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Article

The tyranny of the averages and the indiscriminate use of risk factors in public health: The case of coronary heart disease

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ABSTRACT

Modern medicine is overwhelmed by a plethora of both established risk factors and novel biomarkers for diseases. The majority of this information is expressed by probabilistic measures of association such as the odds ratio (OR) obtained by calculating differences in average "risk" between exposed and unexposed groups. However, recent research demonstrates that even ORs of considerable magnitude are insufficient for assessing the ability of risk factors or biomarkers to distinguish the individuals who will develop the disease from those who will not. In regards to coronary heart disease (CHD), we already know that novel biomarkers add very little to the discriminatory accuracy (DA) of traditional risk factors. However, the value added by traditional risk factors alongside simple demographic variables such as age and sex has been the subject of less discussion. Moreover, in public health, we use the OR to calculate the population attributable fraction (PAF), although this measure fails to consider the DA of the risk factor it represents. Therefore, focusing on CHD and applying measures of DA, we re-examine the role of individual demographic characteristics, risk factors, novel biomarkers and PAFs in public health and epidemiology. In so doing, we also raise a more general criticism of the traditional risk factors' epidemiology. We investigated a cohort of 6103 men and women who participated in the baseline (1991–1996) of the Malmö Diet and Cancer study and were followed for 18 years. We found that neither traditional risk factors nor biomarkers substantially improved the DA obtained by models considering only age and sex. We concluded that the PAF measure provided insufficient information for the planning of preventive strategies in the population. We need a better understanding of the individual heterogeneity around the averages and, thereby, a fundamental change in the way we interpret risk factors in public health and epidemiology.

1. Introduction

Modern medicine is overwhelmed by a plethora of both traditional risk factors and novel biomarkers for diseases. All over the world, large amounts of economic and intellectual resources are allocated to the identification of new biomarkers and risk factors for diseases. For this purpose, we normally use simple measures of average association such as the relative risk (RR) or the odds ratio (OR). When using those measures, the implicit expectation is that of our capacity to accurately distinguish the individuals who will develop the disease from those who will not, improves (Pepe, Janes, Longton, Leisenring, & Newcomb, 2004) in order for the provision of targeted preventive intervention. From a population-level perspective, we also use the RR or the OR of those risk factors to calculate the population attributable fraction (PAF). The PAF aims to distinguish the share of the disease burden in a population that is attributable to a certain risk factor and, therefore, is potentially preventable (Merlo and Wagner, 2013; Rockhill., Newman, and Weinberg, 1998).

Abbreviations: AUC, Area under the ROC curve; ACE, Average causal effect; CABG, Coronary artery bypass graft; CHD, Coronary heart disease; CRP, C-reactive protein; DA, Discriminatory accuracy; FPF, False positive fraction; HR, Hazard ratios; HDL, High-density lipoprotein cholesterol; ICE, Individual causal effect; Lp-PLA2, Lipoprotein-associated phospholipase A2; LDL, Low-density lipoprotein cholesterol; NTBNP, N-terminal pro–brain natriuretic peptide; OR, Odds ratio; PCI, Percutaneous coronary intervention; PAH, Phenylalanine hydroxylase; PKU, Phenylketonuria; PAF, Population attributable fraction; RCT, Randomized clinical trial; ROC, Receiver operating characteristic; RR, Relative risk; MDC study, The Malmö Diet and Cancer; TPF, True positive fraction

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A classic example of the prevailing risk factors approach concerns preventive strategies for coronary heart disease (CHD) in which traditional risk factors such as, for example, smoking habits and blood pressure are systematically evaluated in healthcare, frequently within a risk score equation such as the Framingham, SCORE, QRISK, etc. (Cooney, Dudina, and Graham, 2009; Greenland et al., 2003). Thereafter, individuals receive treatment according to their predicted level of disease risk. Namely, screening and preventive interventions are closely linked since the measurement of risk factors is aimed at discriminating which individuals are, and which are not, candidate for different degrees of preventive treatment (Rockhill, 2005).

Nevertheless, during the last few decades, a number of relevant publications (Boyko and Alderman, 1990; Khoury, Newill, and Chase, 1985; Pepe et al., 2004; Royston and Altman, 2010; Wald, Hackshaw, and Frost, 1999; Ware, 2006) have pointed out that measures of association alone are unsuitable for this discriminatory purpose. In fact, what we normally consider as a strong association between a risk factor and a disease (e.g., an OR for a disease of 10), is related to a somewhat low capacity of the risk factor to discriminate cases and non-cases of disease in the population (Pepe et al., 2004; Wald et al., 1999). Pepe et al. (2004), illustrated that, in order to obtain a suitable discriminatory accuracy (DA) of, for example, a true positive fraction (TPF) = 90% and a false positive fraction (FPF) = 5%, we would need an OR = 176. See Fig. 1 and elsewhere (Pepe et al., 2004) for an extended explanation.

