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Repetitive health examinations as an intervention measure

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A cohort of 107 men aged 51–53 years with borderline levels of blood pressure, serum cholesterol, or glucose tolerance was recruited from a general population in central Zagreb, Yugoslavia, and randomized into two groups; one was treated with drugs and the other observed in a similar fashion but not treated. Ninety-five men appeared regularly for the check-ups over a 2-year period. Levels of systolic blood pressure, cholesterol, and glucose showed a substantial decrease over a period of 2 years in both treated and control groups. The possible effect of repeated check-ups and their implications are discussed.

Many intervention population studies (or trials) have been completed or are in progress, e.g., in the field of cardiovascular disease, which attempt to evaluate the effectiveness of various measures such as change of habits, cessation of smoking, dietary modifications, or drug treatment on disease incidence in a population.[a] These studies commonly use repeated health examinations of the population under study to assess the effect of the intervention measure. In so doing the studies measure levels of disease or levels of relevant characteristics in both treated and control groups or, if it is not a controlled trial, before and after an intervention. What is often overlooked, or at least not taken sufficiently into consideration in the evaluation of the results of such studies, is the effect of the repeated examinations themselves on the population in terms of modifying its risk factor levels or disease levels by means other than the intervention measures being particularly studied.

Conducting a feasibility study of multifactor prevention of ischaemic heart disease and stroke by drug treatment in Zagreb, Yugoslavia, we tried to assess the effect of repetitive examinations of the study population on its risk factor levels, such as blood pressure, serum cholesterol, and glucose tolerance.

METHODS

The design of, and methods used in, the Zagreb preliminary study are described in detail elsewhere; here we merely summarize briefly the methods relevant to this report.

A group of 601 males aged 51–53 years, representative of the male population in this age group, living in a geographically defined central part of Zagreb, Yugoslavia, and staying in Zagreb during the 3 months of the screening period, were invited for screening examinations, the aim being to select for trial a cohort of men with borderline levels of blood pressure, and/or serum cholesterol, and/or glucose tolerance on any 2 out of 3 occasions. The cut-off points for the borderline range, fixed after consultation with local cardiologists, were: a systolic blood pressure of 160–189 mm Hg and/or a diastolic pressure of 95–114 mm Hg (the average of two consecutive measurements with the subject in the sitting position), a fasting serum cholesterol level of 261–350 mg per 100 ml determined by the method of Abell et al. (1), and a plasma glucose level of 121–160 mg per 100 ml, determined by the glucose oxidase method (7) 2 hours after 50 g [b] load.

The number of subjects who appeared for the first screening was 441. A trial cohort was recruited

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[a] It is not the purpose of this article to review the extensive literature on this topic.

[b] At the first screening examination 50 g and 75 g loads were given alternately, but at all successive examinations a 50 g load was used. More subjects with borderline levels of glucose tolerance were found with the 75 g load at the first screening, but about the same number appeared in the trial cohort for those given a 50 g or a 75 g load initially, namely, 6 and 5 subjects respectively.

Table 1. Intervals at which blood pressure, serum cholesterol, and glucose tolerance were measured in 3 groups of subjects (+, measurement made; —, measurement not made)

Group and measurement	Examination and no. of months in study						
	Initial screening 0	Rescreening 3	Start of trial 6	1.5 months in trial 7.5	6 months in trial 12	12 months in trial 18	18 months in trial 24
treated or controlled for blood pressure							
blood pressure	+	+	+	+	+	+	+
serum cholesterol	+	–	–	+	+	+	+
glucose tolerance	+	–	–	+	+	+	+
treated or controlled for cholesterol							
blood pressure	+	+	+	+	+	+	+
serum cholesterol	+	+	+	+	+	+	+
glucose tolerance	+	–	–	+	+	+	+
treated or controlled for glucose tolerance							
blood pressure	+	+	+	+	+	+	+
serum cholesterol	+	–	–	+	+	+	+
glucose tolerance	+	+	+	+	+	+	+

consisting of 107 men with borderline levels of the above-mentioned risk factors and having no conditions preventing them from being randomized into treated and control groups.

