Do Coronary Heart Disease Risk Factors Change Over Time?

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The stability over a 12-year period of several coronary heart disease (CHD) risk factors was evaluated in 348 individuals who had remained healthy following baseline measurements made of the same variables in 1981. CHD risk factors evaluated were fasting and post–glucose challenge (120-minute) plasma glucose and insulin concentrations, plasma triglyceride (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) concentrations, and the ratio of LDL/HDL cholesterol concentrations. Approximately 40% to 60% of individuals in the highest CHD risk quartile (or lowest in the case of HDL cholesterol concentrations) in 1981 were still at highest risk in 1993. A similar proportion of individuals at lowest risk in 1981 were still in that category in 1993. At least 50% of the participants in this prospective analysis experienced a change by 1 quartile or more in each of the metabolic CHD risk factors measured, and these differences were highly statistically significant for all variables measured with the exception of the TG and HDL cholesterol concentrations. These results demonstrate that the implicit assumption in epidemiological studies that CHD risk factors at baseline remain stable may require examination.

THE GENERAL EPIDEMIOLOGICAL approach to evaluating metabolic risk factors for coronary heart disease (CHD) is to measure a series of what are thought to be relevant variables in healthy individuals at baseline, determine the number of clinical end points at some point in the future, and use various statistical approaches to assess the relative impact of the CHD risk factors measured at baseline on the observed outcomes. Since this analysis is often based on a single determination of the CHD risk factors in question, made many years before the clinical event, it is implicitly assumed that the baseline metabolic characteristics of a given participant in the study remain relatively constant over the period of observation.

As important as this issue is, we are not aware of any experimental evidence that has evaluated the validity of this fundamental assumption. In an effort to fill this void, we decided to repeat the measurements of metabolic risk factors for CHD in 348 individuals who had remained healthy 12 years after collection of the initial baseline data. The results of this analysis comprise this report.

MATERIALS AND METHODS

In 1981, we surveyed 732 factory workers for a variety of metabolic risk factors for CHD.[1] At that time, all subjects were instructed to consume 300 g of carbohydrates daily for 3 days preceding the measurements. The following tests were performed for baseline determinations: (1) height, weight, and body mass index (BMI); (2) venous blood was drawn after an overnight fast for measurement of plasma glucose, insulin, triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol concentrations; and (3) plasma glucose and insulin concentrations 60 and 120 minutes after a 75-g oral glucose challenge.

In 1993, a decision was made to perform a follow-up evaluation of the original 732 individuals. We were able to make contact with 647 of the initial cohort, of whom 615 were both alive and living in the vicinity of Parma. Fifteen of the 615 individuals contacted were excluded because of documented history of CHD (n = 10) or diabetes (n = 5), and 252 were unwilling to have the blood tests repeated. Consequently, the data presented here represent the baseline and follow-up results of 348 of the subjects originally studied. All members of this cohort were without apparent disease when originally studied, and in the interim had remained free of type 2 diabetes or CHD, and had not been treated with pharmacological agents known to affect carbohydrate or lipid metabolism.

Baseline and follow-up measurements were made in the same laboratory using identical methodologies.[1-7]

To examine the stability of the risk factors of interest, the 348 volunteers were divided into quartiles on the basis of their values at the follow-up examination (1993), and then compared to their quartile position at baseline (1981). By so doing, we attempted to minimize the confounding effect of any time-related change in quantification of the biochemical risk factors being evaluated. In addition, the decision to use quartiles for evaluating changes in these CHD risk factors over time was based on the results of our recent study showing that the 25% of individuals with highest insulin levels in 1981 had a statistically significant increase in the development of CHD, states of glucose intolerance, and hypertension when evaluated 12 years later.[2]

Results are expressed by separating the individuals studied in 1993 into quartiles on the basis of the value of each variable determined, and displaying their quartile distribution in 1993 as a function of their quartile location in 1981. In addition, an evaluation of whether an individual was in the same quartile (invariate) in 1993 as in 1981, or had changed by at least 1 quartile (changed), was analyzed by chi-square test.

