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MINISTRY OF HEALTH
THE CHAIM SHEBA MEDICAL CENTER
Affiliated to the Tel-Aviv University
Sackler School of Medicine
TEL-HASHOMER, ISRAEL
HEART INSTITUTE

משרד הבריאות
המרכז הרפואי ע"ש חיים שיבא
מסונף לבית הספר לרפואה ע"ש סאקלר
באוניברסיטת תל-אביב
תל-השומר, ישראל

V. Goldbourt to
IJE editor

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Sir,

In deviating from the normal procedure of reply-rebuttal, I have found it necessary to comment once again on the substantial difference in analytic approach that become clear from the correspondence by Professor Keys and myself relating to the subject of HDL cholesterol and long-term mortality. This difference is probably the major source of controversy and confusion. It is important, that researchers distinguish between the analysis of mortality as a mere dichotomous phenomenon of a yes-no nature and the life-table approach. Over short term (such as the 5-year follow-up of the Israeli IHD Study[1]) the distinction between the mere analysis of the fact of mortality and a life-table approach is moot. Over a 24-year follow-up (the Finnish cohort[2]), let alone a nearly life-long follow-up such as that of the Minnesota businessmen cohort, a sizable proportion will have died. Deaths are spread over a long period. Death at year 2 of follow-up cannot be equated, in severity, to dying 20 years after the initial observation, if one considers, for example, two men aged 55 when starting the follow-up. Clearly, for such lengthy observations one would choose to adapt a method which, while adjusting for the contribution of covariates, does not treat <u>all deaths</u> during follow-up as events of equal significance.

It is important to ascertain whether <u>early</u> deaths are associated with HDL cholesterol, BP, smoking etc. - not merely whether the very fact of death is. In the Minnesota cohort[3], such a large percent of mortality has occurred, that the <u>life expectancy,</u> rather than the fact of mortality, will soon become the dependent variables of significance.

To summarize, it is necessary to use the Cox's model from long-term mortality (or other life-table methods, if adjustment for covariates in the manner handled by Cox is not deemed neccessary) and to accommodate competing risks of mortality.

It is also important to reiterate, that two out of the three Finnish cohorts <u>do support</u> other findings suggesting that HDL cholesterol is related to mortality. We should refrain from comparing p-values between studies! The p-values are <u>not</u> proportional, across studies, to the HDL differences between survivors and those who have died. The p-values are very sensititve to the number of events (deaths). We had better attempt to pool data from the different studies. The situation is somewhat reminiscent of that often found in clinical trials, when trials just miss the "magic" (?) significance level of $p = .05$ to which some persons in clinical science have become enslaved.[4]

../2

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We have admitted that our HDL cholesterol values are low. We have shown, however, that they relate to several risk factors (weight, smoking, activity) in exactly the same manner found in other studies[5]. The relationship to coronary incidence[1] is also in strong agreement with that found internationally. The 1965 remeasurement of HDL cholesterol (this time yielding means above 40) produced a relationship with subsequent mortality that virtually duplicated the one found with the 1963 levels. These facts can all be taken as validating criteria in assuming that the lower, 1963 levels represent a systematic unbiased deviation from the "true" ones.

I would like to conclude by emphazing, that regression between quintile death rates has no relation to causality. A high relation between quintets of death rates will be also found between quintiles of cholesterol and SBP - this will say nothing about the independent impact of each factor, or whether one factor adds anything or not to the information conveyed by the other.

Dispute which centers around semantics is, I believe, futile. Also, not all studies may agree on a given hypothesis. It remains important to use the most appropriate analytical methods for particular situations, as well as to interpret comparative data mainly on the basis of whether estimated factor-disease associations resemble each other by size, rather than by p-values.

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