

## What's in a risk factor? "He who strikes the ball"

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### SUMMARY

A major aim of epidemiology is to explore the prognosis and aetiology of diseases, in order to improve treatment and prevention. To avoid misleading interpretations of observed associations between a modifier and the occurrence of a disease, the all-purpose idiom "risk factor" should be replaced by 3 locutions with narrower meanings: a risk marker is a modifier which is associated (correlated) with disease prevalence (case-control studies) or incidence (cohort studies); a risk marker truly becomes a risk factor if its experimental correction (intervention studies) does improve the disease incidence or prognosis; a risk factor is promoted to the rank of cause if it is proved to be necessary (*sine qua non*) for the occurrence of the disease. A more rigorous vocabulary avoids premature claims for unsubstantiated treatments or preventions, and helps defining sound priorities in aetiological research.

**Key-words:** Risk Factor · Risk Marker · Cause · Coronary Artery Disease · Epidemiology.

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### RÉSUMÉ

**Qu'est-ce qu'un facteur de risque ? « Celui qui frappe la balle »**

Un objectif majeur de l'épidémiologie est d'étudier le pronostic et l'étiologie des maladies, en vue d'améliorer leur traitement et leur prévention. Pour éviter les interprétations fallacieuses des associations observées entre un modificateur et la survenue d'une maladie, la locution « facteur de risque » est à remplacer par 3 expressions d'acceptions plus étroites : un marqueur de risque est un modificateur qui est associé à (en corrélation avec) la prévalence (études cas-témoins) ou l'incidence (études de cohorte) de la maladie ; un marqueur de risque devient un authentique facteur de risque si sa correction expérimentale (études d'intervention) améliore effectivement l'incidence ou le pronostic de la maladie ; un facteur de risque accède au rang de cause s'il est démontré qu'il est nécessaire (*sine qua non*) à la survenue de la maladie. Un vocabulaire plus rigoureux évite les promotions prématurées de traitements et de préventions sans fondement, et aide à définir les justes priorités en recherche étiologique.

**Mots-clés :** Facteur de risque · Marqueur de risque · Cause · Maladie coronaire · Épidémiologie.

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**M**any diseases still lack causes. "Risk factor" is a widely used expression in many fields of clinical practice and aetiological research. In cardiovascular medicine, the concept has emerged in the late 1950s, with Ancel Keys [1] and Jeremiah Stamler [2] as two of its keenest promoters. Yet, several authors, such as Philip Burch [3], have criticized insistently some very frequent misconceptions about risk factors, and urged to interpret epidemiological results more thoughtfully.

The most common abuse is to view as causal any epidemiological association between a condition – henceforward called a modifier – and a disease. Such a mistake is not entirely innocuous, as it leads to unwarranted medical recommendations (mainly life style modifications, and life-long drug prescriptions), and to the intellectual illusion that a disease is almost entirely explained, and thus preventable (if all identified "risk factors" are correctly dealt with), rendering further research needless, because it should add very little to our useful knowledge. In other words, a fallacious interpretation of risk factors allows many to say "I know", when in fact we do not know so well. The moral comfort of risk factors is the main reason for their misuse: "I avoid or do not have the risk factor, therefore I am protected against the deadly disease". There lays a pernicious conflict of personal interest that feeds false hopes about risk factors and prevention in the medical world and, to a much more naïve extent, in the lay public. In an effort to put the record straight, I shall start from the basic principles of epidemiology, before progressing to the concepts of causality in medical research.

## Etiological epidemiology

"Epidemiology is the study of disease in relation to populations. Like the clinical findings and pathology, the epidemiology of a disease is an integral part of its basic description" [4]. A first aim of epidemiology is measuring the frequency of a disease in a population: prevalence is the number of disease cases present in the population at one point in time; incidence is the number of new disease cases occurring in the population within a stated period of time.

Epidemiology also contributes to understanding the aetiology of this disease: aetiological epidemiology examines the relationship between the prevalence or incidence of a disease, and the existence of a modifier that might interfere with the existence of the disease. Case-control studies and cohort studies are the main tools of this descriptive part of epidemiology. Experimental epidemiology resorts to intervention studies (clinical trials) to assess whether intentionally changing the modifier, using some type of medical intervention, influences the incidence of the disease.