The recruitment of the cohort continued from February to September 1969 (the interval between the first screening and start of trial averaged about six months) and the initial screening from 10 February to the end of April; the second and third screenings were conducted during May and June. At the beginning of October baseline levels of the risk factors were obtained for both treated and control groups, and drug treatment was started in the treated group.

All subjects in the treated group were given placebos for the relevant drugs for a period of 1.5 months. After that, the treated groups received: for raised blood pressure, mepobromate for 4.5 months, and then a combination of reserpine and dihydralazine; for raised serum cholesterol, clofibrate; for raised glucose tolerance, buformin. The control groups received no tablets.

Levels of blood pressure, serum cholesterol, and glucose tolerance were measured at the intervals indicated in Table 1.

For those who received drug treatment, no withdrawal of the drug was made before or during the periodic measurements.

At the time of each examination, information was also obtained from each subject on changes in diet, physical activity, and smoking habits and on adherence to the drug treatment; weight and skinfold thickness were also measured.

The total period of observation of the cohort was 24 months: 6 months of recruitment, 1.5 months of placebo treatment, and 16.5 months of treatment for the treated group.

Here we report data on 95 subjects in the cohort, on whom all the measurements were performed at the 7 time-periods.

RESULTS

Table 2 shows changes in blood pressure, serum cholesterol, and glucose tolerance levels, expressed as mean differences from the initial screening levels, over the 24-month period of observation, in those whose levels of the 3 risk factors were found to be borderline at the initial screening examination.

A statistically significant greater reduction for

Table 2. Decrease in levels of blood pressure, serum cholesterol, and glucose tolerance from initially recorded levels at screening in treated and control groups (mean difference ± standard deviation)

Time of examination after initial measurement (screening)	Blood pressure (mmHg)				Cholesterol (mg/l)		Glucose (mg/l) 120 minutes after load	
	Systolic		Diastolic					
	treated	control	treated	control	treated	control	treated	control
3 months (rescreening)	4.8 ± 10.0	8.4[a] ± 15.6	0.2 ± 5.5	− 1.6 ± 7.6	30 ± 330	88 ± 334	120 ± 219	242[a] ± 149
6 months (start of trial)	17.1[a] ± 12.0	17.7[a] ± 14.5	0.0 ± 8.2	− 0.5 ± 9.1	[c]181[a] ± 293	106 ± 323	217[a] ± 247[b]	438[a] ± 262
7.5 months (1.5 months in trial)	21.5[a] ± 14.2	23.5[a] ± 13.8	5.4[a] ± 7.4	3.5 ± 9.2	[d]320[a] ± 337[b]	154[a] ± 429	499[a] ± 253	636[a] ± 215
12 months (6 months in trial)	20.0[a] ± 12.3	19.3[a] ± 14.9	4.3 ± 8.	2.9 ± 9.3	581[a] ± 384[b]	378[a] ± 341	323[a] ± 351[b]	536[a] ± 144
18 months (12 months in trial)	26.6[a] ± 14.9[b]	14.4[a] ± 15.4	7.0[a] ± 8.7[b]	− 0.9 ± 10.4	543[a] ± 386[b]	412[a] ± 376	351[a] ± 248	468[a] ± 242
24 months (18 months in trial)	18.9[a] ± 11.5	12.4[a] ± 14.9	4.6[a] ± 7.6	− 0.7 ± 9.9	661[a] ± 356[b]	562[a] ± 392	297[a] ± 232	164 ± 216
number of subjects in cohort	14	18	14	18	30	32	7	5

[a] Mean difference from initial (screening) level is significant at the 5% level.
[b] Difference between mean differences of treated and control group is significant at the 5% level.
[c] Only 29 subjects in cohort.
[d] Only 27 subjects in cohort.

treated groups, as compared with controls, was recorded only at 18 months for both systolic and diastolic pressure; cholesterol was lower in those treated by drugs at 7.5 months (end of placebo administration), 12, 18, and 24 months. Glucose levels were statistically significantly lower in controls at the 6-month (start of trial) and 12-month examinations. Differences between the treated and control groups were, therefore, only sporadically significant for blood pressure and glucose, and more consistent for cholesterol.

