ELSEVIER Artificial Intelligence in Medicine 12 (1998) 227–270

Artificial Intelligence in Medicine

Fundamentals of clinical methodology: 2. Etiology[1]

Kazem Sadegh-Zadeh *

University of Münster Medical Institutions, Theory of Medicine Department, 48149, Münster, Germany

Accepted 31 August 1997

Abstract

The concept of etiology is analyzed and the possibilities and limitations of deterministic, probabilistic, and fuzzy etiology are explored. Different kinds of formal structures for the relation of causation are introduced which enable us to explicate the notion of cause on qualitative, comparative, and quantitative levels. The conceptual framework developed is an approach to a theory of causality that may be useful in etiologic research, in building nosological systems, and in differential diagnosis, therapeutic decision-making, and controlled clinical trials. The bearings of the theory are exemplified by examining the current Chlamydia pneumoniae hypothesis on the incidence of myocardial infarction. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Etiology; Causation; Positive cause; Negative cause; Causal relevance; Fuzzy causal relevance; Deterministic etiology; Probabilistic etiology; Fuzzy etiology; Causal diagnosis; Clinical methodology; Medical knowledge engineering; Chlamydia pneumoniae; Coronary heart disease; C-reactive protein; Aspirin; Treatment efficacy analysis

* E-mail.: kzadeh@smi.stanford.edu

[1] To the memory of Professor Karl Eduard Rothschuh on the occasion of the 90th anniversary of his birthday. This paper is the first part of the updated version of [13] that I had once dedicated to Professor Rothschuh as a contribution to his '65 Festschrift. We are still waiting for the Festschrift, however. The second part on nosology will appear as [21].

PII S0933-3657(97)00053-5

1. Introduction

Clinical knowledge-based systems research may be viewed as the advent of an engineering science of clinical judgment that will pave the way for the development of clinical reasoning machines and the automation of clinical decision-making. This automation will outperform the physician's confined diagnostic-therapeutic problem-solving capabilities to simply allocate to her the role of a mobile peripheral for gathering patient data. The adequate representation of the relevant medical knowledge clinical reasoning is based on therefore requires that the clinical knowledge engineer be aware of the methodological and epistemological problems associated with (1) the concept of patient data, (2) the relations between these data and (a) diseases and pathological processes on the one hand, and (b) their causes, on the other. The area concerned with 2a is referred to as *nosology*, and the area concerned with 2b is termed *etiology*. (Nosos = disease; aitia = cause.)

This paper deals with some basic problems of etiology mentioned above, and may therefore be classified as metaetiology. (Nosology will be dealt with in the sequel [21]). The conceptual foundations of etiology are analyzed and the possibility of deterministic, probabilistic, and fuzzy etiology is explored. Different kinds of conceptual structures for the relation of causation are introduced which enable us to reconstruct the notion of cause on four distinct levels and with two shapes, positive and negative:

A is a positive cause of B in class X	(qualitative level)
A is a stronger positive cause of B in class X than is C	(comparative level)
A is to the extent 0.8 a positive cause of B in class X	(quantitative level)
A is a highly positive cause of B in class X	(fuzzy level)
A is a negative cause of B in class X	(qualitative level)
A is a stronger negative cause of B in class X than is C	(comparative level)
A is to the extent -0.3 a negative cause of B in class X	(quantitative level)
A is a weakly negative cause of B in class X	(fuzzy level)

The qualitative level may be exemplified by the following two conjectures we have probabilistically extracted from current literature and thoroughly analyzed: (1) Chlamydia pneumoniae infection is a positive cause of coronary heart disease in the population of non-diabetics; (2) aspirin is a negative cause of myocardial infarction in men with elevated C-reactive protein concentrations.

The framework developed in this way may help adequately manage some of the methodological difficulties emerging in etiology, epidemiology, in systematizing nosology and in causal differential indication on the one hand [19], and in the engineering of causal knowledge, on the other. Our analysis of etiology in this paper precedes our discussion on nosology in the sequel because the cause-effect terminology is needed for the latter.

2. Preliminaries

Etiology is the inquiry into clinical causation. It deals with the question of how a particular *clinical event* such as

a symptom or a set of symptoms,
a sign or a set of signs,
a pathological state or a set of pathological states, and
a disease or a set of diseases

in class level, not in an individual patient, is generated. For example, 'What is the cause of lupus erythematosus?' is an etiologic question. The goal is to identify the causes of human and animal suffering insofar as this suffering presents itself as illness to call upon medical responsibility. The rationale behind this etiologic endeavor comprises the following two basic postulates: First, cure for and prevention of clinical events presuppose knowledge about their causes. Second, a clinical event will disappear if its cause is removed [14,17]. Although these protoetiologic postulates are not quite true, they demonstrate how important in medical research and practice the belief in the role of causes may be. Since this belief strongly governs both medical actions and public trust in medicine, it is highly desirable that the knowledge on causes etiology is producing, be well-grounded. But a prerequisite for it being well-grounded is the clarity about the foundational question: what is a cause? Let us relate this question with an etiologic revolution in rehearsal.

2.1. Is myocardial infarction an infectious disease?

In the mainstream of the psychoanalytic movement in the first half of this century many diseases with empty or speculative etiology became 'psychosomatic' ones. Among the prominent examples was, and still remains in some niches of the therapeutic power, the gastric ulcer. Countless patients underwent gastrectomy or vagotomy because psychosomatic and other modes of treatment failed to cure their ulcers. During the last 15 years or so we have been witnessing the dramatic move of this health disorder to another etiologic realm, i.e. to the theory of infectious diseases. Helicobacter pylori infection is viewed as a cause of gastric ulcer, and is successfully treated by antibiotics.

Another, even more dramatic move of a second disease group to the same etiologic paradigm seems to be underway: atherosclerotic cardiovascular disease, well-known as ischemic heart disease, coronary artery disease, and coronary heart disease, is a major health problem in the industrialized countries causing nearly half of the deaths through myocardial infarction and related clinical events. We had been told until now that hypercholesterolemia, hypertension, cigarette smoking, stress, and lack of physical exercise were the main risk factors for coronary heart disease, and thus for myocardial infarction. And we were advised accordingly: don't smoke, don't eat too much fat! There is a brand-new story, however (current date: October 1996). It seems that coronary heart disease is in the process of abandoning its venerable causes mentioned above, and of assuming a new, major cause.

Chlamydia pneumoniae is a recently discovered, Gram negative, intracellular bacterium that causes acute respiratory infections in all age groups [3]. We are currently being told that this bacterium is an important cause of coronary heart disease and may in the near future dislodge the classic risk factors mentioned above [8,9,22,26]. Should this etiologic hypothesis be able to intrigue the clinical community and to get ground in the years ahead, myocardial infarction is likely to become an infectious disease as well. Also we will be advised anew: take antibiotics! "…the rise and fall of the incidence of coronary artery disease in the USA from the 1940s through the 1970s appears to emulate that of an infectious epidemics" ([10], p. 1555).

The medical community, more or less surprised by a new bacterium taking reign in a classic clinical domain, is currently asking the question: is it true that Chlamydia pneumoniae infection is a major cause of coronary heart disease? "The simple demonstration of a prevalent microbe in atherosclerotic lesions does not prove a causal role for the agent" ([1], p. 872). "Evidence includes elevated serologic titers as well as the presence of Chlamydia pneumoniae within atherosclerotic lesions…However, these are preliminary and uncontrolled findings that do not yet prove an etiologic link. Whether Chlamydia pneumoniae exists as an 'innocent bystander' or has a direct causative role in the development of coronary artery disease remains to be seen", ([10], p. 1555).

That is true. But remains to be seen until when? Until the etiologic and clinical community will have found acceptable answers to following proto- and metaetiologic questions: what is an etiologic link? What is causation? What is a causative role? What is a cause at all, and what is a major or a minor cause? How do we prove whether or not a particular factor plays a causal role in the development of a clinical event?

Without addressing these basic questions we will only get used to the strange historical fact that clinical events from time to time change their etiologic camp, but we do not know why. Maybe through social fluctuations of the therapeutic power? Let us therefore turn our attention to the questions above.

2.2. Multiplicity, plurality, and temporal priority of causes

We do not know yet what a cause is. Our usage of this term therefore is provisionally a colloquial one and will be purified stepwise. Whatever else causes may be, we take them to be events that cause other events, the latter ones called their effects. The term 'event' is general enough to also cover processes as chains of time-sequential events, networks of simultaneous events, temporal dynamics of such networks as complex processes and histories, etc.

In natural languages causal relationships between events are purported by expressions like: because, due to, for, therefore, leads to, contributes to, develops, brings about, generates, affects, is effected by, etc. 'Due to' the laxity of these terms, in causal claims a clear distinction must be made between (a) singular causes referred to in individual-level causal talks like 'your hypercholesterolemia caused you to suffer coronary heart disease' and (b) generic causes asserted in population-

level causal talks such as 'hypercholesterolemia is a cause of coronary heart disease'. The former case, the individual instance, is the concern of diagnostic reasoning, while etiology is concerned with the latter case, the class.

The popular talk on causation and causes, however, is a source of misunderstanding in that it refers to an event as *the* cause of another one as if there were or could be no other causes of the same event. It is asked, for example, 'what is the cause of myocardial infarction?'. We will without further ado abandon this doctrine of monocausationism and will assume a *multiplicity* of causes instead. An event such as myocardial infarction may have a 100 or more different types of causes, Cause_1, Cause_2, Cause_3,..., and so on. Chlamydia pneumoniae infection may be one of them. Helicobacter pylori infection may be a second one, Cytomegalovirus infection a third one, etc. ([2,7])(see Fig. 1).

A second step in our differentiation of causes is this: each or some of the distinct causes Cause_1, Cause_2, Cause_3,... of an event may consist of a *plurality* of $n > 1$ partial causes $C_1, C_2, \ldots, C_n$, also called factors, co-factors or conditions, such that, for example, $\text{Cause}_i = C_{i_1}$ & C_{i_2} & ... & C_{i_n}. For instance, it may be that one of the causes of myocardial infarction is the following complex event comprising six co-factors: 'diabetes and hypercholesterolemia and cigarette smoking and hypertension and stress and lack of physical exercise'.

Human knowledge rapidly changes and fades away. Search for causes therefore is useless if the causal knowledge it promises is void of practical values such as in cosmogony. In practical areas like medicine knowledge of causes is meaningful only to the extent to which it contributes to the advancement of our actions against human and animal suffering. An action, generated and guided by a particular causal belief, is itself a cause, i.e. an intentional cause implemented by someone to produce an effect [14]. Thus, alleged knowledge of causes in medicine generates new causes in terms of human agency in diagnostic, therapeutic, preventive, social, economic, and political domains. In virtue of this worldmaking instrumentality, knowledge of causes should be well-grounded as already expressed above.

In spite of some quantum theorists' belief in backward causation, it is ontologically and action-theoretically problematic to presume that in human sphere one could by doing something today produce an effect yesterday. In human sphere, the arrow of causation is not directed backwards, so to speak. Moreover, in order for cause and effect to be distiguishable from one another they must not be supposed

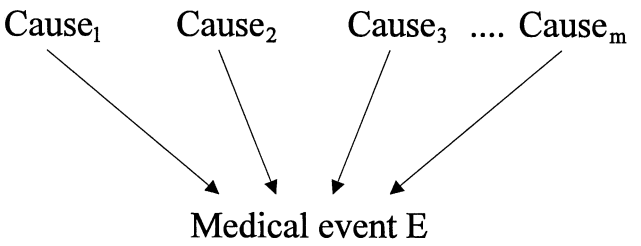

Fig. 1. Multiple causes of an event.

to be simultaneous entities. Given two such events, we will never be able to recognize which one of them causes the other one because they always appear and vanish simultaneously. Hence, in etiology retrograde and simultaneous causation is excluded. The arrow of causation is directed forwards. The first axiom of an etiologic calculus therefore would run as follows: A cause precedes its effect in time. We call this basic requirement *temporal priority* of causes, or *temporal succession* of effects.

However, temporal succession is not sufficient for an event to be the effect of a preceding one. A frequent mistake made both in everyday life and science is the erroneous causal belief 'after that so because of that'. An illustrative example of this post-hoc-ergo-propter-hoc fallacy would be the assumption that the storm was caused by the rapidly falling of barometric reading because it always occurs after the latter. A fallacious etiology of this type will be referred to as a *barometer-causes-storm* fallacy. That both events have a common cause and that the falling of barometric reading is only a spurious cause of the storm is a warning hint at doubtful etiologic studies which on a closer look exhibit the same line of fallacious reasoning. Regarding the correlation between elevated Chlamydia pneumoniae antibodies and the incidence of myocardial infarction reported in Section 2.1 above the question arises: is this antibody increase the barometer, and myocardial infarction the storm? Despite the critical appeal such questions may have, in situations like this one, waiting for confirmation of ''preliminary and uncontrolled findings'' ([10], p. 1555) is inappropriate. Maximize utility according to the Bayesian decision rule, i.e. supplement theoretical, epidemiologic studies by therapeutic experiments against the suspected causative factor through antibiotics!

3. Deterministic etiology

In an etiologically ideal world we would have clear-cut and logically well-treatable if-then relationships of the following form between causes and their effects: if cause Cause_i occurs, then effect E_j occurs. Assuming that cause Cause_i consists of a plurality of $n \geq 1$ partial causes $C_{i_1},\ldots, C_{i_n}$, the general structure of this cause-effect relation would be:

If conditions C_{i_1} & … & C_{i_n} occur, then effect E_j occurs.

A simple example would be the etiologic statement: 'if a child is exposed to measles virus and is not inoculated, it will suffer measles'. However, there are scarcely *deterministic* etiologic relationships of this kind. Most etiologic relationships are merely of *probabilistic* nature having only a probability connection between the antecedent event and the consequent event such as, for instance, 'a non-inoculated child exposed to measles virus will suffer measles with probability 0.23'. That means that the present world is etiologically not ideal. We will nevertheless clarify in this section the logical structure of deterministic etiologic relationships to see that even if they would exist they could be embedded into the probabilistic etiology discussed in Section 4 below (c.f. [18]).

