New cardiovascular risk determinants do exist and are clinically useful

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Can we improve our understanding of cardiovascular disease (CVD) causality and prediction? Intuitively, we can. Recent publications, however, could be misinterpreted as suggesting the opposite. First, the Interheart study, which concluded that nine conventional risk factors explain >90% of premature myocardial infarction, is at risk for being interpreted as saying that other, ‘new’ cardiovascular risk factors can only cause a small remaining fraction of disease of at most 10%. Secondly, papers addressing the predictive value of new risk factors or markers of early CVD risk have concluded that risk prediction does not improve by adding these variables to risk models. In this paper, we will explain that searching for ‘new causes’ of CVD is still highly relevant, and that improvement of risk prediction is often assessed using inappropriate statistical methodology.

Keywords
Cardiovascular disease • Risk factors • Risk estimation • Epidemiology

Introduction

One way of effective cardiovascular disease (CVD) prevention is targeting preventive strategies towards high-risk individuals. For risk estimation, we rely on risk models, such as the Framingham-score⁷ or the Adult Treatment Panel-III risk assessment tool² (both often used in the USA), and the SCORE model³ (often used in Europe). These risk models have in common that they use the classical risk factors (usually age, sex, blood pressure, dyslipidaemia, smoking, and diabetes) to estimate the 10-year risk of CVD.

To better understand the pathogenesis of CVD and improve risk estimation, considerable research effort has been invested in identifying variables that, on top of the conventional risk factors, improve CVD risk stratification. This search has included both causal risk factors as well as markers of early arterial disease. Recently, these new CVD risk determinants have met scepticism, apparently for two reasons. The first reason relates to identification of ‘new’ causes for CVD after the INTERHEART study. This large case–control study concluded that over 90% of CVD is attributable to 9 conventional risk factors.⁴ The interpretation of these results by many has been that this 90% population attributable risk (PAR) leaves little, if any, room for additional, new risk factors. The second reason why people seem to loose interest in new CVD risk determinants is based on recent publications suggesting that including these variables, regardless of whether these are risk factors or markers of early disease, in risk models does not improve the performance of these models. In this paper, we argue that both contentions are wrong, and are based on misinterpretation of epidemiological data and erratic use of statistical methods.

New cardiovascular risk determinants

A variety of for example genetic, biochemical, or vascular properties may be identified as determinants of CVD risk, independent of conventional risk factors. Some of these new risk determinants are thought to be causally related to atherothrombosis (e.g. genetic polymorphisms, lipoprotein (a), prothrombotic factors, etc), whereas others are regarded as epiphenomena of causal mechanisms (e.g. C-reactive protein representing inflammation) or as markers of early stages of the disease itself (e.g. increased carotid intima-media thickness, coronary calcium score). Quite often, it is unclear whether a new CVD risk determinant

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represents a cause, marks early vascular damage, or does both. C- Reactive protein, for example, may represent a low-grade inflammatory state associated with early-stage atherosclerosis, but may also be a causal contributor to vascular damage, and in principle there is no reason why it could not be both. The same is true for endothelial markers, which reflect early vascular damage, but may also contribute to further development of atherosclerosis. From the perspective of risk prediction, the issue of causality is irrelevant, and both causal factors and markers of early CVD can be referred to as ‘risk determinants’. In this paper, we will discuss potential misconceptions regarding both ‘new’ risk factors (i.e. previously unidentified causes of CVD), as well as regarding the value of novel risk determinants for improving prediction of CVD risk.

**The interheart study: has it been misinterpreted?**

The first reason why some have lost faith in new CVD risk factors is based on a misinterpretation of the INTERHEART study. Many colleagues state that this study, as it has shown that more than 90% of CVD is explained by conventional risk factors, leaves at most marginal room for new risk factors. The study results, it thus seems, have led some to believe that the issue of which factors cause and predict CVD is pretty much settled, and that we should shift our focus entirely to disease prevention by tackling the conventional risk factors.

The INTERHEART study, published in 2004, was a case-control study in which blood was drawn within 2 h of an acute myocardial infarction in 15,152 cases and 14,820 controls from 52 countries. The study indeed concluded that nine potentially modifiable conventional risk factors, all presumably causally related to CVD (smoking, dyslipidaemia, hypertension, diabetes, abdominal obesity, psychosocial factors, diet, alcohol consumption and physical activity) account for at least 90% of the PAR for myocardial infarction. The authors went on to conclude that modification of these conventional risk factors would thus, at least theoretically, have the potential to prevent the vast majority of premature cases of myocardial infarction. Optimal control of these nine risk factors is clearly difficult to achieve, and would involve intervention in a vast majority of the population, as only 0.4% of the INTERHEART study population had none of these nine risk factors. Most of those subjected to intervention would thus never develop premature myocardial infarction.