Striking falls in all 3 risk factor levels, as compared with the initial screening levels, occurred in both treated and control groups at successive examinations. Cholesterol values fell during the recruitment period and continued to fall throughout the period of observation, the difference between the initial and 24-month levels being 660 mg/l in the treated group and 560 mg/l in the control group. The systolic blood pressure showed a sustained decrease over the period of observation, although the trend was less noticeable for diastolic pressure, particularly in the control group. Glucose values fell sharply over the first 7.5 months (500 and 640 mg/l less than initial values for the treated and control groups respectively) and then began to level off, but still remained lower than at initial screening, even at 24 months. Most of the differences from the initial levels were statistically significant, as shown in Table 2.

The same trend of decrease was also recorded for systolic (but not diastolic) blood pressure, cholesterol, and glucose in subjects who had normal levels at the screening examinations for recruitment.

Table 3 presents mean differences of the risk factor levels between the initial screening and the 24 months observation for those who belonged neither to the treated nor to the control groups for those risk factors but had them determined only as a part of the routine check-up. Though the absolute magnitude of change in those who were initially in the normal range group was somewhat less than for the borderline group, the decrease in systolic pressure from the value at the initial screening was the most statistically significant of all the follow-up examinations; for cholesterol the decrease was significant at 12, 18, and 24 months, and for glucose it was significant at 12 and 18 months.

Table 3. Mean differences between screening and other periods during trial of those subjects in the 18-month cohort who were normal at screening

Difference from screening to:		Systolic BP	Diastolic BP	Cholesterol	Glucose tolerance
rescreening	$\bar{X}$	4.0[a]	−1.4		
	SD	9.2	6.3		
	N	62	63		
start of trial	$\bar{X}$	16.5[a]	1.2		
	SD	10.7	8.7		
	N	62	63		
1.5 months	$\bar{X}$	15.1[a]	0.9		
	SD	11.2	7.8		
	N	63	63		
6 months	$\bar{X}$	11.8[a]	−0.2	12.2[a]	26.1[a]
	SD	11.7	8.6	32.1	27.1
	N	63	63	33	81
12 months	$\bar{X}$	14.0[a]	0.0	14.9[a]	14.2[a]
	SD	12.0	8.2	34.3	27.8
	N	63	63	33	81
18 months	$\bar{X}$	12.1[a]	0.6	15.8[a]	0.7
	SD	13.9	7.4	30.1	32.2
	N	63	63	33	82

[a] Decrease from screening level significant at the 5% level.

DISCUSSION

Why did such a reduction occur in the levels of blood pressure, serum cholesterol, and glucose tolerance during the 24-month period of the study, both in subjects treated with drugs and in those untreated, and in both those who had borderline and those who had normal initial values? We have no complete answer to this question, although we shall present certain relevant analyses and some speculative explanations.

Does the trend observed by us represent a random variation in the values, i.e., is it the so-called "regression towards the mean over time" phenomenon that is familiar to workers in this field?

Assuming a model in which the measurements are normally distributed with equal means and variances at both the first and second examination and with a correlation of given size between first and second measurements, it is possible to predict the expected size of shifts in means of measurement due to selection of a portion of the original distribution for re-examination.