Let Σ be an interpreted language of the first order. P, Q, R,... may be n-ary predicates of Σ with $n \geq 1$. Individual variables are symbolized by $x, y, z,\ldots$, $t, t_1, t_2,\ldots$, the latter ones being time variables. If P is an n-ary predicate, $P(x_1,\ldots, x_{n-1}, t)$ is an atomic sentence. It says that P at time t applies to $x_1,\ldots, x_{n-1}$. For example, 'John is suffering from gastric ulcer today', that is, Pxt, where $t =$ today.

Atomic sentences and their negations will be called state descriptions in Σ and will be symbolized by Greek letters $\alpha, \beta, \gamma,\ldots$ If α and β are state descriptions in Σ, their conjunction $\alpha \wedge \beta$ is also a state description in Σ. Thus, state descriptions in Σ are temporalized simple statements or conjunctions of any length. They represent simple or complex events occurring at particular instants or periods of time.

If α is a positive, atomic state description $P(x_1,\ldots, x_{n-1}, t)$ or its negation $\neg P(x_1,\ldots, x_{n-1}, t)$, the set $\{t\}$ is referred to as the time set of α, and is written time(α). The set {P} is referred to as its predicate set and written predicate(α). If $\alpha \wedge \beta$ is a state description, then time($\alpha \wedge \beta$) = time(α) $\cup$ time(β). Also, predicate($\alpha \wedge \beta$) = predicate(α) $\cup$ predicate(β). For example,

time('John has a cough today and he had fever yesterday') = {today, yesterday};
predicate('John has a cough today and he had fever yesterday') = {has a cough, has fever};
time($Pxt_1 \wedge Qxt_2 \wedge \neg Pxt_3$) = $\{t_1, t_2, t_3\}$;
predicate($Pxt_1 \wedge Qxt_2 \wedge \neg Pxt_3$) = {P, Q}.

Let ΣL be the extended language $\Sigma \cup$ L where L is any system of the first-order predicate logic added to Σ. If α and β are state descriptions in ΣL with the free individual variables $x_1,\ldots, x_m$, $t_1,\ldots, t_n$, then γ is a *deterministic law of succession* in ΣL if and only if (1) γ is the predicate-logically closed generalization $\forall x_1 \ldots \forall x_m \forall t_1 \ldots \forall t_n(\alpha \rightarrow \beta)$; (2) γ is an empirical sentence, i.e. not logically valid and not inconsistent and not undecidable in ΣL; (3) every $t_i \in$ time(α) is earlier than every $t_j \in$ time(β); and (4) every predicate P $\in$ predicate(α) is extensionally different from every predicate Q $\in$ predicate(β). For instance, the following statement is a deterministic law of succession: 'if a massive thrombosis occurs in a main coronary artery of someone now, she will suffer myocardial infarction within the next few minutes'.

For the sake of convenience, the quantifier prefix $\forall x_1 \ldots \forall x_m \forall t_1 \ldots \forall t_n$ of a deterministic law of succession is written Π. If γ is a deterministic law of the form $\Pi(\alpha \rightarrow \beta)$, the statements α and β are respectively referred to as its antecedent and consequent, symbolized by antecedent(γ) and consequent(γ). For example, if γ is $\forall x \forall t_1 \forall t_2 \forall t_3(Pxt_1 \wedge \neg Qxt_2 \rightarrow Rxt_3)$, then we have: antecedent(γ) = '$Pxt_1 \wedge \neg Qxt_2$' and consequent(γ) = 'Rxt_3'.

The sentence $\alpha_1 \wedge \cdots \wedge \alpha_n \backslash \alpha_i$ is the conjunction $\alpha_1 \wedge \cdots \wedge \alpha_n$ minus the ith link α_i, where $1 \leq i \leq n$. If $\Pi(\alpha_1 \wedge \cdots \wedge \alpha_n \rightarrow \beta)$ is a deterministic law of succession in ΣL, then α_i is *deterministically relevant* to β with respect to $\alpha_1 \wedge \cdots \wedge \alpha_n \backslash \alpha_i$ if and only if $\neg\Pi(\alpha_1 \wedge \cdots \wedge \alpha_n \backslash \alpha_i \rightarrow \beta)$ is true in ΣL. That means that the removal of the part α_i from the whole $\alpha_1 \wedge \cdots \wedge \alpha_n$ of the antecedent falsifies the statement $\Pi(\alpha_1 \wedge \cdots \wedge \alpha_n \backslash \alpha_i \rightarrow \beta)$. For example, in the following statement the part 'x is a

male' is *not* deterministically relevant to myocardial infarction with respect to thrombosis in the coronary artery: 'for all x, if x is a male and a massive thrombosis occurs in one of his main coronary arteries now, he will suffer myocardial infarction in a few minutes'. Being a male is a redundant condition in the antecedent.

A statement γ of ΣL is a *deterministic causal law* in ΣL if and only if γ is a deterministic law of succession in ΣL and every $\alpha_i \in \text{antecedent}(\gamma)$ is deterministically relevant to consequent (γ) with respect to antecedent $(\gamma)\backslash\alpha_i$. That is, if its antecedent does not contain any redundant part.

It is of course possible that for a particular clinical event such as 'myocardial infarction' there are $q > 1$ deterministic causal laws:

$$\Pi_1(\alpha_{11} \wedge \cdots \wedge \alpha_{1m} \rightarrow \beta),$$
$$\vdots$$
$$\Pi_q(\alpha_{q1} \wedge \cdots \wedge \alpha_{qr} \rightarrow \beta),$$

each of them expressing a particular $\text{Cause}_i = C_{i_1}$ & C_{i_2} & ... & C_{i_n} with $n \geq 1$ factors in its antecedent $\alpha_{i_1} \wedge \cdots \wedge \alpha_{i_n}$ and the myocardial infarction event in its consequent β. In such a deterministic case of multiple causation, each antecedent cause Cause_i is a sufficient cause of the consequent event, but none of them is a necessary one because in its absence any one of the rest will also do as well. The well-known and acclaimed *INUS condition* of John Leslie Mackie may now be clearly interpreted as each part α_{i_j} of these antecedents, i.e. each of the factors C_{i_j} of the Cause_i. "It is an insufficient but non-redundant part of an unnecessary but sufficient condition" ([6], p. 62). "What is typically called a cause is an INUS condition..." (ibid., p. 64).

As we will see at the end of Section 4.3, however, a cause is not an INUS condition as Mackie suggests. And it is also not recommendable in medical etiology to wait for INUS conditions simply because the set of deterministic causal laws is nearly empty. For this reason we will be reflecting on the possibility of non-deterministic etiology.

4. Probabilistic etiology

Does Chlamydia pneumoniae infection play a *genuine* causative role in the development of coronary heart disease or is it merely a *spurious* cause of the disease? This example question that we had already anticipated above is the typical etiologic question asked with regard to any factor which is suspected to play a causative role in the pathogenesis of a particular clinical event. Thus, the main problem and task of etiology is to discriminate genuine causal factors from spurious ones. What is needed, therefore, is a theory of etiology that helps manage this task adequately. Some thoughts in this direction are offered in this section. Although Patrick Suppes' [25] theory of probabilistic causality has been the main source of

inspiration to me, the conceptual framework developed has an entirely different structure and introduces also a new causal terminology and apparatus.[2]

There is a widespread, initial presumption, indeed a prejudice, against probabilistic causality because people who equate probability with indeterminism believe that there are no causes where only probabilities can be calculated. However, it will not be our concern to convert these religious deterministics.

4.1. Probabilistic relevance of events

The sort of etiologically useless association between events we will have to neglect is the *spurious correlation*. And the sort of etiologically important association between events we will have to follow closely is the *causal interaction*. What is a spurious correlation, and what is a causal interaction? We will base these concepts upon the technical term of probabilistic independence. To this end we need some terminologic arrangements.

We distinguish between singular events and generic events, the latter ones also called event types. A singular or *individual event* is an occurrence localized in time and space, such as, for example, a particular patient's myocardial infarction occurring on a particular day. The class of individual events of the same type is referred to as a *generic event*, e.g. *the* myocardial infarction occurring in every patient who suffers this disease.

We will tackle causation as a relation between generic events and not between individual events. We will not be interested in causal explanations and individual causal assertions such as 'your smoking caused you suffer myocardial infarction' (see [18]). We will therefore be concerned with generic events only, simply called events. They are symbolized by Roman capitals A, B, C,…, and are treated as sets so as to enable us to use methods of set theory and logic.

Let A and B be two events. By using a stroke symbol '|' we will compose of them a complex event $B \mid A$ which we will call a *conditional* event. The conditional event $B \mid A$ is 'event B on the condition that event A has already occurred'. Stated simply, it reads 'event B given event A', or 'B conditional on A'. For example, someone's suffering myocardial infarction given that she is a diabetic is a conditional event.

Maybe a conditional event $B \mid A$ will certainly occur or will never occur. The latter is the case if the event B never occurs. We can therefore speculate upon the probability of a conditional event in advance, and ask how likely $B \mid A$ may be. Using the probability function p which assigns a number to an event, we write '$p(B \mid A) = r$' to express the statement that 'the probability of B given A is r' where r is a real number ranging from 0 to 1. We call $p(B \mid A)$ the probability of the conditional event $B \mid A$, or the *conditional* probability of B, while p(B) is the unconditional, *absolute* probability of the event B.[3]

[2] For details, see [20]. The history of the probabilistic-casual idea goes back to Hans Reichenbach [11]. Further elaboration was done by Wesley Salmon [23]. Patrick Suppes' theory, however, was the first comprehensive, creative, and ingenious work on the subject. I hope my framework is a genuine amendment and has overcome the faults his theory has been accused of in the literature.

[3] Let us not dispute about the nature of 'probability', about whether it is something subjective, objective, logical, or a propensity, a relative frequency in the long run, or what not. Whatever the probability may be, we talk about it using some words which we will introduce in this section.

The syntactical convention in using the conditional event sign | 'given' is this: intersection ($\cap$) and union ($\cup$) dominate |. For example, $Y \cap Z \mid X$ is $(Y \cap Z) \mid X$, but not $Y \cap (Z \mid X)$. Further, it may be recalled that the notion of conditional probability is defined in terms of the absolute probability as follows:

$$p(B \mid A) = \frac{p(B \cap A)}{p(A)}. \tag{1}$$

Two events B and A are said to be *probabilistically independent* of one another if and only if $p(B \cap A) = p(B) \cdot p(A)$, i.e. if the probability of their joint occurrence equals the product of the probabilities of their individual occurrence. If we divide through both sides of this equation by p(A) we obtain:

$$\frac{p(B \cap A)}{p(A)} = p(B). \tag{2}$$

Eq. (1) and Eq. (2) imply:

$$p(B \mid A) = p(B). \tag{3}$$

We have thus arrived at the corollary that an event B is probabilistically independent of an event A if and only if its probability conditional on the occurrence of A equals its unconditional probability. Its probability is not changed by A occurring. Put in other words, event A has obviously no influence on the occurrence of B. The two events are *uncorrelated*.

The corollary implies that an event B is *probabilistically dependent* on an event A if and only if $p(B \mid A) \neq p(B)$. 'Dependent' does not mean that there is an interaction between A and B, any kind of 'causal influence' so to speak. The relation of probabilistic dependence remains, prima facie, merely a numerical phenomenological characteristic we observe, usually referred to as *correlation*. It may in a particular case exhibit any of the following two directions of the inequality mentioned:

$$p(B \mid A) > p(B) \quad \text{(positive correlation)} \tag{4}$$

$$p(B \mid A) < p(B). \quad \text{(negative correlation)} \tag{5}$$

The probabilistic dependence of B on A may be a positive one, as in case (Eq. (4)), or a negative one as in the latter case (Eq. (5)). Thus, positive dependence or correlation turns out to be a *probability increase*. An event B is positively probabilistically dependent on an event A if and only if the occurrence of A raises the probability of B. Conversely, negative dependence or correlation is a *probability decrease*. An event B is negatively probabilistically dependent on an event A if and only if the occurrence of A lowers the probability of B.

For example, it may be that for a member of German population the probability of suffering coronary heart disease is 0.00001, while the probability of the same event given Chlamydia pneumoniae infection is 0.0001. By using the shorthand notation

chd	for	coronary heart disease is present,
chlamydia	for	Chlamydia pneumoniae infection is present,

we would then have the following positive correlation:

$$p(\text{chd} \mid \text{chlamydia}) > p(\text{chd}). \tag{6}$$

This example says that Chlamydia pneumoniae infection raises the probability of suffering coronary heart disease. Would we according to this evidence have reason to presume that Chlamydia pneumoniae infection is a *cause* of coronary heart disease, that it has a causal role for this disease? Is an 'etiologic link' we are trying to understand, a *probability increase* or some particular kind of that? For analyzing this question we will need a second concept of dependence, i.e. the notion of conditional dependence.

Two events B and A are said to be *probabilistically independent* of one another *conditional* on a third event C if and only if

$$p(B \cap A \mid C) = p(B \mid C) \cdot p(A \mid C), \tag{7}$$

probabilistically dependent on one another *conditional on* C, else:

$$p(B \cap A \mid C) \neq p(B \mid C) \cdot p(A \mid C). \tag{8}$$

That means that two events B and A given a third event C are probabilistically dependent if according to Eq. (8) the probability of their joint occurrence $B \cap A$ conditional on C differs from the product of their individual probabilities conditional on C. They may be positively or negatively dependent on one another:

$$p(B \cap A \mid C) > p(B \mid C) \cdot p(A \mid C), \quad \text{(positive)} \tag{9}$$

$$p(B \cap A \mid C) < p(B \mid C) \cdot p(A \mid C). \quad \text{(negative)} \tag{10}$$

In the following discussion this relation of *conditional dependence*, also called conditional correlation, will be of particular importance. It will enable us to understand what it means to say that two events B and A are interactive, i.e. that one of them exerts some kind of causal influence on the other one. For instance, with reference to a recent epidemiologic study which we will quote below, let us conditionalize our two clinical example events (coronary heart disease, Chlamydia pneumoniae infection) on the events of being a diabetic patient or a non-diabetic patient, respectively. Based on the study we will refer to we can postulate in advance that:

$$p(\text{chd} \cap \text{chlamydia} \mid \text{diabetics}) = p(\text{chd} \mid \text{diabetics}) \cdot p(\text{chlamydia} \mid \text{diabetics}), \tag{11}$$

$$p(\text{chd} \cap \text{chlamydia} \mid \text{non-diabetics}) > p(\text{chd} \mid \text{non-diabetics}) \cdot p(\text{chlamydia} \mid \text{non-diabetics}). \tag{12}$$

In this case, we would obviously have reason to say that according to Eq. (11) coronary heart disease and Chlamydia pneumoniae infection are, in the population of diabetics, probabilistically independent of one another. But according to Eq. (12), in the population of non-diabetics they are probabilistically dependent. Following questions arise: why are they independent in diabetics and dependent in non-diabetics? And what kind of dependence is it? Is it merely a spurious correlation or is it a causal interaction? Which one of the two clinical events may play the

causative role? Does Chlamydia cause atherosclerotic lesions in heart arteries, and thus coronary heart disease, or is the atherosclerotic plaque merely a fertile ground for Chlamydia to be deposited and grow? Or is there a third possibility, a common cause for both events?

