with p-1 degrees of freedom, be significantly large. It can be shown also that d^* is asymptotically normally distributed with mean d and variance $M/mnI\, G^{-1}I'$, approximated by $(mnIC^{-1}I')^{-1}$. Furthermore, asymptotically $\underline{b}^*, \underline{b}^* + \underline{d}^*$ are each multivariate normally distributed with means $\underline{b}, \underline{b} + \underline{d}$ and variance-covariance matrices $m^{-1}G, n^{-1}G$, respectively.

The data from the WEIHOFEN-PRINGLE paper is presented in table 1 (see our comment (1)). It is assumed that the matrix A is identical to that of B, since the former is not available. Also, we must accept the result that $\bar{\underline{x}} = (0.58, 0.09)$, (see our comment (2)). By numerical calculation, it follows that $\bar{\underline{y}} = (-1.0939, -1.6614)$,

$$C = \begin{bmatrix} 181.09310 & 109.78459 \\ 109.78459 & 152.45052 \end{bmatrix}$$

$$C^{-1} = \begin{bmatrix} 0.00980069 & -0.00705780 \\ -0.00705780 & 0.01164205 \end{bmatrix}$$

$$Q = \begin{bmatrix} 0.00877390 & -0.00877390 \\ -0.00877390 & 0.00877390 \end{bmatrix}$$

and $-2 \log_e L = 0.0569$. Since H_o is not rejected, it is meaningful to calculate d^*, and it follows that $d^* = 1.7224$ with an estimated standard deviation of 0.3559.

Discussion

We have several specific comments concerning the WEIHOFEN-PRINGLE paper, and these are presented as follows.

(1). We requested the original data for height, weight, height-Z, and weight-Z for normal children, since this information was not published in the WEIHOFEN-

PRINGLE paper, and were told by Mrs. WEIHOFEN that she „must have discarded this material". This points out the necessity of publishing raw data in scientific articles and if this is not feasible (which is not the case in this situation), then the authors must maintain a file of the data and records of all calculations involved. There is no such thing as the perfect analysis, since time may bring more appropriate statistical methodological sophistication, or a better understanding of the process, and it must be possible to restudy the results.

Table 1. Caloric, protein, and iron intake, height and weight of thirty-six children with cystic fibrosis (Reprinted from WEIHOFEN and PRINGLE)

AGE		Per cent of the 1964 recommended dietary allowance			Standard Deviation from mean	
Years	Months	Calories	Protein	Iron	Height	Weight
4	7	296	310	160	0	—2.00
1	10	221	314	500	—3.00	—1.60
3	8	193	299	155	—0.06	0.25
4	3	189	231	100	—1.00	—0.60
16	6	186	274	126	—0.20	—1.36
2	11	182	225	65	—1.33	—0.62
5	2	175	154	85	—1.00	—1.40
23	7	175	193	150	0	—2.72
8	11	171	212	100	—4.00	—4.25
5	8	164	228	100	0	—2.00
	8	164	357	191	—4.25	—4.25
3	9	161	185	94	—0.50	—2.30
3	0	155	345	145	—5.50	—3.60
3	11	143	210	88	—1.00	—1.66
14	0	138	212	118	—1.20	—1.61
2	6	135	184	86	0	—0.66
3	3	133	187	75	—0.50	0.25
3	7	126	213	66	1.33	0.66
6	4	124	166	87	0	—1.60
6	0	118	172	72	—1.66	—1.20
4	10	112	203	81	—1.33	—1.25
17	10	111	180	90	0.33	—1.38
4	0	111	144	62	0	—0.77
	7	109	328	43	—0.50	—1.95
9	8	108	200	90	—1.00	—2.00
2	7	107	231	140	2.00	2.29
1	0	96	240	156	—2.75	—0.12
13	5	94	223	97	0	—1.20
1	11	91	152	78	—3.00	—4.50
14	2	89	112	60	—0.60	—1.85
7	0	89	146	60	—2.00	—5.00
3	7	86	140	66	—4.66	—3.25
9	6	79	192	72	—2.50	—2.12
7	1	72	149	48	0	—3.33
14	5	63	78	57	—0.50	—1.36
6	1	59	127	55	1.00	0.25

Table 2. Heights and weights of normal children and children with cystic fibrosis as given in standard Z-scores (Reprinted from WEIHOFEN and PRINGLE with corrections)

	Measurement	Mean
Height		
	Normal children	0.58 ± 1.37*
	Children with cystic fibrosis	—1.09 ± 1.68
Weight		
	Normal children	0.09 ± 1.07
	Children with cystic fibrosis	—1.66 ± 1.54

*) Estimated standard deviation of an individual observation.