The appendix gives details of the argument. If we let P_{12} = the correlation coefficient between the first measurement X_1 and the second measurement X_2, which are taken only from a restricted range of the distribution of X_1, then it can be shown that

$$E(X_2 \mid X_1) = \mu_1 + P_{12}(X_1 - \mu_1) \ldots \quad (1)$$

and

$$E(X_2 - X_1) = -(1 - P_{12})(E(X_1) - \mu_1) \ldots \quad (2)$$

where $E(X_2 \mid X_1)$ refers to the expected value of the second measurement given a particular value of the first measurement when both come from a normal distribution with mean μ_1.

Since $P_{12} < 1.0$ we see from equation (1) that we expect the second measurement to lie closer to the mean than the first measurement. From equation (2) we see that the expected difference between the second and first measurement is negative, i.e., the expected value of the second measurement is less than the expected value of the first, whenever $E(X_1) > \mu_1$, given that the first measurement had a particular value and came from a normal distribution with a mean of μ_1.

To see what effect this phenomenon may have upon the specific risk factors screened we may look at the mean values at screening and at start of trial for systolic blood pressure, diastolic blood pressure, serum cholesterol, and glucose tolerance.

It is not possible to estimate directly the correlation coefficient between measurement at screening and measurement at start of trial for the whole population since only a selected portion of the total distribution is measured on both occasions, but estimates can be made from the total cohort since there are persons who have elevated values of one risk factor but normal values of other risk factors. By using the total cohort's measurements and not only those of the borderline group we obtain estimates of correlations between measurement at screening and measurement at various stages of the trial (see Table 4). The observed correlations may not give a true reflection of the correlation occurring in the total distribution, because the persons selected for the cohort are not a random selection from the original distribution and because any differential effect of a factor on individuals occurring between screening and other points of time in the trial is likely to lower the correlation from that observed if only random variations were operating or if there were a uniform change in all values.

We shall confine our attention to the changes observed between screening and start of trial when no treatment was administered to a part of the cohort. By noting the relative stability of the cholesterol and glucose correlations we may use estimates of the correlations between screening and start

Table 4. Correlation coefficients of serial measurements made at screening and during the course of the trial for those with borderline risk factors

Time of measurement	Systolic blood pressure	Diastolic blood pressure	Serum cholesterol	120-min glucose
screening–start of trial	0.70	0.55	—	—
screening–1.5 months	0.73	0.63	—	—
screening–6 months	0.75	0.63	0.54	0.48
screening–12 months	0.68	0.54	0.54	0.46
screening–18 months	0.70	0.68	0.46	0.34

of trial as 0.55 for cholesterol and 0.50 for glucose. Table 5 shows both the expected and observed mean changes for both the group with elevated levels of a risk factor and the group with normal levels. It should be noted that while the decreases in levels of diastolic blood pressure and cholesterol are of a magnitude that could be accounted for by regression towards the mean (comparing columns 3 and 4 of Table 5) no increase is observed in the levels of the unraised risk factor levels of the normal group as predicted by the hypothesis (comparing columns 6 and 7 of Table 5). The whole distribution of each risk factor appears to have shifted to lower levels, and in fact continues to shift to lower levels in the treated, control, and normal groups for the remainder of the trial.

A more detailed account of the possible explanation of decreases in a risk factor level by regression to the mean has been given by Ederer (4).

Reduction in the levels of blood pressure, serum cholesterol, and glucose tolerance also cannot be explained by seasonal variations in their values. Table 2 provides comparisons for yearly intervals from screening—12 and 24 months—where the same trend persists.

It can be concluded from Tables 2 and 3 that influences other than drug treatment played a substantial role in reducing the levels of the risk factors. What were those influences? The examining physician who supervised screening and follow-up checks was permitted by the study protocol to give any advice on change of habits which she felt was warranted. At each of the follow-up checks in the trial, changes during the previous 6-month period in diet and physical activity reported by the subject were recorded. Dietary change was recorded when a subject decreased the total amount of calories, the amount of saturated fat, or the amount of carbohydrates in the diet. Change in physical activity was recorded if the subject reported an increase in physical activity. Changes reported by the subject were reviewed by the research team on the basis of other information and finally recorded for each individual. These data, obviously rather crude, are presented in Fig. 1, 2, and 3.