RESULTS

The 348 subjects evaluated at the follow-up do not represent a unique group of the original study population, as 21.8% of them were in the first quartile, 27.3% in the second quartile, 27.6% in the third quartile, and 23.3% in the fourth quartile at the time of the initial examination. Similarly, the distribution of the 32 subjects who died was also similar across the 4 quartiles, with 28% in quartile 1, 19% in quartile 2, 22% in quartile 3, and 31% in quartile 4. Finally, the distribution of the 85 subjects who could not be located was also spread quite evenly, repre-

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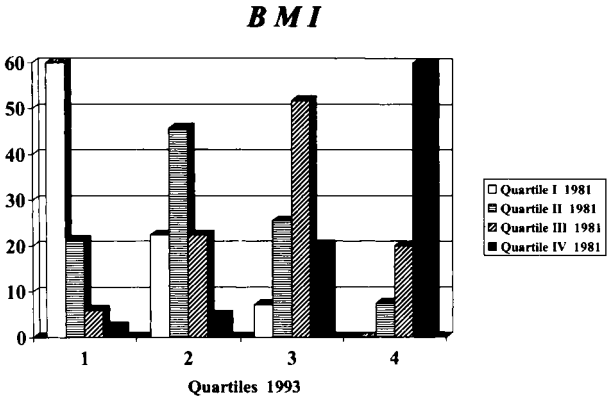

Fig 1. Quartile distribution of study population values of BMI in 1993 as a function of their distribution in 1981.

senting 15%, 6%, 13%, and 12% of the original quartiles 1 to 4, respectively. Thus, there seems to be solid support that the 348 subjects being compared in this analysis are reflective of the population as a whole.

Figure 1 depicts the changes in BMI observed over the 12-year period of the study. It is apparent that this variable changed very little with time. For example, 60% of individuals in either the highest or the lowest BMI quartile at baseline did not change with time. Furthermore, about 80 of those in the highest BMI quartile in 1981 were in the upper 2 BMI quartiles in 1993. Similarly, 80% of those in the lowest BMI quartile at baseline were in the lower 2 quartiles when observed 12 years later.

Regarding the metabolic comparisons, Fig 2 illustrates the relationship between the quartile distributions for plasma glucose concentrations, before and 2 hours after the oral glucose challenge of individuals originally studied in 1981 as a function of their quartile distribution in 1993. Approximately 50% of those individuals with the highest fasting and post–glucose challenge plasma glucose concentrations in 1993 were in the same group in 1981. The vast majority of individuals in the highest glucose quartiles in 1981 who were no longer there in 1993 appeared in the 2 intermediate quartiles. Thus, only 12% of individuals in the highest glucose quartile in 1981 had moved to the lowest quartiles in 1993.

Figure 3 displays the changes over time in distribution of fasting and post–glucose challenge plasma insulin concentrations. In general, the results are quite similar to those in Fig 2, although somewhat less stabile when comparing the fasting insulin concentrations over the 12-year period to the values 120 minutes after oral glucose. For example, only 6% of those in the lowest quartile as regards the 2-hour insulin level in 1993 came from the highest quartile in 1981, whereas 18% of those in the lowest quartile of fasting insulin concentrations in 1993 were in the highest quartile in 1981. In addition, 50% of those in the lowest quartile of 2-hour insulin concentrations in 1981 were in the same quartile in 1993, whereas only 37% of individuals with the lowest fasting plasma insulin concentration in 1981 were in the same quartile in 1993.

The changes in the distribution of TG and LDL cholesterol concentrations over the 12-year period of observation are illustrated in Fig 4. In general, the time-related behavior of these two variables was comparable, and possibly the TG concentrations were somewhat more stable. For example, 55% of those in the highest quartile for TG concentration in 1993 were in the same quartile in 1981, as compared to 46% of those whose LDL cholesterol concentration was in the highest quartile at both time points. Similarly, 54% of those in the lowest quartile for TG concentration in 1993 were in the similar quartile in 1981, whereas 48% of those in the lowest quartile in 1993 were in the same quartile in 1981.

Figure 5 displays the distribution of HDL cholesterol concentration, and the ratio of LDL to HDL cholesterol concentrations. Although the distribution of these variables resembles the results in Figs 2 through 4, the values over time for HDL cholesterol concentration appear to be particularly consistent. Indeed, the stability of HDL cholesterol concentrations over time was similar to that seen with BMI (Fig 1). However, in terms of biochemical measurements, it is the only instance in which more than 60% of those in the highest and lowest quartile for HDL cholesterol concentration in 1993 were in the same quartile in 1981. At the other extreme, only approximately 3% of those in the lowest quartiles in 1993 were in the highest quartile in 1981. Somewhat surprising was the finding that the stability of the LDL to HDL cholesterol concentration