To account for etiologic questions of this kind, we now will put the above preliminaries in a concept of *probabilistic relevance* upon which to build our concepts of causal relevance and irrelevance below. The definition of conditional dependence in Eq. (9) and Eq. (10) above is equivalent to:

$$p(B \mid A \cap C) > p(B \mid C) \quad \text{(positive conditional correlation)} \tag{13}$$

$$p(B \mid A \cap C) < p(B \mid C) \quad \text{(negative conditional correlation)} \tag{14}$$

These two interesting relations we have arrived at will be used as the conceptual base of our theory below. Like the events B and A, also the reference event C conditional on which the independence and dependence relationships were studied in the formulas above, is in every real-life situation a more or less complex class, e.g. the calss of diabetics, of warm summer days, of leucocytes, of cigarette smokers, etc. Of methodological and mnemonic reasons we will want to hold this reference event linguistically constant throughout. We will therefore in neutral terms refer to it as *population*, also called reference class, background context, causal field, propensity field, and the like, and denoted by the variable X throughout.

Definition 0. An event A in a population X is
1. *positively probabilistically relevant* to an event B if and only if $p(B \mid X \cap A) > p(B \mid X)$,
2. *negatively probabilistically relevant* to an event B if and only if $p(B \mid X \cap A) < p(B \mid X)$,
3. *probabilistically irrelevant* to an event B if and only iff $p(B \mid X \cap A) = p(B \mid X)$.

In part 1 of this triple definition, the addition of event A to event X raises the probability of B. In part 2, the addition of event A to event X lowers the probability of B. In part 3 nothing happens by adding A to X. Note that these notions of probabilistic relevance we have obtained are three-place predicates of the structure:

is_positively_probabilistically_relevant(A, B, X),
is_negatively_probabilistically_relevant(A, B, X),
is_probabilistically_irrelevant(A, B, X).

For instance, from the epidemiologic information given in Eq. (1) above we can infer, using the equivalence between Eq. (9) and Eq. (2), the following probabilistic relevance information on the relationship between Chlamydia and coronary heart disease:

$$p(\text{chd} \mid \text{non-diabetics} \cap \text{chlamydia}) > p(\text{chd} \mid \text{non-diabetics}), \tag{15}$$

where $B = \text{chd}$; $X = \text{non-diabetics}$; $A = \text{chlamydia}$, i.e. $p(B \mid X \cap A) > p(B \mid X)$.

It says that within the population of non-diabetics, Chlamydia pneumoniae infection is positively probabilistically relevant to coronary heart disease. It is beyond any doubt that a probabilistic relevance information of this kind is

predictively valuable in that one is allowed to view the Chlamydia infection as a prognostically unfavorable factor in non-diabetics, usually called a 'risk factor' because of the undesirability of the effect. However, that does not yet mean that the probabilistic relevance information is also *causally* significant. The rapidly falling of barometric reading on warm summer days is positively probabilistically relevant to the subsequent storm, and thus predictively informative. But, it does not cause the storm. Although we will be willing to use the barometric reading as an indicator, we will not want to try to prevent or to produce storm by manipulating this indicator. Like this prognostic relevance cum causal irrelevance situation where a third factor is causally operative behind both the barometer *and* the storm, i.e. the drop in atmospheric pressure, it is also possible that there is another, common factor operating behind Chlamydia infection *and* coronary heart disease. We will try to find a solution to this problem below.

4.2. Spurious and quasi-paradoxical etiologic correlations

Let there be a positive probabilistic relevance between two events A and B within a particular population X as in Eq. (15) above, i.e.

$$p(B \mid X \cap A) > p(B \mid X). \tag{16}$$

It is possible that this probabilistic relevance of A to B will vanish if an additional event C is introduced into the context, i.e.

$$p(B \mid X \cap A \cap C) = p(B \mid X \cap C). \tag{17}$$

The previously positive correlation between A and B no longer exists in the presence of the new factor C which is equally able to bring about B in the absence of A (right-hand side). The question therefore arises if it was only a spurious correlation. An example is provided by the well-known view that within the population of non-diabetics smoking is a risk factor for coronary heart disease, and that means that it raises the probability of this disease:

$$p(\text{chd} \mid \text{non-diabetics} \cap \text{smoking}) > p(\text{chd} \mid \text{non-diabetics}). \tag{18}$$

However, according to the findings reported in a recent epidemiologic study on the association of Chlamydia pneumoniae infection and acute coronary heart disease events [9], following probabilistic relevance relationships must be supposed:[4]

[4] See, for example, [9]: "It was found that the prevalence of elevated chlamydial antibodies at baseline was higher in non-diabetic subjects who had serious coronary heart disease events dring the follow-up than subjects without coronary heart disease events (32 vs. 15%, relative risk 2.56 $P = 0.013$) in East Finland. In non-diabetic subjects in West Finland we did not find this association. The association between C. pneumoniae antibodies and coronary heart disease events did not markedly change after controlling for other risk factors for coronary heart disease (OR 2.44, $P = 0.055$) in non-diabetic subjects living in eastern Finland" (ibid. p. 682).

"The association between elevated chlamydial antibodies and incident coronary heart disease events before controlling for other risk factors for coronary heart disease was statistically significant… This ascociation remained similar after controlling for age, gender, and smoking" (ibid., p. 685).

"We did not find any association between chlamydial antibodies and coronary heart disease events in diabetic patients from either East or West Finland. A possible explanation for the difference between diabetic and non-diabetic subjects could be that diabetes increases the risk for coronary heart disease events so much that it masks the effects of other, weak risk factors from coronary heart disease" (ibid., p. 686).

$$p(\text{chd} \mid \text{non-diabetics} \cap \text{smoking} \cap \text{chlamydia})$$
$$= p(\text{chd} \mid \text{non-diabetics} \cap \text{chlamydia}), \tag{19}$$

$$p(\text{chd} \mid \text{non-diabetics} \cap \text{chlamydia}) > p(\text{chd} \mid \text{non-diabetics}), \tag{20}$$

$$p(\text{chd} \mid \text{diabetics} \cap \text{chlamydia}) = p(\text{chd} \mid \text{diabetics}). \tag{21}$$

Eqs. (18) and (19) show that the positive probabilistic relevance of smoking to coronary heart disease in the population of non-diabetics, present in Eq. (18), disappears when Chlamydia enters the scene (Eq. (19)). Thus, the new factor Chlamydia seems to degrade smoking to a spurious one. Moreover, according to Eq. (20) Chlamydia is with respect to non-diabetics positively probabilistically relevant to coronary heart disease. But once again, Eq. (19) demonstrates that Chlamydia's relevance to heart disease is not changed by smoking when added to (left-hand side). Someone may therefore suppose that in the presence of Chlamydia, smoking loses the potential etiologic role it had been assigned to until now. On the other hand, according to Eq. (21), Chlamydia is with respect to diabetics probabilistically irrelevant to coronary heart disease.

The first lesson we learn from these examples is the evidence that probabilistic relevance is always relative to a particular population (reference class, background context, propensity field, etc.). That means, however, that if we change the background context relative to which the relevance of Chlamydia to coronary heart disease is measured, maybe the positive correlation will vanish as it happened to smoking above.

It is not a difficult task to change the background context of an etiologic research to see what will happen. Just divide the reference population X into $n > 1$ disjoint subpopulations $X_1, X_2, \ldots, X_n$ and inquire into the probabilistic relevance that factor A within each one of them has to factor B, i.e. ask

$$p(B \mid X_i \cap A) \; ? \; p(B \mid X_i) \quad \text{with } 1 \leq i \leq n \tag{22}$$

where the question mark is a variable for the relations $=$, $>$, and $<$. What can happen is a collapse of the initial probabilistic relevance that A had to B within the undivided population. Positive relevance may become negative relevance or irrelevance, irrelevance can become positive or negative, and negative relevance can become positive, etc. (See Eq. (20) and Eq. (21) above.) This dynamics of the correlations by changing the reference population, known as Simpson's paradox [24], is due to the circumstance that within any of the subpopulations X_i, factor A may be correlated with a particular, X_i-local factor C_i which modifies the effect B in a particular manner (see Fig. 2).[5]

Fig. 2 illustrates that whenever one or more additional correlations enter the field, the etiologic situation between A and B may become increasingly opaque and hopeless. Something that is a risk factor in class X_i may surprisingly appear as a preventive factor in the new class X_j. But we will see below that this situation is not

[5] Simpson ([24], p. 240 f.) gives an interesting and amusing example that cannot be discussed here.

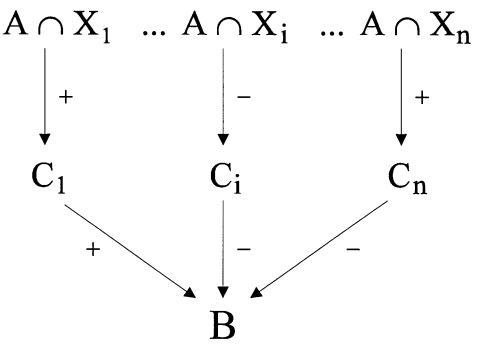

Fig. 2. Event A occurring in different contexts X_i where a particular local factor C_i may be present modifying effect B in a specific manner.

a paradoxical one at all as it has been thus diagnosed by Simpson and named after him. It is a commonplace that a particular drug, for example, that is used as a remedy in a diseased group may develop an excellent overall effect against this disease, while having adverse effects in the presence of a particular, additional disease called 'contra-indication'. This example shows that in an inhomogeneous reference class X almost anything is possible. An event A in a subpopulation of class X may raise the probability of an event B while lowering it in another subpopulation. Some philosophers of causality have thus come to the conclusion that a cause need not be something that raises the probability of its effect. It may lower that probability as well, they say. Their strange discussion on this exotic view followed an example provided by Germund Hesslow on the thrombogenic effect of oral contraceptives [4]. His argument runs as follows:

"It has been claimed, e.g. that contraceptive pills (C) can cause thrombosis (T)… But pregnancy can also cause thrombosis, and C lowers the probability of pregnancy. I do not know the value of p(T) and $p(T \mid C)$ but it seems possible that $p(T \mid C) < p(T)$, and in a population which lacked other contraceptives this would appear a likely situation. Be that as it may, the point remains: *it is entirely possible that a cause should lower the probability of its effect*" ([4], p. 291).

It will be shown below that the conceptual base of this reasoning is faulty and its conclusion cannot be accepted [20]. We must have the opportunity of relying upon the modality of causes in order to be able to manipulate them therapeutically and preventively. A cause therefore has to be definitely positive or negative. Tertium non datur. An equivocal, 'mixed cause' which occasionally raises the probability of its effect and at other times lowers it, is not a cause if it exists at all. For example, we cannot allow for Chlamydia to be a cause of coronary heart disease on the one hand, and a protective factor for the same disease in the same group, on the other. The action-theoretic clarity we need for differential indication decisions in clinical practice and preventive medicine requires that *causal structures* in etiology should be unanimous.

4.3. Causal structures

A *causal structure* consisting of causally associated events will be construed as a special, set-theoretical extension of a *probability space*. To prevent misunderstandings, let us therefore negotiate our notion of probability space.

The class of generic events among which causal associations are being analyzed in etiologic research, must be known and designed before. In a research setting, for instance, where someone is inquiring into whether or not cigarette smoking has any causal relevance to myocardial infarction, she is not allowed to tell us afterwards that thanks to her investigation she had discovered Chlamydia pneumoniae infection having a causal relevance to myocardial infarction. For this infection did not belong to the *event space* she was considering. What we will need in our discussion below first of all, therefore, is the formal characterization of the event space.

Any inquiry, observation, analysis, experiment and the like intended to be performed will be called a random experiment. For example, we would want to find out if a particular patient is suffering from gastritis, or we would want to toss a dice twice to see what the sum of the two subsequent faces will be. Such an experiment's being a random one means that we do not know before what will actually happen. But of course we know before what will happen at all. For relative to a particular logic L, we can L-logically calculate the set of all possible outcomes of our experiment. Regarding our patient, for example, and relative to classical logic the set of all possible outcomes is {gastritis is present, gastritis is not present}. Such a set of all classical-logically possible outcomes of a random experiment will be referred to as the *sample space* and will be symbolized by Ω.

Let E be an algebra of sets on the sample space Ω, i.e. E is a family of subsets of Ω, it also includes Ω and is closed under complementation and union. That means that if A is in E, its complement $\bar{A}$ is also in E, and if A and B are in E, their union $A \cup B$ is also in E. The set E is referred to as event space or *event algebra*, and its elements are called the events proper. For instance, our random experiment which we will frequently refer to below may be this: we want to know if our patient above is suffering from any of the two diseases 'Chlamydia pneumoniae infection' and 'coronary heart disease'. In this case we will have the following sample space and event algebra. As the latter one is too large, only a minor part of it will be displayed:

Ω = {Chlamydia pneumoniae infection is present, Chlamydia pneumoniae infection is not present, coronary heart disease occurs, coronary heart disease does not occur}.