It is seen that pronounced changes occurred in both dietary and physical activity habits in the group, the latter habits having a definite seasonal pattern. The attempt to relate risk factor levels directly to the changes in habits revealed no significant association, perhaps because of the small numbers of observations when the subjects were split into subgroups. It was merely found that the subjects who were treated by drugs always had lower cholesterol levels if they changed their diet than if they did not do so.

The number of subjects changing their smoking habits was small and the change did not show any relationship with the risk factor levels.

Mean body weight changed substantially over 24 months only in the group treated or controlled for glucose tolerance. This group was also more

Table 5. Observed and expected changes in mean values of risk factor levels between screening and start of trial

Risk factor	Total sample mean at screening	Selected cohort mean at screening	Selected cohort mean at start of trial	Expected mean from estimated correlation coefficient in Table 3	Normal group mean at screening	Normal group mean at start of trial	"Expected" normal group mean at screening
systolic blood pressure (mmHg)	144.4	166.4	146.2	159.8	137.2	120.5	139.4
diastolic blood pressure (mmHg)	85.1	95.7	95.2	90.9	81.0	79.8	82.8
cholesterol (mg/l)	2 418	2 886	2 738	2 675	2 189	2 121 [a]	2 292
glucose tolerance (mg/l)	898	1 419	1 083	1 159	842	693 [a]	814

[a] Estimated as the average of the mean value at screening and the mean value at 6 months after start of trial.