From an epidemiological and statistical point of view, the conclusions of INTERHEART with respect to the 90% PAR are correct. To conclude, however, that this finding leaves only 10% of the disease to be explained by additional, new CVD risk factors, is wrong. In fact, modification of other than the nine risk factors studied could also prevent a large proportion of disease. The key issue is a correct interpretation of the PAR statistic. To understand this, some introductory remarks on disease causality are important.

Causes are defined as characteristics or conditions without which a disease would not have occurred at all or would have occurred at some later time. CVD, like most diseases, is a complex disease in that it does not have a single cause, but many causes acting together in various combinations. In this context, individual risk factors are component causes. Once a number of component causes occur simultaneously and together are sufficient to cause disease, this constellation of risk factors is referred to as a sufficient cause. Only if a component cause is necessary for disease development will elimination of this single cause completely eliminate the disease. A necessary component cause is thus part of all possible sufficient causes for a disease, and disease cannot occur without its presence. As we have learned from clinical practice, none of the currently known cardiovascular risk factors qualifies as a necessary component cause (except perhaps for LDL-cholesterol, although levels need to be exceptionally low for CVD to be eliminated completely). Hence, in daily practice, CVD causality is based on a large, theoretically infinite number of possible combinations of component causes.

There is a tendency to think that the sum of the fractions of disease attributable to each of the component causes of a complex disease should be 100%. However, as explained by the American epidemiologist Rothman and others, the fraction of disease that can be attributed to each of the causes of the disease in all the causal mechanisms has no upper limit. This is illustrated in Figure 1. In contrast to the example in Figure 1, the number of constellations of causes that are sufficient to result in disease is extremely large. Particularly, if one considers the role of numerous, largely unmeasurable, ‘stochastic’ genetic and environmental factors that determine if disease occurs in a person or not, it is easy to understand that the maximum for the sum of the fractions of disease attributable to all the component causes is not 100%, but infinity.

**Figure 1** Why attributable fractions of disease causes add up to >100%

Consider a complex disease with component causes A to K, and four possible constellations of these component causes forming sufficient causes for disease, each responsible for 25% of disease cases after mutual adjustment. Elimination of component cause A would render constellations I–III insufficient and could thus prevent 75% of disease cases. Likewise, elimination of component cause B–D could each prevent 50% of disease, and elimination of component causes E–K would each prevent 25% of disease cases. In this theoretical model of 10 component causes and only four sufficient causal constellations, the sum of the fractions of disease occurrence attributable to each of the component causes adds up to 400%. In reality, the situation is more complex, as the distribution of attributable fractions of component causes within each of the causal constellations is variable, depending on the sequence of inclusion into risk models. However, the principle that attributable fractions can add up to >100% remains valid just the same.
Thus, although the high PAR of the nine risk factors in INTERHEART may well be correct in terms of the 90% proportion of CVD that could be prevented if these nine risk factors would be eliminated, this does not limit the available room for other risk factors in the context of disease causation. A recent report in Science, for example, described a single genetic polymorphism with an independent PAR for myocardial infarction of 21%.

Even though 90 + 21% exceeds 100%, this finding is not at odds with the INTERHEART conclusions. In fact, many combinations of CVD risk factors other than those included in the INTERHEART study, including ‘new’ risk factors, can produce a similarly high PAR of 90% or more.

**Do new risk determinants improve risk stratification?**

Even among those who interpret INTERHEART correctly, the clinical usefulness of new cardiovascular risk determinants, regardless of whether it concerns risk factors or markers of early CVD, is subject to doubt. The reason for this has been the publication of a series of papers suggesting that the performance of cardiovascular risk models does not improve upon inclusion of new risk determinants in these models on top of the conventional risk determinants. One example is a recent publication from the Framingham Study group. They studied 10 new biomarkers for cardiovascular risk assessment and found B-type natriuretic peptide and microalbuminuria as strong independent determinants of major cardiovascular events. However, adding these variables to the Framingham risk model reportedly did not improve the ability to classify risk. The key to understanding this apparent discrepancy between independent risk prediction but no improvement in risk classification is in the statistical methodology used for the assessment of the quality of risk models. As in most papers addressing this issue, the Framingham group used the so-called concordance, or c statistic to assess risk model performance. This c statistic refers to the area under the receiver operator characteristic curve, or ROC curve. The ROC curve is a plot of sensitivity vs. 1-specificity, thus representing diagnostic test characteristics of a continuous test score across the full range of cut-off points. In general, ROC curves serve two purposes. The first is to identify an optimum cut-off level for a diagnostic test outcome (represented by the most left-upper hand point of the ROC curve), and the second is to quantify the overall ability of a test to discriminate between two groups (represented by the c statistic). Ideally, the c statistic equals 1, representing 100% sensitivity and 100% specificity for a given level of the test outcome.