E = {{Chlamydia pneumoniae infection is present}, {Chlamydia pneumoniae infection is not present},..., {Chlamydia pneumoniae infection is present} $\cup$ {coronary heart disease occurs},..., {Chlamydia pneumoniae infection is present} $\cap$ {coronary heart disease does not occur},..., Ω, Ø},

or equivalently:

$$E = \{\{\text{chlamydia}\},\ \{\overline{\text{chlamydia}}\},\ \{\text{chd}\},\ \{\overline{\text{chd}}\},\ \{\text{chlamydia}\} \cup \{\text{chd}\},\ \{\text{chlamydia}\} \cup \{\overline{\text{chd}}\},\ \{\overline{\text{chlamydia}}\} \cup \{\text{chd}\},\ \{\text{chlamydia}\} \cap \{\text{chd}\},\ \{\text{chlamydia}\} \cap \{\overline{\text{chd}}\},\ \{\overline{\text{chlamydia}}\} \cap \{\text{chd}\},\ldots,\ \Omega,\ \emptyset\}.$$

Finally, let us now add into the frame $\langle \Omega, E \rangle$ we have constructed thus far a function p which maps the event algebra E into the real interval [0, 1]. The triplet $\langle \Omega, E, p \rangle$ we obtain in this fashion is a finite *probability space* if it satisfies the Kolmogorov axioms.[6]

We are now ready to demonstrate how a probability space $\langle \Omega, E, p \rangle$ can be extended to a probabilistic causal structure that may be used in etiology as a methodological ground in searching for causes of clinical events. We should remind at the outset that "Too much philosophical ink has been spilled on causality since Aristotle. But the problems remain with us as they were before him. The elimination of the notion of causality and all of its derivatives from the human language is probably the only satisfactory solution to these problems …" ([18], p. 201). An elimination of that kind certainly will not happen, however. So we have still to seek for another solution. Half of the solution would come from the correct diagnosis of the problems. In my view, *the basic* one of them generating most of the difficulties lies in the following, widespread misunderstanding.

It is commonly assumed that causation is a two-place relation of the kind 'A causes B', e.g. HIV infection causes AIDS. However, the perpetual history of the fruitless debates on causality demonstrates that this belief must be logically defective. We should first of all observe that whatever else causation may be, it rests on the interaction of causes with their background contexts. What is a cause in a particular context, e.g. HIV in man, may not be a cause in another context, e.g. HIV in ants. One can therefore not expect of causes any contextual impartiality that would enable something to be a cause everywhere if it is one somewhere. The contextual relativity of their causal role and significance, their 'context sensitivity' so to speak, must be taken into account by constructing an appropriate syntax for causal language, a syntax that makes a reasonable causal semantics possible in that it contextualizes causes. For it may be, for example, that measles virus causes measles within a human population which is not inoculated against measles, while it doesn't do so in an inoculated population. We thus obtain the new verb 'causes' as a three-place predicate: 'A causes B within X',

causes(A, B, X),

where A is the cause event, B is the effect event, and X is a population within which the relation between A and B is being considered. For instance:

[6] Definition: A structure $\langle \Omega, E, p \rangle$ is a probability space if Ω is a sample space, E is an algebra of sets on Ω, and p is a function from E to [0, 1] such that (1) $p(A) \geq 0$ for every $A \in E$; (2) $p(\Omega) = 1$; and (3) if $A \cap B = \emptyset$, then $p(A \cup B) = p(A) + p(B)$. Kolmogorov axioms are the latter three clauses 1–3. A probability space $\langle \Omega, E, p \rangle$ of the kind just defined is according to Axiom 3 a finitely additive one. We will not be concerned with infinite probability spaces. With reference to footnote 3 we can now state what we understand by 'probability'. Probability is a set-function as defined above: a normed, additive measure on E.

causes(measles_virus, measles, non-inoculated),
not causes(measles_virus, measles, inoculated),
not causes(measles_virus, measles, ants).

This is the simple, syntactic reason why it doesn't make any sense to ask questions of the form 'does A cause B?', for example, 'does measles virus cause measles?'. We should always refer to a particular reference class X as above and put our question accordingly: 'does Chlamydia pneumoniae infection cause coronary heart disease within the reference class X?', e.g.:

causes(chlamydia, chd, human)???
causes(chlamydia, chd, non-diabetics)???
causes(smoking, lung_cancer, teenangers)???
causes(helicobacter_pylori, gastric_ulcer, female)???
causes(oedipus_complex, gastric_ulcer, psychoanalysts)???
causes(anopheles, malaria, sickle_cell_carriers)???

That means, construe causation as a *three-place relation* of the structure 'causes(A, B, X)', to be read, for example, in one of the following ways:

A causes B within the background context X,
A causes B in the population X,
A causes B with respect to X,
A causes B conditional on X,
B is caused by A with respect to X,
B is caused by A relative to X,

and the like. And by so doing you have resolved *the basic problem* of causality and etiology alluded to above! We will do, with some supplements, just that.

We will in the following consider causes and effects as generic events whose individual instances occur at particular moments or periods of time. For this purpose we will use a discrete time interval $[t, t']$ whose elements are points of time and linearly ordered according to the binary relation $<$ of precedence. The shorthand statement '$t_i < t_j$' means that the time point t_i is *earlier than* t_j, and '$t_i \leq t_j$' says that t_i is *earlier than or simultaneous* with t_j. These points of time will serve as the times of occurrence of our events. We will not complicate the temporal aspect of our analysis, though a detailed consideration of terms such as 'occurrence', 'duration', 'overlapping occurrence' and 'partial simultaneity' would be desirable and beneficial (for details, see [20]). If A is an event occurring at time t_i, we write A_{t_i} to indicate by the subscript t_i its moment of occurrence. The phrase 'iff' abbreviates the biconditional connective 'if and only if'.

Definition 1 below introduces our basic concept everything else will be built upon. An intuitive understanding of this base is this: let there be a particular probability space, such as tossing a dice, whose events successively occur during a particular period of time. Thanks to the mathematical laws of probability theory we know of course in advance the probabilities of these events presupposing they are independent of one another. But among the actual occurrences of this particular

probability space there may be events which may prove probabilistically relevant to some later events, thus disproving our prior independence assumption. In such a case of obvious difference between our actual observation and mathematical truth we are allowed to consider the whole contraption as something that may accommodate a relation of causation between its earlier and later events, i.e as something that *possibly is a causal structure*.

Definition 1. ξ is a *potential causal structure* iff there are Ω, E, p, T, A_{t_1}, B_{t_2} and X such that

1. $\xi = \langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X \rangle$,
2. $\langle \Omega, E, p \rangle$ is a probability space,
3. T is a discrete time interval,
4. A_{t_1}, B_{t_2} and X are non-empty elements of E,
5. $t_1, t_2 \in T$ such that $t_1 < t_2$,
6. $p(B_{t_2} \mid X \cap A_{t_1}) \neq p(B_{t_2} \mid X)$.

A probability space thus develops into a potential causal structure if there is an earlier event type A_{t_1} in the event algebra which according to axiom 6 and relative to the reference event type X, is probabilistically relevant to the later event type B_{t_2}. Thanks to the inequality relation in axiom 6, the probabilistic relevance of A_{t_1} to B_{t_2} may be positive or negative. In either case, the event A_{t_1} gives the prima facie impression to be causally relevant to B_{t_2} within X because it changes the probability of B_{t_2}'s occurrence.

For instance, our familiar example of Chlamydia infection and coronary heart disease within the population of non-diabetics together with all ingredients (sample space, event algebra, etc.) already constructed in the previous sections, and the following finding quoted as Eq. (20) in Section 4.2.:

$$p(\text{chd}_{t_2} \mid \text{non-diabetics} \cap \text{chlamydia}_{t_1}) > p(\text{chd}_{t_2} \mid \text{non-diabetics}) \tag{23}$$

yield a potential causal structure of the kind defined above if the clinical events in this finding are supplied with an appropriate time axis to guarantee that Chlamydia infection precedes coronary heart disease as required in Definition 1.

In our theory of etiology at least two types of potential causal structure are distinguished. In the first type, written:

$$\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X \rangle, \tag{24}$$

as in Definition 1, the potential cause-effect events (A_{t_1}, B_{t_2}) are *elements* of the event algebra E, i.e. elementary generic events such as 'Chlamydia infection occurs' and 'coronary heart disease occurs', or any combinations of them. A potential causal structure of this type should therefore be termed *elementary*. In the second type, written:

$$\langle \Omega, E, p, T, \pi_1, \pi_2, X \rangle, \tag{25}$$

the potential cause-effect component (π_1, π_2) is a more complex one. Each π_i may be a random function or a more or less complex partition like $\pi_1 = \{$Chlamydia

infection occurs, Chlamydia infection does not occur} and $\pi_2 = \{$coronary heart disease occurs, coronary heart disease does not occur$\}$, and thus a *subset* of the event algebra E. Due to page limitations, I will confine myself to elementary structures of the kind Eq. (24) only and will not be concerned with the second, complex kinds of causal structures, though they are more powerful, axiomatic extensions of the ones considered. For this reason, the discriminating affix 'elementary' that we should have used in the name of the basic, potential causal structure constructed in Definition 1 was omitted (for details, see [20]).

The next definition determines that an earlier occurrence is a *potential* positive or negative cause of a later occurrence within a particular population if the earlier event is positively or negatively probabilistically relevant to the later event, respectively.

Definition 2. If $\langle \Omega, \mathrm{E}, \mathrm{p}, T, \mathrm{A}_{t_1}, \mathrm{B}_{t_2}, \mathrm{X} \rangle$ is a potential causal structure, then
1. A_{t_1} is a *potential positive cause* of B_{t_2} within X iff $\mathrm{p}(\mathrm{B}_{t_2} \mid \mathrm{X} \cap \mathrm{A}_{t_1}) > \mathrm{p}(\mathrm{B}_{t_2} \mid \mathrm{X})$,
2. A_{t_1} is a *potential negative cause* of B_{t_2} within X iff $\mathrm{p}(\mathrm{B}_{t_2} \mid \mathrm{X} \cap \mathrm{A}_{t_1}) < \mathrm{p}(\mathrm{B}_{t_2} \mid \mathrm{X})$.

In our example potential causal structure above, Chlamydia pneumoniae infection is due to Eq. (23) a potential positive cause of coronary heart disease within non-diabetics if it precedes the heart disease. On the other hand, because of the following finding

$$\mathrm{p}(\mathrm{chd} \mid \mathrm{diabetics} \cap \mathrm{chlamydia}) = \mathrm{p}(\mathrm{chd} \mid \mathrm{diabetics}),$$

which we had already quoted as Eq. (21) in Section 4.2, we are not allowed to suppose that Chlamydia infection also plays a comparable, positive causal role in the population of diabetics. Obviously it doesn't do so. In this population it is a causally irrelevant happening, 'an innocent bystander' as Muhlestein et al. would say ([10], p. 1555).

Another interesting example demonstrating both kinds of potential cause, positive and negative ones, can be drawn from a recent study on the association of C-reactive protein, myocardial infarction, and the reduction of the latter by aspirin [12]. In this long-term study known as The Physicians' Health Study, in a period of over 13 years (1982–1995) a total of 22.071 US male physicians 40–84 years of age with no history of myocardial infarction, stroke, or cancer were assigned to different groups of a randomized, placebo-controlled trial of aspirin and beta carotene in the primary prevention of cardiovascular disease and cancer.[7] The

[7] Inflammation processes in heart and brain arteries are currently viewed as important etiologic factors in the pathogenesis of coronary heart disease, stroke, and related health catastrophes. As we have already pointed to, microorganisms such as Chlamydia pneumoniae, Helicobacter pylori, etc. are therefore being studied as potential agents of the inflammation. C-reactive protein is a marker for systemic inflammation. Elevated plasma concentrations of C-reactive protein are known to be associated with acute myocardial ischemia and infarction. The present, major study we refer to [12] has analyzed, among many other things, the association of C-reactive protein and the diseases mentioned on the one hand, and the effect of the antiinflammatory agent aspirin within this pathogenetic background context, on the other.

authors report, among many other findings, that elevated plasma C-reactive protein concentration (as an indicator of systemic inflammation) was statistically significantly correlated with myocardial infarction and stroke. These risks were stable over long periods, were not modified by smoking and lipid-related or non-lipid related risk factors. The use of aspirin was significantly associated with reductions in the risk of myocardial infarction [ibid, pp. 973, 977]. ''The aspirin component of the study was terminated early, on 25 January, 1988, primarily because of a statistically extreme 4 percent reduction in the risk of a first infarction in the aspirin group'' [ibid., p. 974]. To interpret these findings within our framework, let us first introduce some shorthand notations. We write:

infarction	for	myocardial infarction occurs
c-reactive	for	C-reactive protein level is elevated
smoking	for	the patient is a smoker
cholesterol	for	hypercholesterolemia is present
aspirin	for	aspirin is used
men	for	the underlying population X

We can conclude from the study quoted above that:

$$\mathrm{p}(\text{infarction} \mid \text{men} \cap \text{c-reactive}) > \mathrm{p}(\text{infarction} \mid \text{men}), \tag{26}$$

$$\mathrm{p}(\text{infarction} \mid \text{men} \cap \text{c-reactive} \cap \text{aspirin}) < \mathrm{p}(\text{infarction} \mid \text{men} \cap \text{c-reactive}), \tag{27}$$

$$\mathrm{p}(\text{infarction} \mid \text{men} \cap \text{c-reactive} \cap \text{smoking}) = \mathrm{p}(\text{infarction} \mid \text{men} \cap \text{c-reactive}), \tag{28}$$

$$\mathrm{p}(\text{infarction} \mid \text{men} \cap \text{c-reactive} \cap \text{cholesterol}) = \mathrm{p}(\text{infarction} \mid \text{men} \cap \text{c-reactive}). \tag{29}$$

Each of the Eqs. (26) and (27) yields a potential causal structure when properly supplemented by the formal accessories required by Definition 1 above. In the first one of these causal structures including Eq. (26), C-reactive protein seems to have a positive causal impact on the occurrence of myocardial infarction. In the second causal structure including Eq. (27), that impact is reversed by aspirin. One may thus suppose that in the reference population of men, C-reactive protein is a potential positive cause of myocardial infarction (Eq. (26)), and that within the population of *men having elevated C-reactive protein* (left-hand side of Eq. (27)), aspirin is a potential negative cause of myocardial infarction. Neither smoking nor cholesterol is able to change the potential causal impact of C-reactive protein on myocardial infarction in men (Eqs. (28) and (29)). Let us see if the possibly causative roles reported can be saved if we continue our methodological considerations.