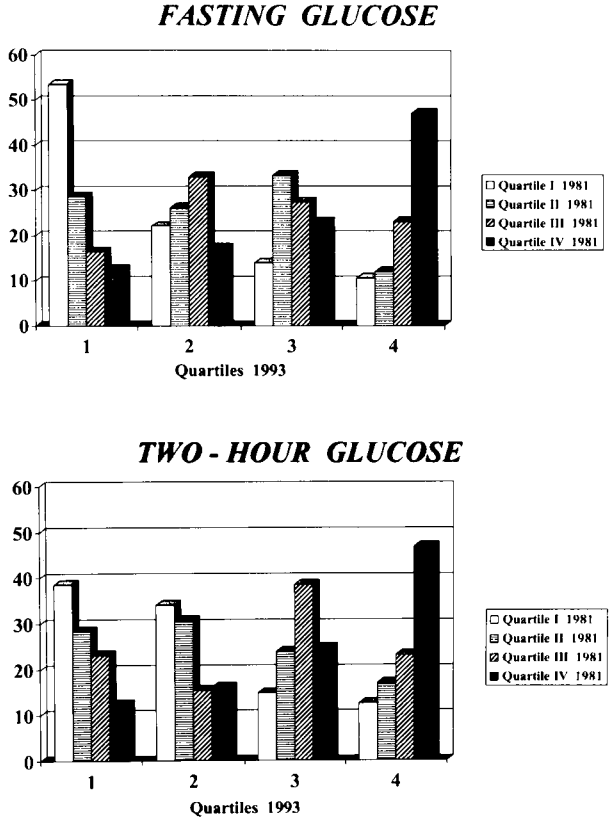

Fig 2. Quartile distribution of study population values of fasting and 2-hour post–glucose challenge glucose concentrations in 1993 as a function of their distribution in 1981.

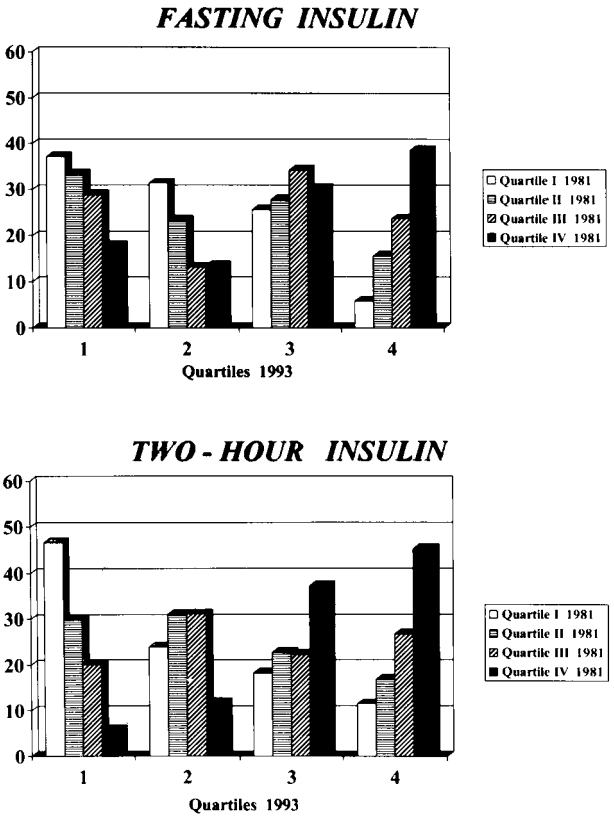

Fig 3. Quartile distribution of study population values of fasting and 2-hour post–glucose challenge insulin concentrations in 1993 as a function of their distribution in 1981.

ratio was similar to that of change in the distribution of plasma TG concentrations over the 12-year period.

Table 1 illustrates the degree to which individuals were either in the same quartile in l993 as in 1981, or had changed their location by at least 1 quartile. In addition to the metabolic variables, BMI data are also provided. BMI was the only variable in which more individuals remained the same (60%) than changed (40%). In all other cases, more than 50% of individuals changed their quartile location over time, and these changes were statistically significant for all variables with the exception of plasma TG and HDL cholesterol concentrations. The least consistent variable over time appeared to be insulin concentration, and the fasting plasma insulin concentration of 67% of the participants varied enough to change their quartile distribution.

DISCUSSION

As indicated in the Methods, our results represent the follow-up information obtained for 348 of the 732 subjects originally evaluated. The 348 subjects retested were distributed quite similarly within the 4 quartiles at the baseline evaluation. The quartile baseline distribution of those who died in the interim, as well as those who could not be located, was spread comparably throughout the original 4 quartiles. Based on these considerations, it seems likely that the results in the 348 subjects that comprise this study would be reflective of the entire population that initially volunteered.