Therefore, from a clinical and even from a public health perspective, it is not enough to know the magnitude of the association between the exposure and the disease, what matters most is its DA, i.e., the capacity of the exposure to discriminate between individuals who will subsequently suffer a disease from those who will not. It does not matter whether the exposure is a novel biomarker, a traditional risk factor (Juarez, Wagner, and Merlo, 2013; Rodriguez-Lopez, Wagner, Perez-Vicente, Crispi, and Merlo, 2017), or any other exposure categorization shaped by socioeconomic (Axelsson-Fisk & Merlo, 2017), ethnic (Wemrell, Mulinari, & Merlo, 2015), geographic (Merlo, Wagner, Ghith, and Leckie, 2016), or other criteria (Merlo and Mulinari, 2015; Wemrell, Mulinari, and Merlo, 2017b). Therefore, and from a public health perspective, it seems necessary to not only revisit the value added of both traditional risk factors and novel biomarkers over and above simple demographic characteristics such as age and sex, but also

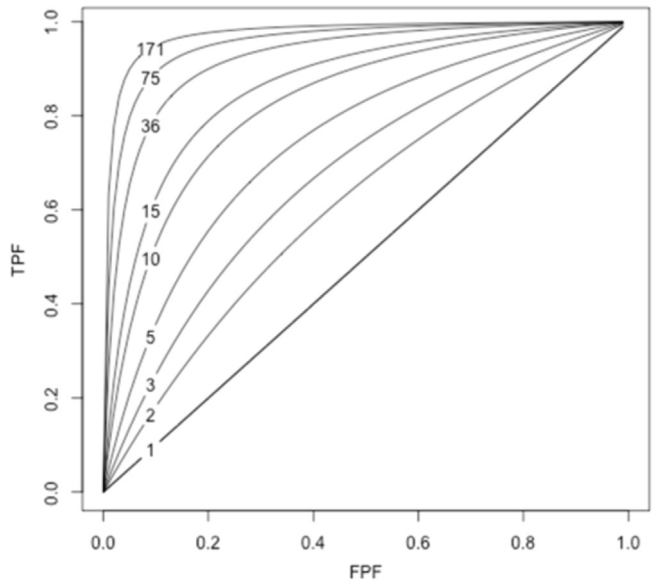

Fig. 1. Correspondence between the true-positive fraction (TPF) and the false-positive fraction (FPF) of a binary risk factor and the odds ratio (OR). Values of TPF and FPF that yield the same OR are connected (The figure has been created following the model described elsewhere by Pepe et al. (2004).

even the interpretation of the PAF, since this measure does not consider the DA of the risk factors it represents (Merlo and Wagner, 2013).

This critical approach is of fundamental relevance since —in analogy with diagnostic tests— promotion of screening and treatment of risk factors/biomarkers with a low DA may lead to unnecessary side effects and costs. The approach also raises ethical and political issues related to risk communication (Li et al., 2009) and the perils of both unwarranted medicalization (Conrad, 2007) and stigmatization of individuals with the risk factor/biomarker. There is also a growing apprehension that financial interests might lead to a market-driven approach to introducing and expanding screening (Andermann and Blancquaert, 2010) and treatment. In the end, an indiscriminate use of risk factors and biomarkers with low DA may shadow the identification of relevant health determinants and harm the scientific credibility of modern epidemiology.

The ideas discussed above are relevant in many areas of clinical and public health research. For instance, the incremental value of assessing levels of biomarkers (e.g., C-reactive protein, Cystatin C, $LpPLA_2$, NTBNP) in combination with traditional risk factors (e.g., cholesterol, blood pressure, smoking, diabetes) for the prediction of cardiovascular diseases has been debated (Cooney et al., 2009; Melander et al., 2009; Wald & Law, 2004; Zethelius et al., 2008). Moreover, some authors have even questioned the value of adding information on various traditional risk factors to risk predictions based exclusively on age (Wald, Simmonds, and Morris, 2011). In fact, the historical identification of risk factors was not based on an exhaustive scrutiny of all candidate factors supported by measures of DA. Indeed, the identification and use of traditional risk factors was promoted by insurance companies on the basis of simple physiopathological mechanisms (e.g., hypertension) and the availability of measurement instruments (e.g., the sphygmomanometer) (Kannel, Gordon, & National Heart Institute (U.S.), 1968; Keys, 1980; Rothstein, 2003).

In the present study, focusing on CHD, we investigate two concrete questions. Firstly, we aim to quantify the extent to which the DA of the simple demographic variables age and sex is improved by adding traditional cardiovascular risk factors and novel biomarkers. Although seemingly straightforward, this question has nevertheless been scarcely discussed in the literature (Wald et al., 2011). Secondly, we aim to analyze the relation between measures of PAF and the DA of the risk factors used for the computation of the PAF. This issue is of central relevance to planning strategies of prevention based on specific risk factors or a combination of them. For the purpose of our study, we reanalyze data from the cardiovascular cohort of the Malmö Diet and Cancer (MDC) study (Melander et al., 2009).

2. Population and methods

2.1. Subjects

The MDC study is a population-based, prospective epidemiologic cohort of 28 449 individuals enrolled between 1991 and 1996. From this cohort, 6103 individuals were randomly selected to participate in the MDC cardiovascular cohort, which was primarily designed to investigate the epidemiology of carotid artery disease (Persson, Hedblad, Nelson, and Berglund, 2007). From this sample, we excluded participants with prior coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), ischemic heart disease, or myocardial infarction or stroke at baseline (n = 176).

Of the remaining 5927 participants, 5054 had complete information on traditional risk factors, 4764 on biomarkers, and 4489 on both traditional risk factors and biomarkers. See Fig. 2 for more detailed information. The analyzed sample did not differ from eligible participants in the original MDC cardiovascular cohort with regards to mean age, sex, mean systolic and diastolic blood pressure, mean body mass index, and smoking prevalence (Melander et al., 2009).

The database is available on request from the MDC study project