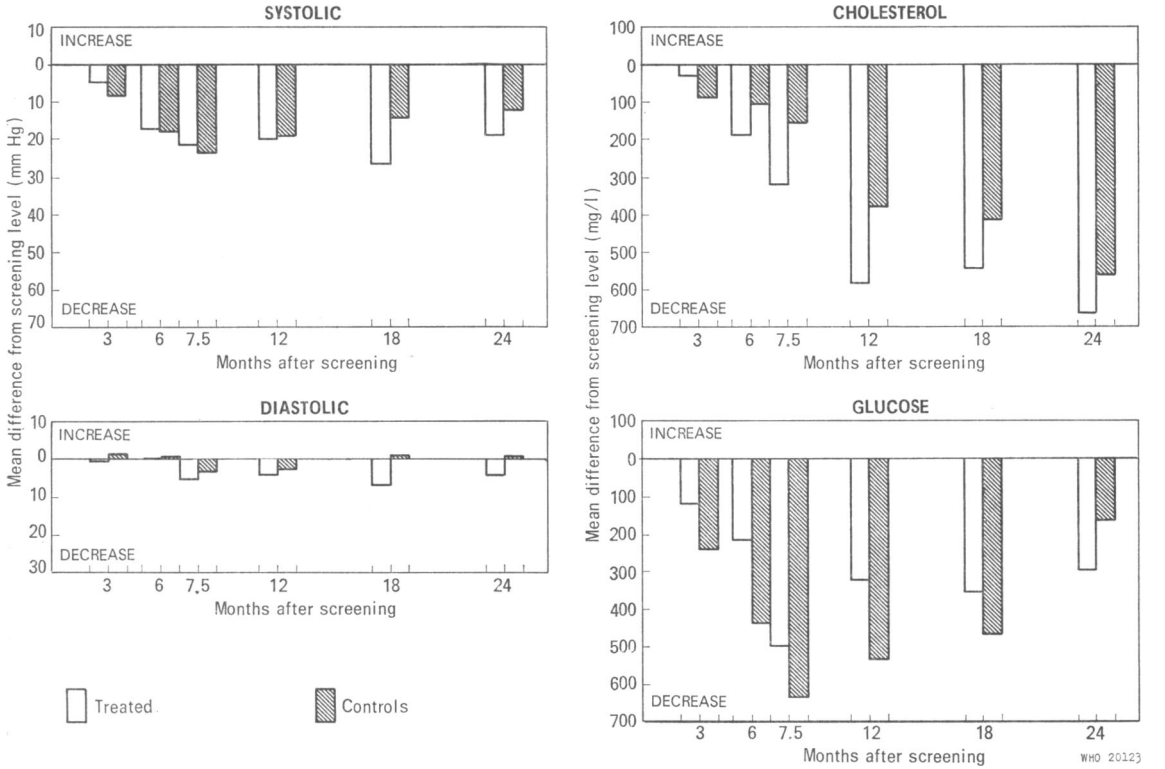

Fig. 1. Changes in levels of blood pressure, serum cholesterol, and glucose tolerance from initially recorded levels at screening in treated and control groups.

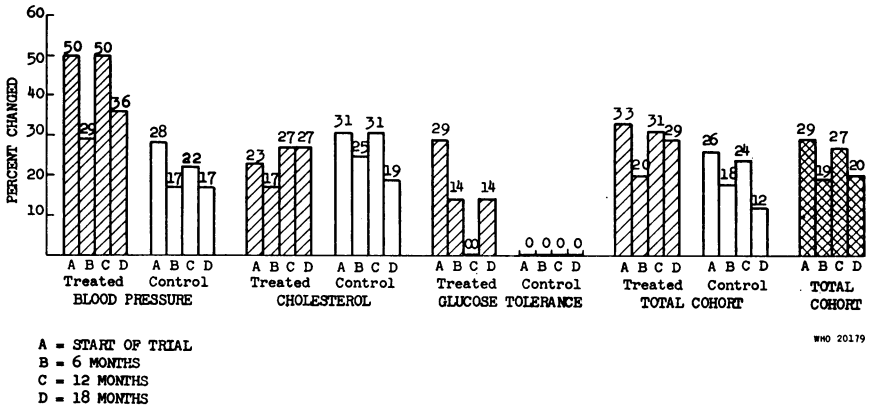

Fig. 2. Change in physical activity (percentage of subjects who altered their physical activity during various periods of the trial—18-month cohort).

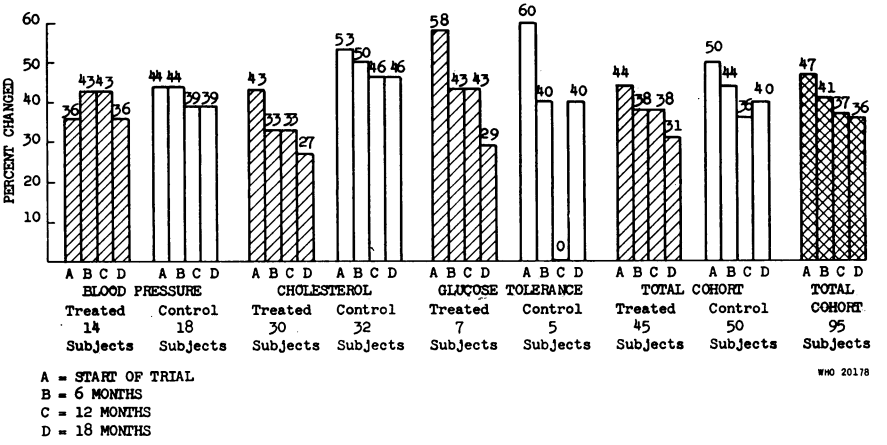

Fig. 3. Change in diet (percentage of subjects who altered their diet during various periods of the trial—18-month cohort).

than 4 kg heavier at the beginning of the trial. The reduction in weight in this group averaged about 3 kg over the 24-month period.

Mean skinfold thickness values decreased over the period of observation, particularly in those treated or checked for blood pressure and glucose tolerance (by 3–4 mm and 4–7 mm respectively) and less so in the sub-cohort treated or controlled for cholesterol (by 2 and 3 mm respectively). It was imposible to find any direct relationship between the body weight or skinfold thickness change and glucose levels.