## Case-control studies

Two types of individuals are extracted from a population: cases (Ca) have the disease; controls (Co) do not have the

**Table 1**  
Case-control study.

Vegetarianism	Cases (Ca)	Controls (Co)
Yes	59	84
No	141	116
Odds (yes/no)	0.42	0.72
Odds ratio (OR = Ca/Co)		0.57

Vegetarianism in 200 Indian patients with a first acute myocardial infarction (cases), and in 200 age- and sex-matched controls without identifiable heart disease from the same hospital population [5]. The OR is significantly smaller than 1 (95% confidence interval: 0.35 to 0.85,  $p = 0.006$ ): vegetarianism is significantly less frequent in cases than in controls; it might protect against coronary heart disease. Knowing this result, are you ready to adopt vegetarianism, with the hope that you will reduce your risk of myocardial infarction by 43%?

disease. The subjects in each of these 2 groups are separated in 2 subgroups: those with (Ca+, Co+), and those without (Ca-, Co-) the potential modifier. The odds (O) for being exposed to the modifier is calculated in each group:  $O_{Ca} = Ca+/Ca-$ ,  $O_{Co} = Co+/Co-$ . Notice that the numerator and the denominator are exclusive of one another. The odds ratio is computed as  $OR = O_{Ca}/O_{Co}$ . If OR is significantly greater than 1 then the modifier is positively associated with the disease (*i.e.* is more frequent when the disease exists). The reverse is true (negative association) if the OR is significantly smaller than 1. Such an example is given in *Table 1* (vegetarianism and myocardial infarction) [5]. Among several other explanations of the association, one could be that the modifier favours ( $OR > 1$ ) or disfavours ( $OR < 1$ ) the disease, which might mean that the modifier could exert an aetiological influence (enhancement or protection). Each conditional tense in this last sentence is a heavy weight: without detailing the many pitfalls of case-control studies [6], there is indeed a very wide gap between a significant OR and the identification of a disease cause. In essence, odds reflect a prevalence: the ratio of "modified" to "non-modified" subjects in a population sample at one point in time. Odds should not be viewed as risks which, as defined below, reflect an incidence.

## Cohort studies

A cohort is a population sample which is submitted to a prospective observation [7]. At the outset, the modifier of interest is assessed in all subjects. During the whole duration of the study, each new (incident) or recurrent case of the disease is recorded. At the end, the disease incidence is examined in relation to the modifier, which is either a dichotomous variable (such as diabetes or tobacco smoking, present or absent), or a continuous variable (such as the level of blood cholesterol concentration, or systolic blood pressure). In each modifier category (categorical or dichotomous variable) or for each modifier level (continuous variable), the incidence

**Table II**

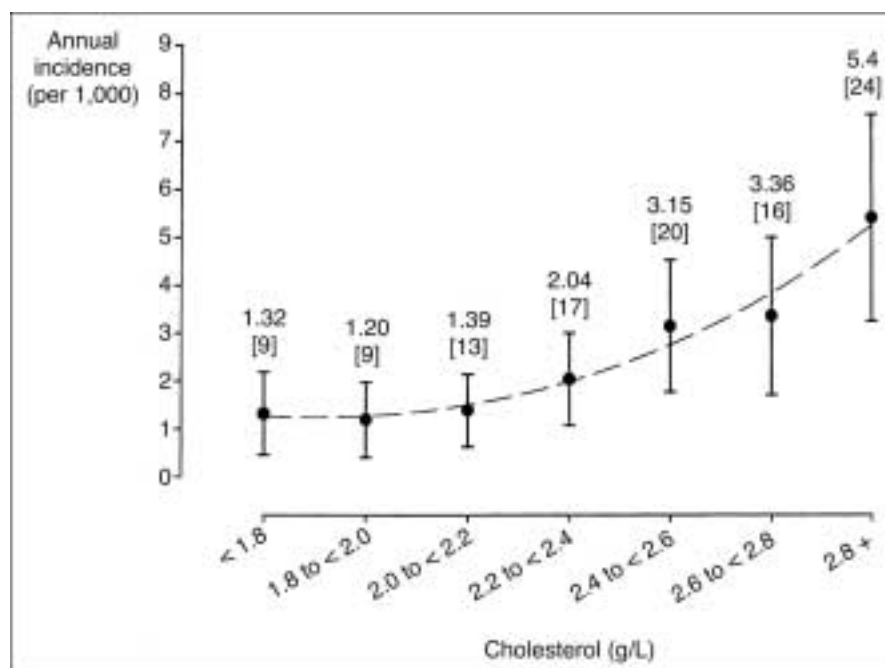
Cohort study (categorical variable).