If the above premise is accepted, it becomes possible to realize the goal of this study—to assess the relative stability of various metabolic risk factors for CHD over time. Perhaps the best way to begin discussion of the results is to use the metaphor of a drinking glass containing half of its original contents, being viewed as half-filled or half-empty. For those of the half-filled persuasion, our results showed that 45% to 66% of individuals in the upper quartile (or lower in the case of HDL cholesterol concentration) of CHD risk factors were still there 12 years later. At the same time, fewer than 10% of the individuals in an extreme quartile moved to the other extreme. Furthermore, approximately half of those in the 25% population at greatest CHD risk at the beginning of the period of observation remained at the same level of risk. Finally, if we look at the 2 extreme quartiles for CHD risk, 77% to 93% of subjects did not change with time. Perhaps the best example of the stability of CHD risk factors over time was the case of HDL cholesterol concentration, in which approximately 60% of those with the highest and approximately 60% of those with the lowest HDL cholesterol concentration in 1981 were in the same category in 1993.

On the other hand, the notion that the glass is half-empty

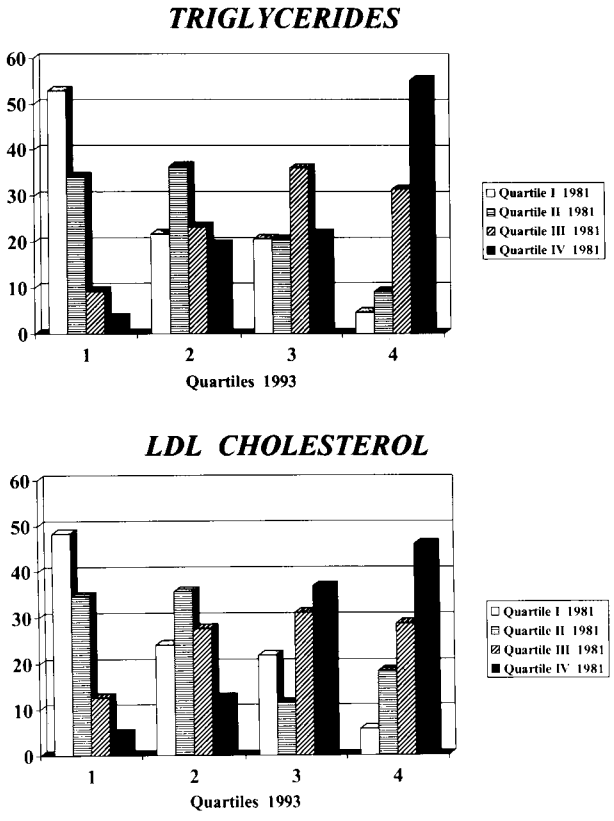

Fig 4. Quartile distribution of fasting plasma triglyceride and LDL cholesterol concentrations in 1993 as a function of their distribution in 1981.

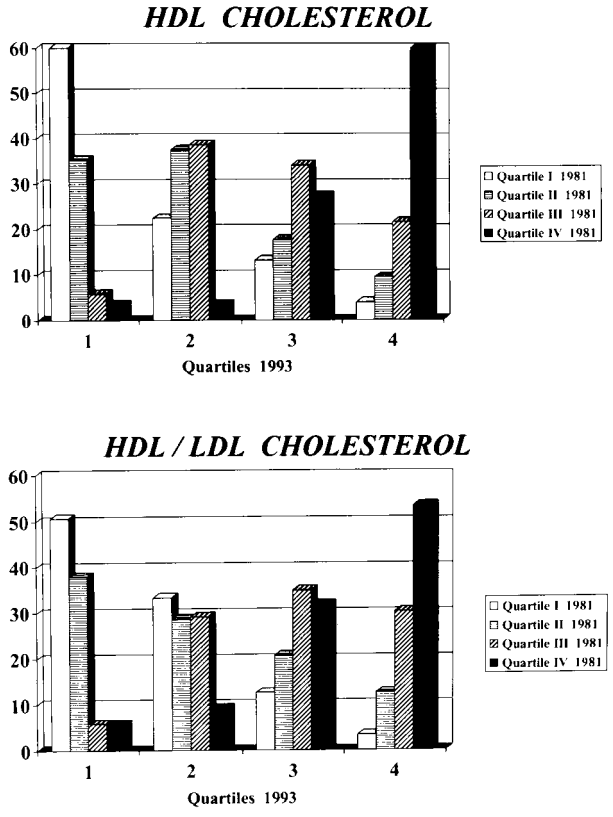

Fig 5. Frequency distribution of HDL cholesterol and ratio of total to HDL cholesterol concentrations in 1993 as a function of their distribution in 1981.