Summing up the evidence from our data, changes of behaviour were recorded in the study group which were expressed by changes in dietary habits and increased physical activity, presumably leading to the reduction in body weight in the glucose tolerance sub-cohort and the decrease in skinfold thickness in all cohorts. No relationship was found between the changes in behaviour or in bodily characteristics and the risk factor levels under discussion.

Possible explanations from the literature

It is known from the literature that diagnosis of a disease at a health examination may lead to modification by the examinee of behavioural characteristics that could be considered risk factors for that disease. This is because the examinee, on learning the results of the examination, may be given the incentive to change his/her behaviour in the hope of preventing the progress of the disease. For example, it was reported in a study by the Health Insurance Plan (H.I.P.) of Greater New York (10) that those surviving myocardial infarction and subjects with diagnosed angina pectoris followed up for 5 years showed a sustained reduction in both the number of smokers and the amount of cigarettes smoked, and also a reduction in body weight.

People who undergo periodic health examinations, even if no disease condition is diagnosed, tend to show a reduction in some risk factor levels. This was so in the controls not having coronary disease in the H.I.P. study; they showed a similar reduction in smoking, although not a similar change in weight, over 5 years.

Hawthorne (6), in an experiment with 2 groups, noted that over a 6-month period there was a decrease in smoking and in body weight in both groups, whether they received specific advice or not, although the group advised to reduce smoking did so 4–5 times more than the group that was not given this advice. Compliance with the advice given increases with repeated health examinations extended over longer periods of time (3, 5).

In the double-blind National Diet–Heart study, where an attempt was made to modify diet but no other factors, the following changes occurred at the end of one year: 25% of cigarette smokers had stopped smoking and a further 25% had reduced the amount smoked, the mean weight loss was 2 kg, and there was a significant reduction in blood pressure of up to 5%, not accounted for by weight loss (2).

This change in bodily and other physiological characteristics of the people experiencing the periodic health examinations can be considered a result

of the nonspecific intervention effect of these examinations.

Another type of explanation may be suggested to account partially for the relationship noted between observation and measurement on the one hand (as represented by the periodic health examinations) and changes in physiological risk factor levels on the other. This behavioural explanation rests on the assumption that messages or expectations from the physician/examination situation are communicated to the subject in such a way and to such an extent that he responds to these messages in a physiologically measurable way. Some authors have discussed the sociopsychological aspects of this phenomenon (8, 9). Such an explanation is not unlike that put forward for the " placebo effect ", in that a subjective element has been widely noted in the placebo reaction—a reaction that is quite distinct from any chemical property of the placebo itself (11, 12). This hypothesis was not tested in the Zagreb study, but the data from the study are consistent with this explanation. Why the effect observed in Zagreb—in terms of risk factor level changes—was a fall rather than a rise in the risk factor levels is not clear.

The phenomenon suggested above is an aspect of trial design and methodology that should receive much more systematic attention in the future.

Implications of the Recorded Analysis

The changes in the risk factor levels which we recorded, and those mentioned in the literature, should always be taken into account when intervention trials are being designed. It is customary to look for differences in the occurrence rates of conditions in the treated and control groups; this difference is assumed to be a function of changes in a particular risk factor level that is subjected to a modification in the treated but not in the control group. The hypothesis usually tested is that reduction in the risk factor level will bring about reduction in the rate of occurrence of the condition in the treated group but not in the untreated group. Regular examinations of both the treated and control groups as a method of monitoring events do themselves act as an intervention effect and may also lower the levels in the control group, thereby substantially reducing the differences in risk between the treated and untreated groups. As was shown in the Zagreb study, the effect of these regular examinations of the study cohort was greater than the effect of drug treatment. On the one hand, this indicates that regular health check-ups are a potent intervention tool, but on the other hand it means that the results of the trial, when they are negative, might be false negative ones.