The c statistic is very useful for assessing the quality of a diagnostic test to distinguish those who are and those who are not affected by a disease. In terms of risk estimation for disease, the c statistic represents the probability that a person who later develops the disease has a higher test score than a person who does not develop the disease. As such, the c statistic is a measure of discrimination between those who will and those who will not develop disease. Discrimination would be perfect (i.e. a c statistic of 1) if the risk scores of all future cases would be higher than of all future non-cases, without overlap. Of note, the c statistic thus does not represent the probability of correct risk category classification. Even with perfect discrimination, only achievable in theory, predicted risks might still not match actual observed risks in prospective studies.

A more important issue in risk prediction than discrimination is how well predicted risks equal observed risks. This is referred to as model calibration. There are statistical measures of model calibration, like the Hosmer–Lemeshow statistic, but the key issue is to have predicted risks approach observed risks as close as possible. Although one might intuitively expect that adding an important new risk determinant to a risk model would improve both model discrimination and calibration, this is often not the case. Generally accepted risk factors such as smoking and dyslipidaemia have been shown to fail to augment the c statistic when added to risk models including just age and a single conventional risk factor. Failure of the c statistic to improve in this situation is not just a matter of relative unresponsiveness of this parameter to improved risk estimation. Even in perfectly calibrated models, where estimated risks match observed risks perfectly, there is a theoretical maximum to the c statistic, depending mainly on the distribution of risk in the population. In populations in which risk models are commonly used, the risk distribution is usually such that the theoretical maximum c statistic of a perfectly calibrated model is only around 0.75 to 0.80. Additional factors limiting the maximum value of the c statistic are competing risks, and regression dilution bias that often occurs in prognostic studies.

Clearly, sole reliance on the c statistic to judge whether new risk determinants offer additional value in risk estimation is wrong. Although failure of the c statistic to substantially improve after addition of a new risk determinant makes it unlikely that the model markedly improves risk stratification in the population as a whole, calibration might still improve, particularly in subgroups, such as those with an intermediate risk. Comparison of several risk models in the Women’s Health Study has recently shown that calibration can be different between risk models despite similar values for the c statistic. Addition of C-reactive protein to a risk model containing only the conventional cardiovascular risk determinants, has been shown to improve calibration of this risk model despite very similar values for the c statistic.

Not in all situations, however, does better calibration lead to a more useful risk prediction model. New risk factors that change risk estimates to a moderate degree only in very low- or very high-risk individuals, for example, will usually not lead to different treatment decisions. The usefulness of a new risk determinant is ultimately best judged by assessing its potential to reclassify individuals into risk categories that are associated with different treatment strategies. Usually, this means that individuals change from low (i.e. <10%) to intermediate (10–20%) risk or from intermediate to high (>20%) risk, or vice versa. Only if a substantial number of individuals change between such risk categories, and these reclassifications are proven correct, will application of the new risk model change clinical practice. An example of how...
reclassification can be addressed statistically is provided in a recent paper.\textsuperscript{23} The criteria on which to judge whether or not reclassifications are clinically relevant are, however, commonly subject to debate.\textsuperscript{23,26}

The ‘natural course’ of newly discovered cardiovascular risk determinants

New cardiovascular risk determinants travel a long way from first discovery to proven added value in risk models. The first step is identification of a high relative risk associated with the risk determinant in multiple regression models in independent prospective studies. These regression models should subsequently be judged for parsimony and practicality, and redesigned accordingly. Then, the risk model derived from the regression models should be tested against other risk models in terms of both discriminatory power (i.e. the c statistic) and optimal calibration (i.e. the Hosmer–Lemeshow statistic). Finally, the degree to which the new risk model causes clinically relevant changes in risk category classification compared to previous models and the fraction of correct reclassifications are the final tests to be passed.

It is important to remind that, even if new risk determinants do not improve risk stratification, studying their role may increase understanding of pathophysiology. Hyperhomocysteinemia, for example, may not qualify as a risk factor that improves risk stratification that has proven treatment effects, but addressing the question of what is the pathophysiological link between homocysteine and atherothrombosis might still provide valuable knowledge.\textsuperscript{27}

A final important point to be made is that when markers of early CVD would play a more important role in future risk models, these models can no longer be used guide treatment. Even for a strong causal risk factor, its weight in risk prediction models does not necessarily reflect its importance for risk reduction. It is, for example, conceivable that a future risk model including a strong marker of early coronary atherosclerosis would put little or even no weight at all on LDL cholesterol as a predictor of CVD risk. Even then, the 30% risk reduction associated with LDL cholesterol reduction would nonetheless remain the same.

In conclusion, new risk determinants exist and can be useful for risk stratification in daily practice. This has been explained for CVD, but the general principles outlined in this paper apply to many other diseases as well (e.g. prediction of cancer). In studies of disease causation, a high PAR of conventional risk factors should not discourage the search for new risk factors. New risk factors as well as markers of early disease should be judged for their potential to improve risk stratification in the proper way, not by relying on incomplete or inappropriate statistical approaches. Only then can we move forward in cardiovascular risk estimation and optimise preventive strategies.

Conflict of interest: none declared.

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