A potential causal structure does not provide genuine causes yet, but merely potential causes (see Definition 2). Genuine causes require us to ensure that the events appearing as potential causes are not spurious ones. To this end we will propose a notion of spuriousness with the following rationale behind it: a potential

cause is a *spurious* cause if it is rendered probabilistically irrelevant by an earlier occurrence. That is, if a potential cause A_{t_1} (e.g. falling barometer reading) is preceded by another event C_t (decreasing air pressure) that generates the same effect B_{t_2} (storm) to the same extent as well, then the later potential cause A_{t_1} is a spurious cause. It cannot be viewed as a genuine cause of the effect B_{t_2} and must be removed from the list of potential causes of this effect. Otherwise, we will be accused of the barometer-causes-storm fallacy.

To keep the following definition of this notion readable, we mention the notion of a partition separately. A partition π of the reference event X is a set $\{C_1,\ldots, C_n\}$ of $n \geq 2$ non-empty, pairwise disjoint events C_i such that the union of all $X \cap C_i$ is X. For example, a particular partition of the population *men* examined in the above-mentioned aspirin trial is provided by {{aspirin is used}, {aspirin is not used}}.

Definition 3. If $\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X\rangle$ is a potential causal structure, then it is a *spurious causal structure* iff there are $t \in T$ and a partition $\pi_t \subseteq E$ of X such that for all events $C_t \in \pi_t$

1. $t < t_1$,
2. $p(B_{t_2} \mid X \cap A_{t_1} \cap C_t) = p(B_{t_2} \mid X \cap C_t)$.

As axiom 2 of this definition demonstrates, each of the earlier events C_t of the partition does without A_{t_1} as well and thus disqualifies A_{t_1} as a potential cause of B_{t_2}. If a structure $\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X\rangle$ is a spurious causal structure, A_{t_1} is called a *spurious cause* of B_{t_2} within X. Let us return to our Chlamydia example in non-diabetics: should etiologic research be able to show in the near future that there is a partition, e.g. {{coronary wall lesion occurs}, {coronary wall lesion does not occur}}, such that each of its events (C_t) satisfies axiom 2 of Definition 3 if it *precedes* the infection by Chlamydia (event A_{t_1}),

$$p(\text{chd}_{t_2} \mid \text{non-diabetics} \cap \text{wall-lesion}_t \cap \text{chlamydia}_{t_1}) = p(\text{chd}_{t_2} \mid \text{non-diabetics} \cap \text{wall-lesion}_t)$$

$$p(\text{chd}_{t_2} \mid \text{non-diabetics} \cap \text{no-wall-lesion}_t \cap \text{chlamydia}_{t_1}) = p(\text{chd}_{t_2} \mid \text{non-diabetics} \cap \text{no-wall-lesion}_t)$$

then we will have reason to view Chlamydia as a spurious cause of coronary heart disease in non-diabetics (event X). Meanwhile we will continue to believe the current epidemiologic hypothesis until we get proof to the contrary. In addition, we don't have yet any reason to believe that smoking and other classic risk factors have become spurious causes of coronary heart disease. Although such a prima facie impression may be evoked by the epidemiologic findings we have already quoted above:

$$p(\text{chd} \mid \text{non-diabetics} \cap \text{smoking} \cap \text{chlamydia}) = p(\text{chd} \mid \text{non-diabetics} \cap \text{chlamydia}),$$

$$p(\text{infarction} \mid \text{men} \cap \text{smoking} \cap \text{c-reactive}) = p(\text{infarction} \mid \text{men} \cap \text{c-reactive}),$$

$$p(\text{infarction} \mid \text{men} \cap \text{cholesterol} \cap \text{c-reactive}) = p(\text{infarction} \mid \text{men} \cap \text{c-reactive}),$$

these findings do not provide us with a partition of the respective reference class to judge about the spuriousness of those risk factors. This research gap is especially awkward regarding the prima facie, potential causal relevance of C-reactive protein to myocardial infarction (Eq. (26)). The available biochemical background knowledge on the nature and role of C-reactive protein in the organism provides convincing evidence that it must be a spurious cause of myocardial infarction, i.e. a mere indicator like falling barometer reading, fever, pain, and erythrocyte sedimentation rate. As a non-specific, systemic reaction to infection, tissue injury and necrosis, C-reactive protein has a multitude of agents behind it each of which may prove to be a preceding, common cause of both its increase *and* myocardial infarction. The life-saving merit of aspirin is not due to a conceivable lowering of C-reactive protein levels per se, but due to its anticoagulatory and presumably antiinflammatory effects, an idea which indirectly corroborates the Chlamydia and other infection hypotheses. A detailed discussion of this *common cause* aspect in etiology is behind the scope of this paper (cf. [20]). Though it may be pointed out that in our theory there is a direct relationship between common causes, non-specificity, and spuriousness. The spuriousness of C-reactive protein is provable in that context. Its elevation prior to coronary heart disease events thus becomes a kind of barometer reading having air pressure changes behind it.

Definition 4. If $\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X \rangle$ is a potential causal structure and is not a spurious one, then

1. A_{t_1} is a *positive cause* of B_{t_2} within X iff $p(B_{t_2} \mid X \cap A_{t_1}) > p(B_{t_2} \mid X)$,
2. A_{t_1} is a *negative cause* of B_{t_2} within X iff $p(B_{t_2} \mid X \cap A_{t_1}) < p(B_{t_2} \mid X)$.

Relying upon the available evidence that our example potential causal structures quoted above are not spurious ones, we will presume that: (1) Chlamydia pneumoniae infection is a positive cause of coronary heart disease within non-diabetics; and (2) aspirin is a negative cause of myocardial infarction in men with raised C-reactive protein levels.

The fragments of our causal language constructed thus far indicate that it is our plan to distinguish *positive* and *negative* causes of different types. Due to space limitations, however, we will in the following concentrate on the positive part only and will not introduce extra definitions and concepts of negative causality. They are more or less formal analogues of positive ones (for details, see [20]).

Definition 5. If $\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X \rangle$ is a potential causal structure, then it is a *causal structure* iff A_{t_1} is a *positive* or a *negative cause* of B_{t_2} within X. In the former case, the structure is referred to as a *positive causal structure*, written ${}^{+}\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X \rangle$, in the latter case as a negative causal structure, written ${}^{-}\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X \rangle$. In a positive causal structure we say, 'A_{t_1} *causes* B_{t_2} within X'. In a negative causal structure we say, 'A_{t_1} *discauses* B_{t_2} within X'.

For example, let the temporally extended probability space $\langle \Omega, E, p, T \rangle$ be an appropriate frame for our purposes, then the following two sets are causal structures:

$^{+}\langle \Omega, E, p, T, \text{chlamydia}_{t_1}, \text{chd}_{t_2}, \text{non-diabetics} \rangle$,
$^{-}\langle \Omega, E, p, T, \text{aspirin}_{t_1}, \text{infarction}_{t_2}, \text{men} \cap \text{c-reactive} \rangle$.

In the former causal structure, Chlamydia pneumoniae infection causes coronary heart disease in non-diabetics. In the latter, aspirin discauses myocardial infarction in men with increased C-reactive protein.[8]

Definition 6. If $\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X \rangle$ and $\langle \Omega, E, p, T, C_t, B_{t_2}, X \rangle$ are causal structures, then A_{t_1} and C_t are *interactive causes* of B_{t_2} iff

1. $p(B_{t_2} \mid X \cap A_{t_1} \cap C_t) \neq p(B_{t_2} \mid X \cap C_t)$,
2. $p(B_{t_2} \mid X \cap A_{t_1} \cap C_t) \neq p(B_{t_2} \mid X \cap A_{t_1})$.

That means that two causes A_{t_1} and C_t of an effect B_{t_2} are interactive if their joint occurrence within X has a different probabilistic relevance to the effect than their separate occurrence. 'Joint occurrence' does not mean that they must occur simultaneously, but merely that both of them, $A_{t_1} \cap C_t$, occur. In Definition 6 therefore, the occurrence times t and t_1 have been left indefinite. They may or may not be distinct. For instance, suppose that in addition to the finding:

$$p(\text{chd}_{t_2} \mid \text{non-diabetics} \cap \text{chlamydia}_{t_1}) > p(\text{chd}_{t_2} \mid \text{non-diabetics})$$

already quoted above as Eq. (23), we had also available the following, plausible probabilistic relevances that we may extrapolate from the aspirin trial:

$$\begin{aligned} &p(\text{chd}_{t_2} \mid \text{non-diabetics} \cap \text{aspirin}_t) < p(\text{chd}_{t_2} \mid \text{non-diabetics}), \\ &p(\text{chd}_{t_2} \mid \text{non-diabetics} \cap \text{chlamydia}_{t_1} \cap \text{aspirin}_t) \\ &\quad > p(\text{chd}_{t_2} \mid \text{non-diabetics} \cap \text{aspirin}_t), \\ &p(\text{chd}_{t_2} \mid \text{non-diabetics} \cap \text{chlamydia}_{t_1} \cap \text{aspirin}_t) \\ &\quad < p(\text{chd}_{t_2} \mid \text{non-diabetics} \cap \text{chlamydia}_{t_1}). \end{aligned}$$

We would then be allowed to conclude from this information that Chlamydia and aspirin are interactive causes of coronary heart disease in non-diabetics, provided they are not rendered spurious. Depending on whether the joint occurrence of two interactive causes exceeds or falls short of their separate probabilistic relevance to the effect, positive and negative interaction may be distinguished. Our hypothetical example above demonstrates a negative interaction: aspirin lowers, and even reverses, Chlamydia's causal impact on coronary heart disease within non-diabetics. Positively interacting causes may be called *synergistic* causes or factors. Negatively interacting ones may be termed *antagonistic* causes or factors.

[8] 'To discause' is a new verb that we have just created for negative causation. Here is an additional example: all efficacious preventive measures discause the diseases against which they are used.

If A_{t_1} and C_t are two interactive causes of an effect B_{t_2} such that A_{t_1} precedes C_t *and* causes or discauses it, then C_t is an intermediate cause of B_{t_2}, or an intermediary for short (Fig. 3a). There may be many intermediaries between a particular cause A_{t_1} and effect B_{t_2}. This is usually the case, for example, in contagious diseases. A pseudoproblem arises whenever the earlier cause A_{t_1} has opposing causal tendencies for intermediaries following it, such as, for example, causing C_t and discausing $D_{t'}$ (Fig. 3b). In this case there are two seemingly conflicting paths between A_{t_1} and B_{t_2}, an excitatory and an inhibitory one. An example is provided by Hesslow's contraceptive pills quoted in Section 4.2 above which he thinks may raise and lower the probability of thrombosis at the same time. But the situation is causal-analytically not so awkward as he believes. In Fig. 3b, oral contraceptives (A_{t_1}) in the population level, not in the individual female, cause thrombosis by triggering some thrombogenic intermediaries (C_t) over the left path, and discause thrombosis by preventing pregnancy ($D_{t'}$) over the right path. The overall statistical outcome yields a new probability value for thrombogenic relevance of Hesslow's pills in an entirely distinct causal structure. This value may be different than their thrombogenic relevance within other background contexts such as, for example:

$$
\begin{aligned}
&p(\text{thrombosis} \mid \text{female}) = r_1,\\
&p(\text{thrombosis} \mid \text{female} \cap \underline{\text{pregnant}}) = r_2,\\
&p(\text{thrombosis} \mid \text{female} \cap \text{pregnant}) = r_3,\\
&p(\text{thrombosis} \mid \text{female} \cap \underline{\text{pregnant}} \cap \text{pill}) = r_4,\\
&p(\text{thrombosis} \mid \text{female} \cap \underline{\text{pregnant}} \cap \underline{\text{pill}}) = r_5,\\
&p(\text{thrombosis} \mid \text{female} \cap \text{pregnant} \cap \text{pill}) = r_6,\\
&p(\text{thrombosis} \mid \text{female} \cap \text{pill}) = r_7,\\
&p(\text{thrombosis} \mid \text{female} \cap \text{diabetics} \cap \text{pill}) = r_8,\\
&p(\text{thrombosis} \mid \text{female} \cap \text{aspirin} \cap \text{pill}) = r_9,\\
&p(\text{thrombosis} \mid \text{female} \cap \text{diabetics} \cap \text{aspirin} \cap \text{pill}) = r_{10},
\end{aligned}
$$

etc. None of these values r_i will equal another one. The strength of causal relevance a factor has to another factor is relative to the causal structures within which it

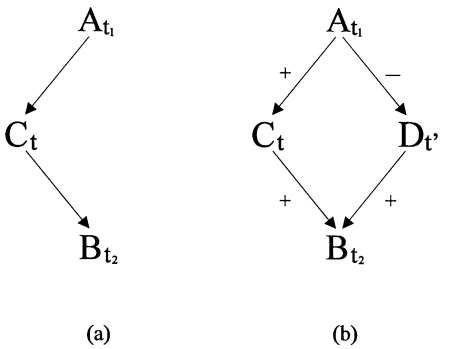

Fig. 3. Intermediaries between A_{t_1} and B_{t_2}. Part 3b displays two seemingly conflicting paths between A_{t_1} and B_{t_2}.

operates, or equivalently, within which it is being considered. There is no such thing as the absolute, positive or negative, causal relevance of something to something else. This is the essence of our relativistic theory of etiology.[9]

Indirect causes, and direct ones, are to be distinguished from intermediate causes. They cannot be defined here (for details and other types of causes, see [20]). A particular kind of cause, however, i.e. the notion of *sufficient cause*, must be mentioned to show that deterministic causation is also covered by the probabilistic approach we are presenting here. A sufficient cause is simply the limiting case where the probability of its effect reaches 1:

Definition 7. If $\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X \rangle$ is a causal structure, then $X \cap A_{t_1}$ is a *sufficient cause* of B_{t_2} iff $p(B_{t_2} \mid X \cap A_{t_1}) = 1$.