Age	Diabetes	CVD death	Total at risk	Risk*	Risk ratio †	
					Crude	Adjusted
35-39	yes	16	422	3.79%	4.8	3.0
	no	576	72,144	0.80%	[2.9 to 7.7]	[1.8 to 5.0]
40-44	yes	43	713	6.03%	3.9	3.0
	no	1,174	76,060	1.54%	[2.9 to 5.3]	[2.2 to 4.0]
45-49	yes	99	1,195	8.28%	3.2	2.4
	no	2,113	81,079	2.61%	[2.6 to 3.9]	[1.9 to 3.0]
50-54	yes	264	1,857	14.22%	3.6	3.3
	no	3,114	78,687	3.96%	[3.2 to 4.0]	[2.9 to 3.8]
55-57	yes	181	976	18.55%	3.3	3.0
	no	1,988	34,845	5.71%	[2.8 to 3.7]	[2.6 to 3.5]
All	yes	603	5,163	11.68%	4.5	3.0
	no	8,965	342,815	2.62%	[4.1 to 4.8]	[2.8 to 3.3]

Diabetes (defined as taking medication for diabetes) and risk (incidence) of death from cardiovascular disease (CVD: coronary artery disease, stroke or other cardiovascular disease) in 347,978 men screened in the Multiple Risk Factor Intervention Trial [8], followed for 12 years. Results are stratified according to age at entry in study. Globally (last 2 lines) and in each age-stratum diabetes significantly increases CVD mortality: all crude or adjusted risk ratios are at least 2.4, and 95% confidence interval never includes 1. Risk increases with age in both diabetics and non-diabetics. \* Risk = incidence = number of CVD death divided by total number of men in age-group (Total at risk). † Risk in men with diabetes divided by risk in men without diabetes [95% confidence interval]; crude means directly computed from data in table; adjusted means after statistical adjustment for certain variables, other than diabetes and age, that are associated with CVD death: ethnic group, systolic blood pressure, serum cholesterol, and cigarettes smoked per day.

or risk of the disease is defined as the number of new disease cases divided by the total number of subjects in that subgroup. Notice here that the denominator includes the numerator. Risk ratio is the risk in one subgroup divided by the

risk in the other (or an other) subgroup. Examples are given in *Table II* for a categorical variable (diabetes and myocardial infarction) [8], and in *figure 1* for a continuous variable (cholesterol and myocardial infarction) [9].

**Figure 1**

Cohort study (continuous variable). Total plasma cholesterol concentration and incidence (risk) of myocardial infarction (fatal or non-fatal) in 7,746 middle-aged men followed for a mean of 6.6 years [9]. A total of 108 myocardial infarctions have been recorded. Seven intervals of cholesterolaemia have been defined to summarize the results. To convert grams to millimoles of cholesterol, multiply by 2.6. Observed risk (incidence) value and number of incident myocardial infarctions (within brackets) from which the risk has been calculated are indicated above each data point. Error bars indicate the 95% confidence interval of each risk value. Dashed curve is the 3<sup>rd</sup> order polynomial regression that best fits the data ( $r^2 = 0.98$ ). There is a significant positive association (correlation) between cholesterolaemia and risk of myocardial infarction. For instance, the risk is almost 4.2 times greater in men with cholesterol  $\geq 2.8$  g/L (5.41 per thousand) than with cholesterol  $< 1.8$  g/L (1.32 per thousand).

**Table III**  
Intervention study.

Endpoint		Simvastatin (S)	Placebo (P)	Risk variation*		
		N = 2,221	N = 2,223	Relative	Absolute	NNT †
Non-fatal MI	N	279	418	0.67	– 6.2%	16
	Risk	12.6%	18.8%	[0.56 to 0.80]	[– 5.7 to – 6.8%]	[15 to 18]
Coronary deaths	N	111	189	0.59	– 3.5%	29
	Risk	5.0%	8.5%	[0.44 to 0.79]	[– 3.1 to – 3.9%]	[26 to 32]
All deaths	N	182	256	0.71	– 3.3%	30
	Risk	8.2%	11.5%	[0.56 to 0.90]	[– 2.9 to – 3.8%]	[27 to 35]