(2). There were several errors of computation. In three of the four numbers of their table 2 that we were able to check, there were errors, and we present a corrected table 2. The standard deviations are calculated the usual way, by dividing by the number of observations minus one. Since it was not possible to obtain the original data for normal children from W-P, we were unable to check more than four of the eight numbers of table 2. Similarly, it has not been possible to check any of the Z-scores that were reported in table 1.

(3). Under W-P's *Results and Recommendations* we make the following corrections.

Second paragraph: change 98% to 97%, 36% to 28%

Third paragraph: change 84% to 77%

(4). In the fourth paragraph of W-P's *Results and Recommendations* two tests are performed, but it was not clear what were the alternative hypotheses. It would seem unreasonable to test that the heights of normal children equal that of CF children versus not equal heights, since CF children could not be expected to be taller than normal ones; the same should be the case for weights. Therefore, the appropriate test is one-tailed, namely equality versus CF children shorter or lighter. Furthermore, for the record the statistics involed for height and weight were each t with 64 degrees of freedom.

(5). For many types of statistical analyses, such as when differences or quotients are examined, it is necessary to have the same number of controls (normals) as the study group (CFs), but in the W-P study there were 36 CFs, and only 30 normals. Furthermore, it is usually desirable and sometimes critical to have the same, proportionately balanced, information for all the groups under consideration. As a protection to the experimenter, it would be highly advisable that there be the same number of CFs as normals in the experimental design. We further doubt the soundness of selecting a „normal" group of children from „the well-baby and family clinic sponsored by the University Hospitals". No mention is made of the lack of independence due to familial relationships, and there is no way to compare the balance of ages and sex for the CFs and normals.

The method we have presented is considerably more general than just comparisons of heights and weights. For instance, it could be tested whether the % recommended dietary allowance (5) of (Calories_{CF}, Protein_{CF}, Iron_{CF}) for CF children is distorted, in the sense we have defined distortion, from the % recommended dietary allowance of (Calories_{N}, Protein_{N}, Iron_{N}) for normal children, and the amount of d-shift involved can be calculated and a confidence interval given.

In the situation when it is possible to consider children of the same age and sex, or in certain cases when normals have been matched, the appropriate model might test $H_0: a = cb$ for some scalar c versus all alternatives, which is studied by KRAFT, OKLIN and VAN EEDEN (6). With this model, the shift is multiplied, and not added.

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Summary

Recently, WEIHOFEN and PRINGLE compared, by means of „Z-scores", the heights and weights of 36 children with cystic fibrosis with the heights and weights of 30 „normal" children, finding that indeed the sick children were both significantly shorter and significantly lighter than healthy ones. However, it would be expected that this be the case, and for that reason, we ask and answer, by means of multivariate statistical theory, whether the height-weight growth in normal children has been not just retarded, but distorted. That is, if growth has been retarded, as could be the case with any ill child regardless of the illness, he could possibly recover what he has lost more readily if his growth is uniformly retarded, as a prematurely born infant can reach full height-weight proportions. Of course, we define mathematically exactly what we mean by the term „distortion".

Next, we correct several calculation errors of WEIHOFEN and PRINGLE and point out the necessity of publishing the raw data. That is, we wrote Mrs. WEIHOFEN for the original data for normal children and were told that she „must have discarded" it. Since not all data is available, it cannot be reviewed for accuracy, and we must make an approximation, which we explain, in order to apply our multivariate statistical procedure. However, we do not feel that the approximation will seriously affect the results, and, in any case, it affords an opportunity to demonstrate the method.

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