Another, more speculative, inference from the observed phenomena is that periodic health examinations as such could be a means of lowering the rate of disease events in the population. At the moment this is only a hypothesis and has still to be substantiated by more direct evidence. However, it seems to us that it should not be overlooked in the design of studies in which this intervention effect could confuse the results.

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RÉSUMÉ

LES EXAMENS DE SANTÉ RÉPÉTÉS EN TANT QUE FACTEUR D'INTERVENTION

Les auteurs exposent les résultats d'une étude préliminaire d'intervention multifactorielle effectuée à Zagreb (Yougoslavie) en 1969.

On a sélectionné, au sein d'une collectivité de la région de Zagreb, 107 hommes âgés de 51 à 53 ans présentant, isolément ou en association, des valeurs limites de pression sanguine, de cholestérol sérique et d'intolérance au glucose. Deux groupes ont été ensuite formés sur une base aléatoire: les sujets du 1er groupe ont reçu des médicaments destinés à traiter le ou les facteurs de risque, tandis que les membres du second groupe, suivis de la même façon, ne recevaient aucun traitement. Au cours des 24 mois d'observation, 95 hommes se sont présentés régulièrement pour subir les examens.

Au cours de cette période de deux ans, on a constaté, tant dans le groupe traité que dans le groupe témoin, une diminution substantielle de la pression sanguine systolique et des taux de cholestérol et de glucose. On n'a relevé qu'occasionnellement des différences sensibles entre sujets des deux groupes concernant les modifications survenues.

Les auteurs examinent les causes possibles du phénomène et notamment le rôle éventuel des examens répétés en tant que facteur d'intervention.

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Annex

REGRESSION TO THE MEAN

Consider a variable X measured at time T_1 and T_2 on each of n persons on both occasions.

Let X_{1i}=measure of X at time 1 on ith person $i=1 \ldots n$
X_{2i}=measure of X at time 2 on ith person $i=1 \ldots n$

Supposing that after time 1 we consider the distribution of X_1. If we order these variables the distribution can be designated at

$$X_{1(1)}\ X_{1(2)} \ldots\ldots X_{1(i)} \ldots\ldots X_{1(n)}$$

Supposing we censor this distribution from both the right and left (but not necessarily symmetrically so that we trim off the lower Lth and the upper Uth percentile). Let us suppose that $L>U$; i.e., we trim more from the lower than upper percentiles.

On the second occasion we now only measure those persons whose X_1 fell between the Lth and Uth percentile of the distribution. Let us suppose also that the original uncensored distribution of X_1 is symmetrical about its mean μ_1 and has variance σ^2. We can assume also that if the full distribution of X_1 was again measured at time 2, X_2 would have the same distribution (μ_1, σ_1^2).

If X_1 and X_2 are in fact normally distributed then

$$f(X_2|X_1) = \frac{1}{\sigma_1 \sqrt{2\pi\,(1-P_{12}^2)}} \exp \left\{ - \frac{1}{2\sigma_1^2\,(1-P_{12}^2)} [X_2-\mu_1-P_{12}(X_1-\mu_1)]^2) \right\}$$

where P_{12}=correlation between X_1 and X_2 and

$E(X_2|X_1)=\mu_1+P_{12}(X_1-\mu_1)$

since $E(X_2)=E(E(X_2|X_1))$

then $E(X_2)=\mu_1+P_{12}(E(X_1)-\mu_1)$

or $E(X_2-X_1)=-(1-P_{12})\,(E(X_1)-\mu_1)$

If correlations are positive between readings, then the expected values of the second measurement given the first will always lie closer to the mean of distribution of the second measurements, since we are multiplying $(E(X_1)-\mu_1)$ by a number less than 1.0 and decreasing its distance from the mean.

When the distribution of first measurements is censored in such a way that $L>\mu_1$ or even if $|\mu_1-L|>|U-\mu_1|$ then the $E(X_2|X_1$ in uncensored region$)\leqq X_1$, with equality holding only when $P_{12}=1$.