Major mortality and morbidity results from the 4S study [10] comparing simvastatin treatment with placebo for a median duration of 5.4 years in 4,444 middle-aged Scandinavian men with coronary heart disease (secondary prevention) and a total plasma cholesterol concentration between 2.1 and 3.1 g (5.5 and 8.0 mmol)/L at randomisation. \* Relative risk variation is (S risk)/(P risk); absolute risk variation is (S risk) – (P risk). Values between brackets are 99% confidence intervals: risk difference between S and P is significant ( $p < 0.01$ ) if interval does not include 1 for relative risk, and does not include 0 for absolute risk. † Number needed treat: number of patients needing to be treated for 5.4 year with simvastatin to avoid one event; computed as  $- (100/\text{absolute risk variation})$ . Values between brackets are 99% confidence intervals. MI: myocardial infarction.

## Intervention studies

Clinical trials (prevention trials) are experimental studies (prospective, controlled, randomised, and most often double-blind) where the incidence of a disease is compared between a treated group (T) where the modifier is changed by a therapeutic intervention, and a control group (C) where such an intervention is not applied. The disease risks (incidences) observed in each group,  $R_t$  and  $R_c$ , are analyzed to assess the result. If the intervention has been beneficial:  $R_t/R_c$ , the relative risk variation, is significantly smaller than 1; and  $R_t - R_c$ , the absolute risk variation, is significantly smaller than 0. The number of patients needed to treat to avoid one incident case of the disease is the reverse of the absolute risk variation. *Table III* gives an example: treatment with a cholesterol-lowering drug and incidence of coronary heart disease [10].

## Interpreting epidemiological results

Clinicians are quite fond of aetiological epidemiology because it aims at uncovering causal associations, to provide means for improved prevention of diseases. Although unwise, it is quite tempting to jump from the least suggestion of an epidemiological association to a causal relationship with prophylactic implications.

In length, difficulty and cost, case-control, cohort and intervention studies are quite different investments. If weighed as evidence in favour of a causal link between a modifier and a disease, the strength of the results vary in the same proportion as the investment.

Case-control studies can only suggest the possibility of an association, provided that no hidden (or overlooked) bias has skewed the odds in favour of the control group: it is almost never possible to be absolutely sure that the only difference

between the 2 groups has been the presence of the disease in cases and its absence in controls.

Cohort studies are far stronger at establishing robust associations, provided that the modifier and the disease diagnosis have been assessed correctly and uniformly in all the cohort's subjects, *i.e.* blindly and prospectively. Common practices are open to criticism and weaken the strength of the result, such as: using the same cohort (in different reports) for assessing many modifiers for several diseases, without increasing the level of statistical significance to account for the multiple risk comparisons that are being made; opening the deep-freezer to measure retrospectively plasma components with no role suspected, whatsoever, as modifiers when the cohort was recruited. With these "good old tricks", some famous cohorts have indeed been "publication Niagara" in highly reputed medical journals.

Wrong interpretation of the association (correlation) between modifier and disease is the most common flaw in case-control and cohort studies: correlation does not imply causation; as epitomized by the "4 Cs rule" (*Tab IV*), cause is but one explanation for correlation, along with consequence and coincidence.

Only intervention studies can establish causality, through direct demonstration of reversibility: changing the modifier experimentally does indeed change the disease incidence, as predicted from the correlation found in case-control and cohort studies. For instance, 4S [10] (*Tab III*) has been the first study to prove that lowering plasma cholesterol does improve the prognosis of coronary heart disease, as suggested by many correlation curves (*Fig 1*) drawn from different populations. Lowering plasma cholesterol with a statin has become a recognized and highly efficient means for preventing coronary events [11].

**Table IV**  
The 4 Cs rule.

Meaning of link		Example		
Cause	Modifier	→	Disease	Hypercholesterolaemia and CHD
Consequence	Disease	→	Modifier	Coronary artery calcifications and CHD
			↗	Modifier
Coincidence	Disturbance	↘	Disease	enhances CHD*

Meaning of link implied by a significant correlation between a modifier and a disease, with examples from coronary heart disease (CHD). Correlation may imply Cause, Consequence or Coincidence.\* Diabetes is a confounding factor (confounder), but not a pathogenic factor, in statistical association between microalbuminuria and CHD.