A deterministic causal law, as explicated in Section 3 above, may now be rewritten as a causal structure with the limiting probability

$$p(B_t \mid Y \cap A_{t_1} \cap A_{t_2} \cap \cdots \cap A_{t_n}) = 1 \tag{30}$$

such that $n \geq 1$ and all partial causes $Y, A_{t_1}, \ldots, A_{t_n}$ are interactive. Mackie's causes as INUS conditions quoted in Section 3 may be interpreted as A_{t_i}s of causal structures with limiting probabilities such as Eq. (30). Ideal, causal structures of this kind are rare enough. And nowhere else we have sufficient causes and thus INUS conditions available, though probabilistic causal structures and causes abound in the world. Causes therefore are in general not INUS conditions. We have to put up with non-deterministic etiology.

4.4. Quantitative and comparative causal structures

Among its numerous methodological advantages the framework sketched above also entails the virtue that it enables us in different ways to view and treat the causal impact of causes as a measurable quantity. We will choose the most obvious and simple measurement, though there are also competing ones (cf. [20]).

To measure the causal strength of causes, let us introduce an appropriate terminology and syntax. We consider all of the following expressions as synonyms: causal strength, causal impact, causal relevance, causal influence, causal support, causal significance, causal propensity, causal contribution, degree of causation. We prefer the term *causal relevance* and use it in the following manner: 'the causal relevance of A to B within X is r', symbolized by $cr(A, B, X) = r$ and defined as follows:

Definition 8. If $\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X \rangle$ is a causal structure, then $cr(A_{t_1}, B_{t_2}, X) = r$ iff $r = p(B_{t_2} \mid X \cap A_{t_1}) - p(B_{t_2} \mid X)$.

[9] It says that the notion of cause is not an absolute, unconditional one such as *causes*(A, B), but a conditional one such as our familiar diction *causes*(A, B, X) that we have already read as 'A causes B conditional on X'. Accordingly, the theory sketched in this paper is a theory of *conditional casuality* [20].

That means that the causal relevance of an event to another one within a particular population is just the extent to which it raises or lowers the probability of the occurrence of the latter within this population, given a causal structure as introduced in Definition 5. For example,

$$\mathrm{cr}(\text{chlamydia, chd, non-diabetics})$$
$$= \mathrm{p}(\text{chd} \mid \text{non-diabetics} \cap \text{chlamydia}) - \mathrm{p}(\text{chd} \mid \text{non-diabetics}).$$

Causal relevance, cr, is thus a three-place, numerical function. Depending on the magnitudes of the two underlying probabilities whose difference yields cr(A, B, X), the causal relevance function cr assumes values in the real interval $[-1, +1]$. For instance,

$$\mathrm{cr}(\text{chlamydia, chd, non-diabetics}) = 0.25$$
$$\mathrm{cr}(\text{chlamydia, chd, diabetics}) = 0$$
$$\mathrm{cr}(\text{smoking, chd, non-diabetics} \cap \text{chlamydia}) = 0$$
$$\mathrm{cr}(\text{aspirin, infarction, men} \cap \text{c-reactive}) = -0.4.$$

The first and the last one of these quantities are fictitious as I was unable to extract accurate base probabilities from the literature sources referred to previously [9,12]. The examples and definitions demonstrate that:

causal irrelevance amounts to	$\mathrm{cr}(A, B, X) \cong 0$	(null-causing)
positive causal relevance is	$\mathrm{cr}(A, B, X) > 0$	(causing)
negative causal relevance is	$\mathrm{cr}(A, B, X) < 0$	(discausing, preventing)
maximum positive causal relevance is	$\mathrm{cr}(A, B, X) = 1$	(maximum efficiency)
maximum negative causal relevance is	$\mathrm{cr}(A, B, X) = -1$	(maximum prevention)

It goes without saying that at least due to its range $[-1, +1]$, the causal relevance function cr is not a probability, possibility, necessity, belief, or plausibility. It is simply a normed, conditional measure over the event algebra. This becomes evident from the following definition which in its axiom 5 also includes Definition 8. This expository definition that we will not use here displays a genuine space in mathematical sense. It demonstrates how our theory of causation may be extended stepwise [20]. The intuitive idea behind it is that triple chunks of the event algebra E, symbolized by E_1, E_2, E_3, may constitute a complex of causal structures that yields a measurable space if a causal relevance measure is available.

Definition 9. ξ is a *causal space* iff there are Ω, E, p, T, E_1, E_2, E_3, and cr such that

1. $\xi = \langle \Omega, E, p, T, E_1, E_2, E_3, cr \rangle$,
2. $E_1, E_2, E_3 \subseteq E$,
3. For every $A_{t_1} \in E_1$ and $B_{t_2} \in E_2$ there is an $X \in E_3$ such that $\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X \rangle$ is a causal structure,
4. cr: $E \times E \times E \rightarrow [-1, +1]$,

5. If $\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X \rangle$ is a causal structure, then $cr(A_{t_1}, B_{t_2}, X) = p(B_{t_2} | X \cap A_{t_1}) - p(B_{t_2} | X)$,
6. $cr(Y, \Omega, X) = cr(Y, \emptyset, X) = 0$ for all non-empty $Y, X \in E$,
7. If $Z_1 \subseteq Z_2$, then
   $cr(Y, Z_1, X) \leq cr(Y, Z_2, X)$ if $cr(Y, Z_2, X)$ is positive
   $cr(Y, Z_1, X) \geq cr(Y, Z_2, X)$ if $cr(Y, Z_2, X)$ is negative
for all non-empty $Y, Z_1, Z_2, X \in E$.

The causal relevance function cr is rendered a normed measure by axioms 4, 6 and 7. According to axiom 6, no event is causally relevant to the sure event Ω and to the impossible event $\emptyset$.

A causal space as just introduced provides a strong ordering for causes in the reals $[-1, +1]$. Thus, metric causal and metacausal studies become feasible. For example, (in analogy to random functions) one may construct causal functions that *cause* causal relevance distributions over the event algebra, cause their temporal changes ('causal kinematics'), etc.[10] The space enables us to also lend a comparative order to causal relationships among causes and effects by comparing their quantitative causal relevances cr(A, B, X). We will thus achieve in medical knowledge engineering a wide-ranging comparative causal terminology and talk such as 'A is a *stronger* positive cause of B in class X than is C', 'A is causally *more relevant* to B within X than is C within Y', 'A is causally *less relevant* to B within X than is C', and the like. For example, the statement

$$cr(\text{chlamydia, chd, non-diabetics}) > cr(\text{smoking, chd, non-diabetics}),$$

says that Chlamydia pneumoniae infection is a stronger cause of coronary heart disease in non-diabetics than is smoking. Analogous examples are:

$$cr(\text{chlamydia, chd, diabetics}) = cr(\text{chlamydia} \cap \text{smoking, chd, non-diabetics}),$$
$$cr(\text{chlamydia, chd, diabetics}) < cr(\text{chlamydia, chd, non-diabetics}),$$
$$cr(\text{helicobacter, gastric\_ulcer, men}) > cr(\text{oedipus, gastric\_ulcer, men}),$$
$$cr(\text{contraceptives, thrombosis, pregnant}) > cr(\text{contraceptives, thrombosis, non-pregnant}).$$

4.5. Conjectural causal structures

Numerical probabilities needed for calculating the causal relevance cr(A, B, X) an event has to another one, are unfortunately not always available in medicine. In most cases we have only to guess if an event like smoking exerts any causal influence on something else like lung cancer. How do we do that? Is there a possibilty to improve this subjective capability of etiologic conjecturing when quantitative knowledge is lacking? As a straight development of our foregoing considerations, we will in what follows sketch methods that can be used to this end.

[10] Ontological facets of the problem 'what does the causal relevance function cr measure?' become now apparent (see [20]).

The best situation in this worst case of lacking numerical probabilities would be if one were in a position to say which one of the events whose cause-effect relationships are being judged is *more likely than* another one. That is, comparative probabilities should be available. They are obtainable by, for example, frequency analyses and comparisons. The comparative probabilities we need are conditional ones holding between pairs of conditional events $(B \mid A)$ and $(D \mid C)$. The two-place relation 'is at least as likely as' or any of its synonyms may serve as the basic predicate. We symbolize it by '$\geq$' to use the shorthand notation:

$$(B \mid A) \geq (D \mid C), \tag{31}$$

to be read as 'B given A is *at least as likely as* D given C'. For example, 'coronary heart disease given Chlamydia pneumoniae infection is at least as likely as stroke given cerebral atherosclerosis'. By standard definitions we draw of Eq. (31) the relations:

$$(B \mid A) > (D \mid C), \tag{32}$$

$$(B \mid A) \approx (D \mid C), \tag{33}$$

$$(B \mid A) \neq (D \mid C), \tag{34}$$

the first one to be read as 'B given A is *more likely than* D given C', the second one as 'B given A is *as likely as* D given C', and the last one as 'B given A is *not as likely as* D given C'. We cannot deal here with a calculus for handling these comparative probability relations (see, e.g. [5,25]). Based upon such a calculus, we say: a triplet $\langle \Omega, E, \geq \rangle$ is a *comparative probability space* iff Ω is a sample space, E is an event algebra on Ω, and $\geq$ is a comparative probability relation on E such that the axioms of that calculus are satisfied.

Definition 10. ξ is a *conjectural potential causal structure* iff there are Ω, E, $\geq$, T, A_{t_1}, B_{t_2} and X such that

1. $\xi = \langle \Omega, E, \geq, T, A_{t_1}, B_{t_2}, X \rangle$,
2. $\langle \Omega, E, \geq \rangle$ is a comparative probability space,
3. T is a discrete time interval,
4. A_{t_1}, B_{t_2} and X are non-empty elements of E,
5. $t_1, t_2 \in \tilde{T}$ such that $t_1 < t_2$,
6. $(B_{t_2} \mid X \cap A_{t_1}) \neq (B_{t_2} \mid X)$.

The analogy with Definition 1 in Section 4.3 is obvious where potential causal structures were constructed on quantitative probability spaces. The only difference is that the comparative probability relation $\geq$ now replaces the quantitative probability function p. For example, supposing that myocardial infarction given both diabetes and obesity is *more likely than* given diabetes only,

$$(\text{infarction}_{t_2} \mid \text{diabetes} \cap \text{obesity}_{t_1}) > (\text{infarction}_{t_2} \mid \text{diabetes}),$$

then, supplemented by remaining ingredients, we have the following conjectural potential causal structure: $\langle \Omega, E, >, T, \text{obesity}_{t_1}, \text{myocardial\_infarction}_{t_2}$, dia-

betes⟩. Note that no statistical knowledge on quantitative probabilities is required.[11]

In a fashion formally analogous to the quantitative cases in Section 4.3, additional causal terminology may be easily defined, but we will not parallel that procedure here. The only notions to demonstrate is this main pair.

Definition 11. If $\langle \Omega, E, \geq, T, A_{t_1}, B_{t_2}, X \rangle$ is a conjectural potential causal structure and is not a spurious one, then

A_{t_1} is a *conjectural positive cause* of B_{t_2} within X iff $(B_{t_2} \mid X \cap A_{t_1}) > (B_{t_2} \mid X)$,

A_{t_1} is a *conjectural negative cause* of B_{t_2} within X iff $(B_{t_2} \mid X \cap A_{t_1}) < (B_{t_2} \mid X)$.

Definition 12. If $\langle \Omega, E, \geq, T, A_{t_1}, B_{t_2}, X \rangle$ is a conjectural potential causal structure, then it is a *conjectural causal structure* iff A_{t_1} is a *conjectural positive* or a *conjectural negative* cause of B_{t_2} within X.

Despite lacking quantitative probabilities in conjectural causal structures a quasi measure of causal relevance like cr can also be constructed in these structures (cf. [20]).[12]

4.6. Subjective causal structures

If in addition to quantitative probabilities comparative ones are also lacking in a particular domain, we will depend on qualitative probabilities. They are usually communicated by expressions like 'probable', 'likely', 'unlikely', etc. For instance, 'lung cancer in men given smoking is likely'. The major part of the personal knowledge and belief one uses in everyday life and medical practice belongs to this type of probabilistic knowledge and belief. The question arises if there is a possibility to elicit causal knowledge and belief from this subjective part of our epistemic sphere. To this end I now will construct a notion of 'qualitative probability space' and will explore if it can also be extended to a causal structure.

We understand by *linguistic function* a function *f* which maps a particular domain into a set of linguistic entities, i.e. words or sentences. This may be exemplified by the linguistic function 'Color-of' which maps the set of objects into the set of color designators:

Color-of: Objects → {red, green, yellow,…, etc.}.

[11] There is a second difference between causal structures of the first kind based upon quantitative probabilities and conjectural causal structures. It is a philosophical one. Conjectural causal structures are beyond any doubt subjective structures in that comparative probabilities are subjective probabilities (see footnote 3).

[12] One can also amalgamate the causal structures as defined on the basis of quantitative probability in Section 4.3, and the conjectural ones. For this approach, see [20].

A statement such as 'blood is red' thus becomes expressible as a functional equation of the form:

$$\text{Color-of(blood)} = \text{red}.$$

The word 'Age' is another example mapping the set of people into the set of age lables such as young, old, very old, etc. e.g. Age(Manuel) = very young. The linguistic function 'Truth' maps the set of statements into the set of truth values. Here are some examples:

Truth: Statements → {true, not true, very true, false, more or less true, quite true,…},
Age: People → {young, very young, adult, old, quite old, more or less old,…},
Weight: Objects → {light, very light, not very light, heavy, not heavy,…},
Ethics: Actions → {good, bad, very good, very very good, excellent, miserable,…}.

Following the inventor of the theory of linguistic functions, Lotfi A. Zadeh, who improperly called them 'linguistic variables' [27–29], the range of a linguistic function f will be referred to as its term set, written $Term(f)$. We can in this way arrange a term set such as {likely, very likely, not likely, unlikely, more or less likely, certain, improbable,…} which may serve as the range of a linguistic probability function, denoted as *Probability*, or P for short:

P: Events → {likely, very likely, not likely, unlikely, more or less likely, certain, improbable,…}.

This will enable us to assign to events linguistic probabilities in the following manner: P({Chalamydia pneumoniae infection is present}) = very likely. P({it will rain tomorrow} ∩ {it will not rain tomorrow}) = improbable.