gains considerable support from inspection of the 2 middle quartiles, where it is obvious that the persistence of an individual within the same CHD risk quartile was approximately 50% in most instances. Furthermore, the fact that approximately 50% of those in the quartiles of most and least risk of CHD at baseline remained in the same quartile, means that about 50% underwent a significant change in their CHD risk factor status. In this context, the use of fasting plasma insulin concentration as an indicator of future risk of CHD appears to be most problematic in that less than 40% of those in the highest and lowest insulin quartile in 1981 were still there in 1993. Furthermore, 18% of those in the lowest insulin quartile in 1993 were in the highest quartile in 1981.

The relative lack of stability of the CHD risk factors measured is further validated by the results in Table 1. Somewhat surprisingly, the most stable variable was BMI, with 60% of all individuals being in the same quartile in both 1981 and 1993. In every other instance, the values changed by at least 1 quartile in more than 50% of the participants, and this effect was highly statistically significant for every variable with the exception of plasma TG and HDL cholesterol concentrations. Of particular interest was the observation that fasting plasma insulin concentration, a measure often used as a surrogate estimate of insulin resistance, changed by at least 1 quartile in 67% of the population.

Although the results presented show that metabolic risk factors for CHD were only relatively stable over a 12-year period of observation, they do not provide an obvious explanation for our findings. However, several important potential possibilities seem unlikely. For example, BMI was by far the most stable time-related variable evaluated, providing evidence that neither substantial weight gain nor weight loss played a major role in changing metabolic risk factors over time. Another possible confounding factor could be changes in the methods used to make the biochemical measurements. This explanation also seems unlikely in that the same laboratory methods were used in 1981 and 1993. Furthermore, since the results are presented as a function of quartile distribution, the impact of small quantitative differences related to variations in experimental technique, as differentiated from changes in experimental methods, should be minimal. It seems more likely that the time-related changes result for a series of unrelated events, including regression to the mean, changes in physical activity, and the difficulty in categorizing an individual on the basis of only 1 measurement of relatively labile metabolic CHD risk factors. On the other hand, irrespective of the reason, or likely reasons, for the variability in the values of CHD risk factors measured in 1993 as compared to 1981, the important lesson to be learned from our results is that these changes do occur.

In a previous prospective study of the same population,[2] it was apparent that the increased risk of baseline hyperinsulinemia in prediction of states of glucose intolerance, high blood pressure, and CHD was confined to the upper 25% of the population. A similar phenomenon is seen when the CHD risk factors were concentration of TG, LDL cholesterol, HDL cholesterol, and ratio of LDL to HDL concentration. This observation suggests that the relationship between metabolic risk factors and clinical events is nonlinear, and the current results demonstrate the impact that time-related changes in these variables could have on the interpretation of population-based epidemiologic studies.

In conclusion, the current results emphasize that the risk factor status of an individual is only moderately consistent during an observation period of several years. These findings raise questions about the potential pitfalls of prospective studies attempting to evaluate the impact of CHD risk on metabolic variables measured on 1 occasion at baseline. For example, could controversies as to the CHD risk of fasting hyperinsulinemia[8-11] be related to our finding that two thirds of subjects

Table 1. Percentage of Individuals Who Changed Quartiles

Variable	Invariate Quartile	Changed Quartile	*P* Value
BMI	59.8%	40.2%	<.001
Fasting glucose	39.4%	60.6%	<.001
2-h glucose	38.5%	61.5%	<.001
Fasting insulin	33.3%	66.7%	<.001
2-h insulin	36.2%	63.8%	<.001
Tryglicerides	45.01%	54.9%	NS
LDL cholesterol	40.2%	59.8%	<.001
HDL cholesterol	48.9%	51.1%	NS
LDL/HDL cholesterol	42.0%	58.0%	<.005

Abbreviation: NS, not significant.

had a change in their fasting plasma insulin concentration to the degree that resulted in their relative rank changing by 1 quartile or more? Although we clearly cannot answer this question, the fact that we can raise it makes it reasonable to suggest that conclusions as to the power of 1 baseline measurement of any given risk factor to predict CHD in a prospective study should be tempered by the realization that its value might vary significantly throughout the course of the study.

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