## Vocabulary of risk and cause

Having described the major epidemiological sources of aetiology, we must come to the semantics, *i.e.* the words used to convey this knowledge, and to apply it to prognostic and therapeutic practice.

In real life, spoken and written medical aetiology is dominated by “risk factors”, one single idiom used to cover all types of associations between a modifier and a disease, from the weakest (hardly significant odds ratio drawn from a strongly biased case-control study) up to the strongest (clinical trial with ground breaking results). Such a simplification is deceptive, because an ill-informed consumer (prescribing doctor) may be unaware of the different realities that are hidden behind the same and only two words – risk factor.

Factor derives from the Latin noun *factor*, meaning a maker, doer, performer, perpetrator, and, in ball-playing, he who strikes the ball [12]: factor unambiguously implies cause. A richer language with clear-cut items must be promoted, based upon 3 terms: risk marker, risk factor, and cause (*Tab V*).

### Risk marker

A risk marker, or risk indicator, is a modifier which is significantly associated with a disease prevalence (odds from a case-control study) or incidence (risk from a cohort study). Owing to their abundance of unavoidable bias, case-control studies only identify potential risk markers, which are less strong than risk markers pointed out by well designed cohort studies (where biases, although not absent, are more reliably controlled).

A risk marker is independent when statistical adjustments and multivariable analyses are unable to show an in-

**Table V**  
Vocabulary of risk and cause.

Modifier	Definition
Risk marker (indicator)	Physiologic or pathologic trait which is associated with prevalence (case-control study) or incidence (cohort studies) of disease
Risk factor	Risk marker which is experimentally (intervention study) linked with prognosis of disease: improvement of risk marker lowers incidence of disease
Cause	Risk factor which is necessary (indispensable) for development ( <i>sine qua non</i> ) of disease

termediate modifier in its association with the disease. Conversely, a risk marker is indirect when such an intermediate (confounder) exists. An example is the relation between elevated plasma triglyceride and high-density lipoprotein (HDL) concentrations, on one hand, and increased risk of coronary heart disease, on the other hand. Both modifiers are tightly and inversely correlated with one another. It is still debated whether HDL concentration is the independent risk marker, and triglyceridaemia the indirect one [13]. Clinical trials have not yet been able to solve the issue definitively.

The number of coronary risk markers is enormous: in 1981, Hopkins and Williams published “a survey of 246 suggested coronary risk factors” [14], a wise wording, indeed, as almost all were drawn from case-control studies. Of course, such a laudatory comment does not apply to the title of reference 5: by now, what is your answer to the question below *Table I*?

### Risk factor

A risk factor is a risk marker whose modification in the right direction, as assessed in an intervention trial, does decrease the incidence of the disease, as compared to no modification. This definition should be preferred because it establishes a more clear-cut difference than the ambiguous distinction between “risk factor” (instead of risk marker) and “causative risk factor” (a pleonasm for risk factor).

Coronary artery disease has many risk markers, but only two established risk factor so far: high concentration of plasma low-density lipoprotein (LDL) cholesterol, and high blood pressure. For these two markers, cohort studies have been unanimous at demonstrating correlations of the type shown in *figure 1*.

Six intervention studies, using simvastatin [10, 11], pravastatin [15-17] or lovastatin [18], have firmly established that lowering LDL-cholesterol with an inhibitor of hydroxymethyl-glutaryl coenzyme A reductase (statin) reduces the incidence of coronary events, in agreement with what had been predicted from the cohort study. An average reduction in LDL-cholesterol of about 1 mmol (0.4 g)/L for about 5

years produces a reduction in non-fatal myocardial infarction and coronary death of about 25%, which is about half the effect associated epidemiologically (cohort studies) with a long-term difference of 1 mmol/L in people without diagnosed vascular disease [11]. In other words, the risk factor is half as influent as the risk marker. In addition, the Heart Protection study [11], the largest and most recently published of these clinical trials, has demonstrated that the preventive effect is independent of cholesterol concentrations (total and LDL fraction) measured before treatment. It mostly depends upon the global risk of coronary event in each candidate for prevention. We are therefore in an awkward situation – a kind of “risk factor suicide” – where the decision for treating is not based any more upon the level of the targeted risk factor, and where the treatment aimed at this factor is likely to act, at least in part, through mechanisms other than decreasing the level of this risk factor – the so called non-cholesterol or pleiotropic effects of statins: anti-inflammatory, antithrombotic, vasomotor, or immunomodulatory actions [19]. Further supporting evidence is derived from the cholesterol controversy: before the statin trials, there remained strong doubt as to whether cholesterol lowering with diets or non-statin drugs did protect significantly against coronary events [20].