Let P be a function of this type with Term(P) as above. It is possible to transform Term(P) into an ordinal or rank-order scale. This will be achieved by a ranking according to whether a term $\tau_j \in$ Term(P) assigns a higher subjective probability to an event than another term $\tau_i \in$ Term(P) does. Such is the case, for example, regarding the two terms 'unlikely' and 'very likely'. The latter assigns a higher subjective probability to an event than does 'unlikely'. Let us string the elements of Term(P) in the order of their increasing subjective probability content as just described:

$$\text{Term(P)} = \langle \text{improbable}, \tau_2, \ldots, \tau_{n-1}, \text{certain} \rangle \tag{35}$$

such that τ_1 denotes the least probable, and τ_n signifies the most probable. Given any two terms τ_i, $\tau_j \in$ Term(P), we say that τ_i is below τ_j, or conversely, τ_j is above τ_i iff $i < j$. For example, it will be commensurate with our intuition if in Eq. (35) 'not likely' is below 'very likely', and 'very very likely' is above 'likely'. We define:

$\tau_j \geq \tau_i$ iff $j \geq i$, that is, iff τ_j is not below τ_i,

$\tau_i \neq \tau_j$ iff $i \neq j$.

Definition 13. ξ is a *qualitative probability space* iff there are Ω, E, P, Term(P), and $\geq$ such that

1. $\xi = \langle \Omega, \text{E}, \text{P}, \text{Term(P)}, \geq \rangle$,
2. Ω is a sample space,
3. E is an event algebra on Ω,
4. P: $\text{E} \rightarrow \text{Term(P)}$,
5. $\text{Term(P)} = \langle \text{improbable}, \tau_2, \ldots \tau_{n-1}, \text{certain} \rangle$ is a rank-ordered term set of P,
6. $\text{P}(\emptyset) = \text{improbable}$,
7. $\text{P}(\Omega) = \text{certain}$,
8. If $\text{Z} \supseteq \text{Y}$, then $\text{P(Z)} \geq \text{P(Y)}$ for all Y, $\text{Z} \in \text{E}$.

According to the last three axioms, the qualitative probability function P must be viewed as a normed linguistic measure. A fuzzy-theoretical method of computation with linguistic probabilities may be found in [29]. It renders the structure above a qualitative probability calculus. Now, it does not appear a difficult task to also extend this probability calculus to a causal structure.

Definition 14. ξ is a *subjective potential causal structure* iff there are Ω, E, P, Term(P), $\geq$, T, A_{t_1}, B_{t_2} and X such that

1. $\xi = \langle \Omega, \text{E}, \text{P}, \text{Term(P)}, \geq, \text{T}, \text{A}_{t_1}, \text{B}_{t_2}, \text{X} \rangle$,
2. $\langle \Omega, \text{E}, \text{P}, \text{Term(P)}, \geq \rangle$ is a qualitative probability space,
3. T is a discrete time interval,
4. A_{t_1}, B_{t_2} and X are non-empty elements of E,
5. $t_1, t_2 \in \text{T}$ such that $t_1 < t_2$,
6. $\text{P}(\text{B}_{t_2} \mid \text{X} \cap \text{A}_{t_1}) \neq \text{P}(\text{B}_{t_2} \mid \text{X})$.

The inequality sign in axiom 6 of course denotes the semantic difference defined above and means that the linguistic probability values τ_i, $\tau_\text{j} \in \text{Term(P)}$ assigned to the two conditional events are distinct. This implies that one of them is above the other one.

The formal analogy between this concept and the other two ones introduced in Definitions 1 and 10 upon which our earlier considerations and constructions were based, is striking. We will therefore not repeat the procedure of introducing analogous notions of spuriousness, causal interaction, etc. Is it possible, however, to also reconstruct in this subjective context the main notions of 'causing' and 'discausing'?

Definition 15. If $\langle \Omega, \text{E}, \text{P}, \text{Term(P)}, \geq, \text{T}, \text{A}_{t_1}, \text{B}_{t_2}, \text{X} \rangle$ is a subjective potential causal structure and is not a spurious one, then

1. A_{t_1} is a *positive subjective cause* of B_{t_2} within X iff $\text{P}(\text{B}_{t_2} \mid \text{X} \cap \text{A}_{t_1})$ is above $\text{P}(\text{B}_{t_2} \mid \text{X})$,

2. A_{t_1} is a *negative subjective cause* of B_{t_2} within X iff $P(B_{t_2} \mid X \cap A_{t_1})$ is below $P(B_{t_2} \mid X)$.

Definition 16. If $\langle \Omega, E, P, \text{Term}(P), \geq, T, A_{t_1}, B_{t_2}, X \rangle$ is a subjective potential causal structure, then it is a *subjective causal structure* iff A_{t_1} is a *positive* or a *negative subjective cause* of B_{t_2} within X.

Comparable to previous causal structures introduced in preceding sections, with respect to a subjective causal structure it is natural and legitimate to assert as well that, for instance, A_{t_1} *causes* B_{t_2} within X if in this structure A_{t_1} is a positive subjective cause of B_{t_2}, and conversely, to say that A_{t_1} *discauses* B_{t_2} within X if in this structure A_{t_1} is a negative subjective cause of B_{t_2}. This propositional attitude reflects the general pattern of qualitative *causal belief* revealing at the same time that and why it may be difficult to discriminate between realism and delusion (cf. [15], p. 173). Not only our everyday life, but also diagnostic and therapeutic decision-making in clinical practice is governed by qualitative causal beliefs where something is believed by someone to cause something else. The question therefore arises if notwithstanding their qualitative and subjective character, clinical causal beliefs are amenable to some kind of *causal relevance* talk and control. We now turn to this question.

5. Fuzzy etiology

When introducing conjectural and qualitative causal structures above we have already entered the realm of fuzzy etiology because comparative as well as qualitative probabilities upon which they are based are fuzzy probabilities. This becomes apparent by a closer look both at the predicate 'is at least as likely as' that we used as our basic comparative probability relation, and at the elements of the term set $\langle$improbable, $\tau_2, \ldots, \tau_{n-1}$, certain$\rangle$ representing the range of the qualitative probability function. All of them are fuzzy predicates denoting fuzzy sets. If we take into account that even a quantitative probability may be a fuzzy number such as 'p(B | A) = approximately 0.7', we will recognize how serviceable in etiology fuzzy theory may be. This service is not confined to the probability component of causation, however. Causal talks including causal relevance itself as a relation among events may also benefit from fuzzy theory.

5.1. Fuzzy causal structures

For example, it appears quite reasonable to use fuzzy predicates and to state that

A causes B within X to a *low* extent,
A *strongly* causes B within Y,
A *moderately* discauses B within Z,

when an appropriate semantics for this chattering is available. To this end, let us agree upon a uniform syntax that will substitute for all fuzzy statements of the type above. We write:

$$\mathrm{CR}(\mathrm{A}, \mathrm{B}, \mathrm{X}) = \tau$$

and read this as 'the causal relevance of A to B within X is τ' where τ denotes a fuzzy strength of causation such as 'low' in the following statement:

$$\mathrm{CR}(\mathrm{smoking}, \mathrm{lung\_cancer}, \mathrm{teenagers}) = \mathrm{low}.$$

Note that this new notion of causal relevance, CR, written in capitals, is a linguistic function and should not be confounded with the numerical function cr of causal relevance that we dealt with in Section 4.4. Let us fix a particular range for it, for example, something like the following term set:

$$\mathrm{Term}(\mathrm{CR}) = \{\text{low, very low, not low, medium, high, very high, not high, very very high, extremely high, more or less high, neutral, negative, weakly negative, very negative,..., etc.}\}.$$

CR is a three-place linguistic function and will map the Cartesian triple of the event algebra E into the set Term(CR):

$$\mathrm{CR}: \mathrm{E} \times \mathrm{E} \times \mathrm{E} \rightarrow \mathrm{Term}(\mathrm{CR}).$$

We will thus become able to understand what it means to say, for example, that within non-diabetics, Chlamydia pneumoniae infection is causally highly relevant to coronary heart disease:

$$\mathrm{CR}(\mathrm{chlamydia}, \mathrm{chd}, \text{non-diabetics}) = \mathrm{high}.$$

According to what we have already studied earlier, it is of course possible that within different reference classes this infection is differently causally relevant to the same disease. For instance, we may face the following situation:

$$\mathrm{CR}(\mathrm{chlamydia}, \mathrm{chd}, \text{diabetics}) = \text{very very low},$$
$$\mathrm{CR}(\mathrm{chlamydia}, \mathrm{chd}, \text{diabetics} \cap \text{rheumatism}) = \mathrm{low},$$
$$\mathrm{CR}(\mathrm{chlamydia}, \mathrm{chd}, \text{non-diabetics} \cap \text{rheumatism}) = \text{very high}.$$

And it is also conceivable that by causal intervention the very high causal relevance just mentioned may be reversed, e.g. by using antibiotics, aspirin, etc.:

$$\mathrm{CR}(\text{chlamydia} \cap \text{antibiotics}, \mathrm{chd}, \text{non-diabetics} \cap \text{rheumatism}) = \text{moderately negative},$$
$$\mathrm{CR}(\text{chlamydia} \cap \text{antibiotics} \cap \text{aspirin}, \mathrm{chd}, \text{non-diabetics} \cap \text{rheumatism}) = \text{highly negative}.$$

These examples demonstrate how causal relevances may be expressed and dealt with non-numerically linguistically, provided they are available. One may therefore inquire into whether or not fuzzy causal structures may be constructed in analogy to non-fuzzy (= crisp) ones discussed earlier. We will not go into detail here, but will only emphasize that fuzzy causal structures may indeed prove useful (see [20]). This may be exemplified by introducing only one type of fuzzy causal structures.

Definition 17. ξ is a *fuzzy causal structure* iff there are A_{t_1}, B_{t_2}, X, CR, and τ such that

1. $\xi = \langle A_{t_1}, B_{t_2}, X, CR, \tau \rangle$,
2. There is a probability space $\langle \Omega, E, p \rangle$ and a time set T such that $\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X \rangle$ is a causal structure,
3. There is a Term(CR) such that CR: $E \times E \times E \rightarrow$ Term(CR),
4. $CR(A_{t_1}, B_{t_2}, X) = \tau$.

For example, with reference to our discussions and considerations in Section 4.3 we may presume that $\langle chlamydia_{t_1}, chd_{t_2}$, non-diabetics, CR, medium$\rangle$ is a fuzzy causal structure. The question now arises how a fuzzy causal relevance value τ such as 'medium' appearing in a fuzzy causal structure is obtained and obtainable. Clause 2 of Definition 17 shows that an underlying probabilistic-causal structure is required, and that means two things. First, without probability no fuzzy causality. For causal structures rest on (quantitative, comparative, or qualitative) probabiliy spaces. Second, the fuzzy, linguistic value τ must be derived from them. To this end we will now straightforwardly construct a concept of *fuzzy causal space* that will enable us to fuzzify causality.

5.2. Fuzzy causal spaces

The idea behind, and the intuitive understanding of, the concept of a fuzzy causal space we are aiming at is this: we may be faced with a particular type of system displaying a more or less complex causal behavior, e.g. with the pathology and epidemiology of all or some infectious diseases in human population. We need not describe this causal system crisply numerically. We may describe it fuzzily linguistically as well in that we may state, for instance, 'event A is causally *strongly* associated with event B, but only causally *moderately* associated with event C, and causally *highly negatively* associated with event D', etc. The totality of these fuzzy causal statements represent a fuzzy causal space where the set of italicized, fuzzy CR values used may be $\{a, b, \ldots, m\} \subseteq$ Term(CR). It appears quite promising to view this set $\{a, b, \ldots, m\}$ as a fuzzy causal relevance *distribution* over the event algebra and to assume that the distribution both is controlled by a particular fuzzy causal function (remember the stochastic analogue: 'random function') and will exhibit a fuzzy causal kinematics (cf. [20]).

The following Definition 18 extends fuzzy causal structures to fuzzy causal spaces by generalizing the structures and by transforming the linguistic function CR to a normed measure. To this end the term set Term(CR) must be rank-ordered in complete analogy to the term set of the qualitative probability, Term(P), in Section 4.6. Let us suppose that the approved, rank-ordered term set is:

$$\text{Term(CR)} = \langle \tau_1, \ldots, \text{neutral}, \ldots, \tau_n \rangle, \tag{36}$$

with τ_1 being the lowest fuzzy linguistic value of CR below neutral, i.e. at the negative side, and τ_n being the highest value above neutral, i.e. at the positive side. We define: $\tau_i \leq \tau_j$ iff $i \leq j$.

Definition 18. ξ is a *fuzzy causal space* iff there are E_1, E_2, E_3, CR, and Term(CR) such that

1. $\xi = \langle E_1, E_2, E_3, CR, Term(CR)\rangle$,
2. There is a probability space $\langle \Omega, E, p\rangle$ and a time set T such that for every $A_{t_1} \in E_1$ and $B_{t_2} \in E_2$ there is an $X \in E_3$ such that $\langle \Omega, E, p, T, A_{t_1}, B_{t_2}, X\rangle$ is a causal structure,
3. $E_1, E_2, E_3 \subseteq E$,
4. $Term(CR) = \langle \tau_1, \ldots, \text{neutral}, \ldots, \tau_n\rangle$ is a rank-ordered term set of CR,
5. $CR: E \times E \times E \rightarrow Term(CR)$,
6. $CR(Y, \Omega, X) = CR(Y, \emptyset, X) = \text{neutral}$ for all non-empty $Y, X \in E$,
7. If $Z_1 \subseteq Z_2$, then
   $CR(Y, Z_1, X) \leq CR(Y, Z_2, X)$ if $CR(Y, Z_2, X) \geq \text{neutral}$
   $CR(Y, Z_1, X) \geq CR(Y, Z_2, X)$ if $CR(Y, Z_2, X) \leq \text{neutral}$
   for all non-empty $Y, Z_1, Z_2, X \in E$.