Old-style antihypertensive treatments (mostly diuretics, and centrally-acting agents) have also decreased the incidence of coronary events by just over half the epidemiologically expected reduction from the correlation curves in cohort studies (14% *vs.* 20-25%) [21]. Modern drugs ( $\beta$ -blockers, calcium-channel blockers, and angiotensin II inhibitors) with additional cardiovascular protective effects may improve the record, but this remains a warmly debated issue [22] (with obvious commercial interests).

Regarding other coronary risk markers with strong correlations in cohort study, promotion to the status of risk factor is still unachieved. Tighter glycaemic control in type 1 or type 2 diabetes [23, 24] has failed to reduce the incidence of coronary events significantly. Multiple risk marker interventions that included efficient advice against tobacco smoking have also failed [25]. This poses an interesting theoretical issue, but in no way a decision dilemma: whether or not they be coronary risk factors, diabetes mellitus and tobacco smoking mandate intervention, owing to their well established noxiousness for general health.

A problem with our restrictive definition of a risk factor is that non-modifiable risk markers, such as age, male sex or genetic make-up, cannot access to the rank of risk factors. This also is a theoretical, rather than operational issue: it does not interfere with the medical decision of a preventive intervention but for estimating the level of risk.

## Cause

Cause is a complex notion, with many legal, religious or philosophical implications. A keen reader of Aristotle, the

Persian physician Avicenna (980-1037) introduced the peripatetic reasoning on causes in medicine. He distinguished various types: four were implied in the mechanisms of diseases – the material (viscera, spirits and humours), the formal (forces and complexions), the acting (occasional interventions of non-natural things) and the final (organ functions) causes; three causes were implied in the aetiology of diseases – the antecedent (*sabikéh*), the originary (*badyyéh*), and the occurring or jointed (*wasilch*), corresponding to what has been called predisposing, occasional and immediate causes in the XVIII<sup>th</sup> century [26].

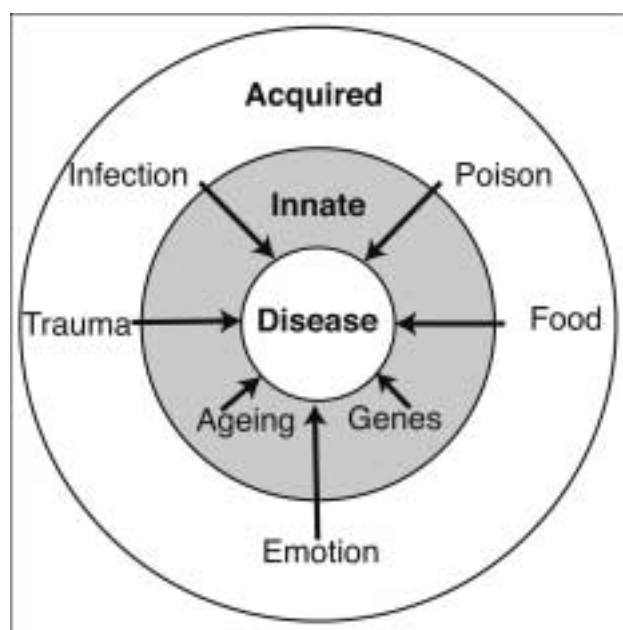
To make things simpler and medically operational (*i.e.* to allow the eradication of a disease), all diseases are to be viewed as multifactorial, with many factors intervening in their hatching. Some are facultative (auxiliary or adjuvant), and are to be called final (secondary) causes, or risk factors. Some factors (often sole and only) are necessary, although generally not sufficient, and are to be called efficient (primary), or simply causes. Human tuberculosis, for instance, has one cause – a contact with *Mycobacterium tuberculosis* – and several risk factors – infectivity of the bacterium, host defences – that render the agent infectious for its host. Although not unique, neutralizing *M. tuberculosis* (prophylactic interventions, vaccination, antituberculous drugs) is the most effective means for avoiding or curing the disease. One might say that life itself is the ultimate primary cause of all diseases, but this is certainly not a medically useful definition. *Figure 2* is an attempt at summarizing the main causes and factors of diseases.

A cause is a *sine qua non* risk factor: in its absence, the disease never exists; in its presence, the disease may occur. None of the known coronary risk factors is a cause of coronary heart disease, which is often observed without increased plasma LDL-cholesterol or high blood pressure. The true causes (or cause) may be hidden in the cohort of risk markers that have been identified so far [14], or elsewhere in an as yet unexplored domain of aetiology. Let's keep our minds open.

## Cave factorem

Coronary artery disease has many risk markers, two risk factors, but no known cause. Ignoring this sterilizes useful research ventures, and maintains the illusion that full prevention is already at hand: its partial efficiency is only due to the mediocre implementation of what we know. Owing to the urgency of better results, instead of eagerly looking for a lacking cause, the priority is put upon correcting risk markers that have scored well in cohort studies, and for which modifying treatments are available.

A sore example of confusion between a risk marker and a risk factor has been the relationship between postmenopausal oestrogen deprivation and the increased incidence of ischaemic heart disease. Much epidemiological evidence from case-control and cohort studies had established the as-



**Figure 2**

A wheel of aetiology. This wheel summarizes the main causes and risk factors of human diseases. Disease (hub) is due to one individual's "nature" (innate, rim) and "nurture" (acquired, tyre), or, most often, to a combination of the two. The effect of an acquired agent is generally modulated by the individual's innate (age, genetic make-up). "Poison" pools external (such as heavy metals or drugs) and internal (such as high plasma glucose or cholesterol) toxic compounds. As most diseases are multifactorial, it can be difficult to single out risk markers (suggested causes), risk factors (auxiliary causes) and primary causes (*sine qua non*). An identified cause is a major – although not sole – contribution to the definition of a disease. For instance, a trauma (which can be heavy or light) is the cause (necessary, but not sufficient) of a hip fracture, but influences that fragilize bone play an essential role: old age; familial susceptibility to bone weakness; poisons such as corticosteroid drugs, postmenopausal oestrogen deprivation in women, or alcohol; food deficiency in calcium and vitamin D. For coronary artery disease, main acquired influences (either potential, risk markers, or established, risk factors) are or could be: internal poisons, such as diabetes or increased LDL-cholesterol; food items, such as excessive consumption of saturated fatty acids or insufficient consumption of fish, fruits and vegetables; stressing emotions; arterial trauma of high blood pressure; viral or bacterial infections. No true cause (*sine qua non*) has yet been identified.

sociation and suggested that hormone replacement therapy (oestrogen with or without progestin) might cut by up to 55% the risk of coronary events. Expert panels judged the evidence strong enough to consider this potential benefit when deciding whether to use postmenopausal hormonal therapy [27]. Yet, several prospective clinical trials have ruined this hope: as compared with a placebo, combined oestrogen and progestin therapy does not decrease, and may even slightly increase the risk of coronary events in postmenopausal women [28-30]. A "healthy cohort bias" probably accounts for this discrepancy: in cohort studies, hormonal substitution is not randomly allocated; women who choose it differ from non-users in crucial ways (such as better general health,

health awareness, or socio-economic status) [31]. Antioxidant vitamin supplementation [32] or cholesterol-lowering diets [33] and even interventions (without a statin) against multiple "risk factors" [25] have been other dismaying failures in extrapolating from suggestive correlations to prevention of coronary heart disease. As a last example, recommending moderate alcohol drinking is not sound medical advice: cohort studies show a negative correlation with coronary heart disease [34], but do not allow an extension to established protection when the quantitative understanding of moderation varies so widely between individuals. The message carries far more undisputed risks than alleged benefits.

Further daring research is needed. New markers for coronary heart disease are being unearthed, such as arterial infections [35] or increased plasma C-reactive protein [36]. Others will come out. We must give each of them a fair opportunity of being tested through each step of well reasoned aetiology, unless we accept the costly risks of rejecting or adopting them prematurely, and unless we are so fond of "we do it... but must not any more" conclusions [20, 25, 30, 32, 33]. Emergency does not justify uncontrolled hurry.

*Cave factorem*: beware of the factor. The warning holds for goalkeepers, and for preventers as well.

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