The linguistic causal relevance function CR becomes a normed measure by axioms 5–7. But it remains undefined. We will not pursue the analogies any further and will therefore not construct conjectural and subjective fuzzy causal spaces, though it would be interesting to observe how in these spaces causal belief kinematics emerge and develop as a consequence of fluctuating subjective base probabilities, i.e. in the wake of epistemic kinematics.[13]

We have two types of causal space at our disposal thus far, the crisp ones provided by the numerical causal relevance measure cr on the one hand (Definition 9), and the fuzzy ones supplied by the linguistic causal relevance measure CR, on the other. Both spaces may be interrelated with one another in the following way: a crisp causal space can be transformed into a fuzzy causal space, i.e. it can be fuzzified such that given any numerical causal relevance value such as

$$cr(A, B, X) = r$$

we can determine if r is low, medium, high, very high, not very low and not very high, etc. that is, if

$$CR(A, B, X) = \tau_i,$$

where $\tau_i \in Term(CR)$. Seen from fuzzy-theoretic perspective, that reads: every linguistic value of the measure CR, e.g. 'high', may be defined as a name for a fuzzy subset of the range $[-1, +1]$ of the measure cr such that any point in $[-1, +1]$ can be linguistically classified in the term set Term(CR). We will understand this possibility of semantic interpretation of CR values in the following way.

The term set $Term(CR) = \langle \tau_1, \ldots, \text{neutral}, \ldots, \tau_n\rangle$ as it was partly displayed in the preceding subsection may be a more or less large set of linguistic terms. Though this large set may base upon only a few undefined primitives such as 'low', 'medium', and 'high'. Let us call them *primary terms* of CR, represented by the set 'primary-

[13] Cf. 'epistemic kinematics' in clinical decision-making in ([16], p. 108).

Terms(CR)'. The remaining elements of Term(CR), such as 'very high', 'not low', 'not very high and not very low', and the like are defined by applying to primary terms semantic modifiers of different type, e.g. connectives like 'not', linguistic hedges like 'very', etc. Thus, the semantic interpretation of primary terms will suffice to obtain an entirely interpreted Term(CR) because semantic modifiers obey particularly specified rules. This basic semantic interpretation and definition of primary terms is provided by a *compatibility function* μ.

Let μ be a binary function which maps the Cartesian product of the range of the function cr and the primary terms of CR into the unit interval:

$$\mu: [-1, +1] \times \text{primary-Terms(CR)} \rightarrow [0, 1].$$

Following Zadeh [27–29], we will call μ a *compatibility function*. It evaluates, within [0, 1], the compatibility of a cr value $x \in [-1, +1]$ with a linguistic term $\tau_i \in$ primary-Term(CR). Thus, it assigns to a pair $\langle x, \tau_i \rangle$ the grade of membership of x in τ_i. That means in fuzzy-theoretic terminology that μ is a two-place fuzzyfying membership function. For instance, we may carry out the definition of our function μ above in such a way that we may obtain:

$$\mu(1, \text{ high}) = \mu(-1, \text{ high}) = 1$$
$$\mu(0.8, \text{ high}) = \mu(-0.8, \text{ high}) = 1$$
$$\mu(0.6, \text{ high}) = \mu(-0.6, \text{ high}) = 0.8$$
$$\mu(0.5, \text{ high}) = \mu(-0.5, \text{ high}) = 0.3$$
$$\mu(0.2, \text{ high}) = \mu(-0.2, \text{ high}) = 0$$

For the sake of convenience, we abbreviate $\mu(\text{x}, \tau_i) = y$ by $\mu_{\tau i}(x) = y$. The above examples would then read:

$$\mu_{\text{high}}(1) = \mu_{\text{high}}(-1) = 1$$
$$\mu_{\text{high}}(0.8) = \mu_{\text{high}}(-0.8) = 1$$
$$\mu_{\text{high}}(0.6) = \mu_{\text{high}}(-0.6) = 0.8$$
$$\mu_{\text{high}}(0.5) = \mu_{\text{high}}(-0.5) = 0.3$$
$$\mu_{\text{high}}(0.2) = \mu_{\text{high}}(-0.2) = 0$$

And we would then have a lot of local membership functions such as μ_{high}, μ_{medium}, μ_{low}, $\mu_{\text{very-high}}$, etc. Each of them may be interpreted as a particular fuzzy restriction of μ on the range $[-1, +1]$ of the numerical function cr. Plots of some of these restrictions are displayed in Figs. 4–7.

Figs. 4–7 illustrate well what it means to say that linguistic CR values such as 'high', 'very high', 'not low', etc. have now become interpreted labels for fuzzy restrictions of the function μ on the values of the numerical function cr.

A *direct*, fuzzy-theoretic interpretation, definition, and understanding of linguistic causal relevance is possible in the following way. With reference to the definition of a fuzzy set as a set of ordered pairs $\langle x, f(x) \rangle$ such that x is an element of a base, crisp set X, and f is a function that maps X into the unit interval [0, 1], we can use any of the functions μ_{high}, μ_{medium}, μ_{low}, etc. as a particular fuzzyfying function on the domain $[-1, +1]$ of the numerical causal relevance function cr, for instance:

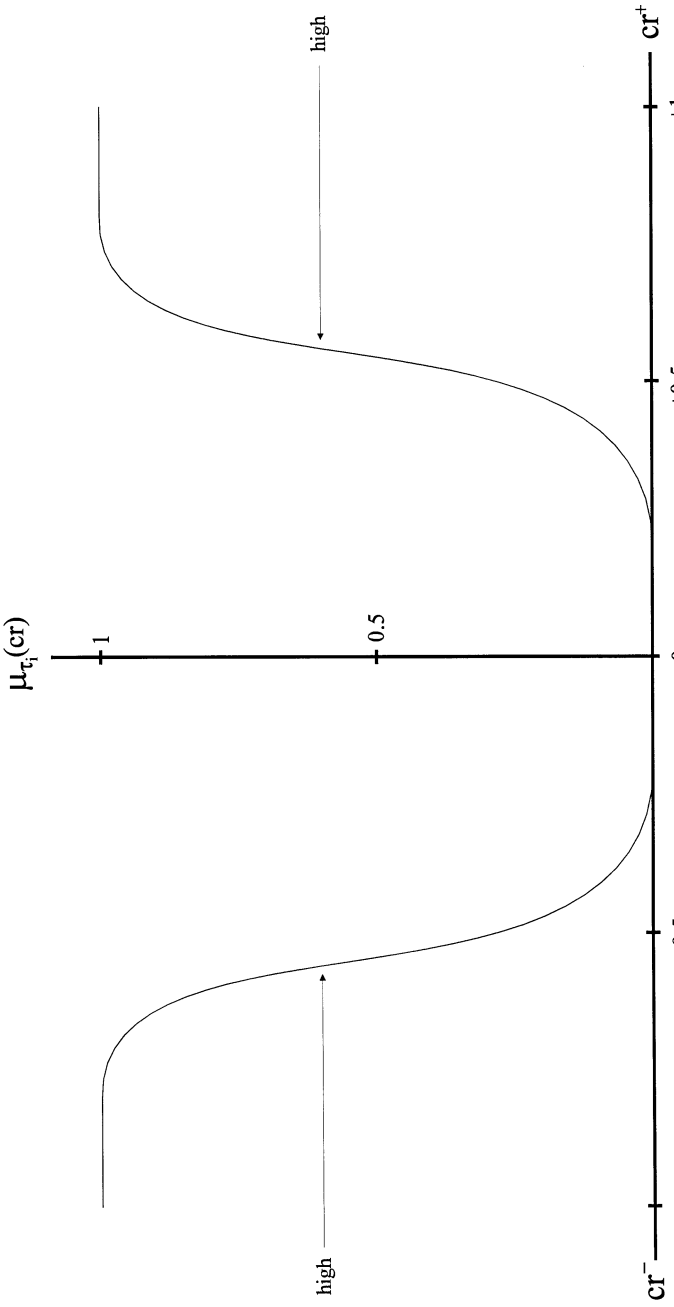

Fig. 4. A tentative compatibility function for *causally highly relevant* on both banks of the numerical causal relevance function *cr*, that is, *causally highly positively relevant* and *causally highly negatively relevant*, both abbreviated to 'high'.

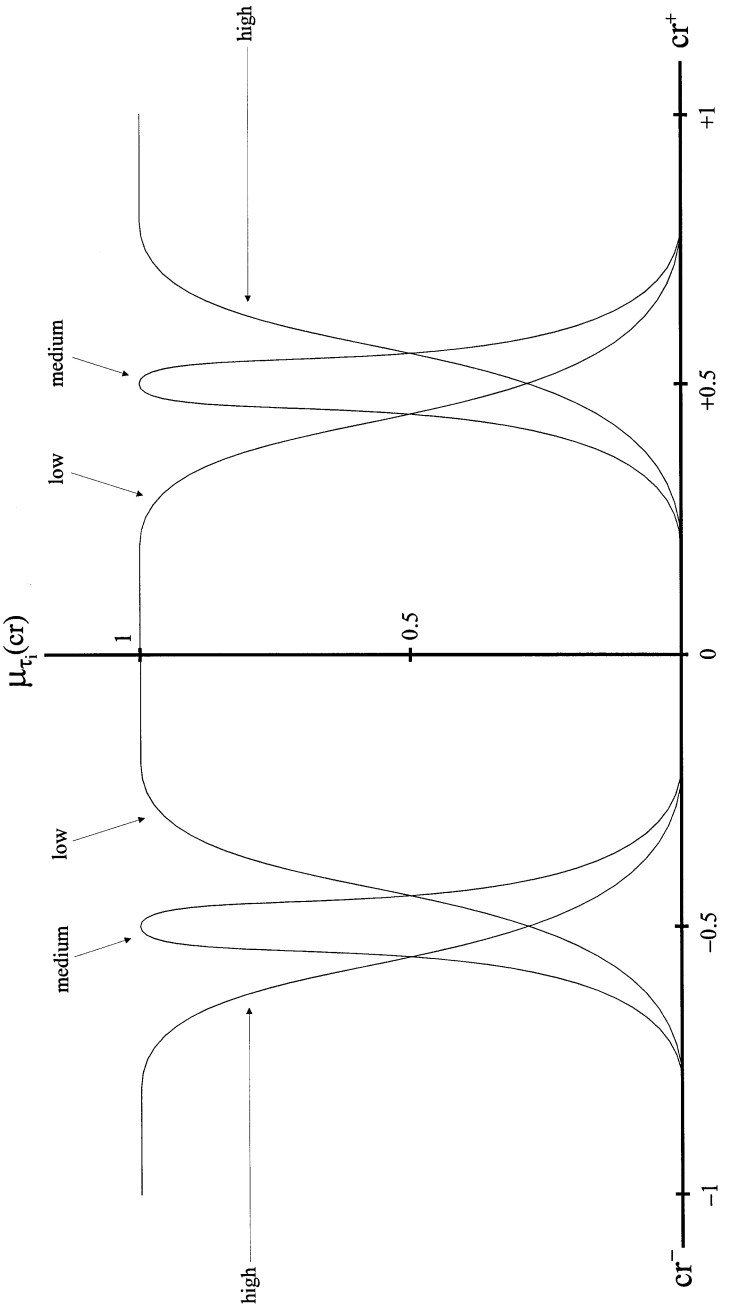

Fig. 5. A tentative compatibility function for *causally relevant* (low, medium, high) on both banks of the causal relevance function *cr*, positive and negative.

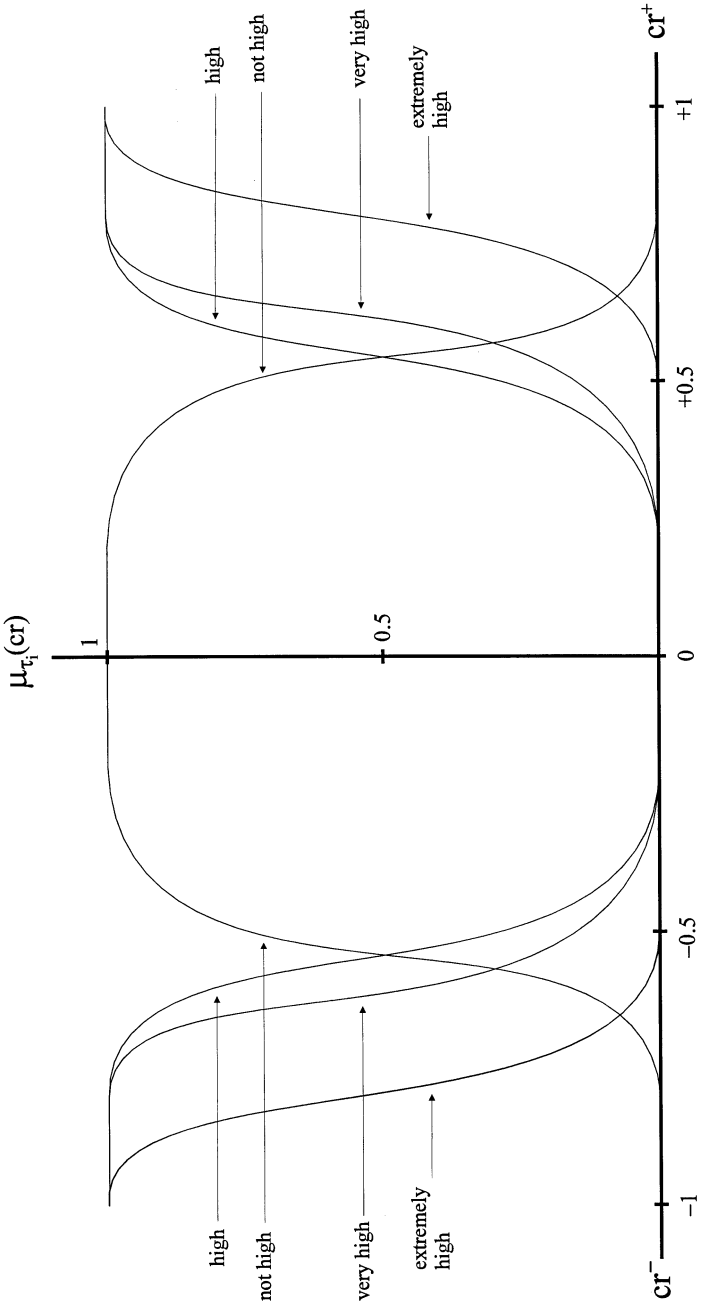

Fig. 6. A tentative compatibility function for *causally relevant* (not high, high, very high, extremely high) on both banks of the causal relevance function *cr*.

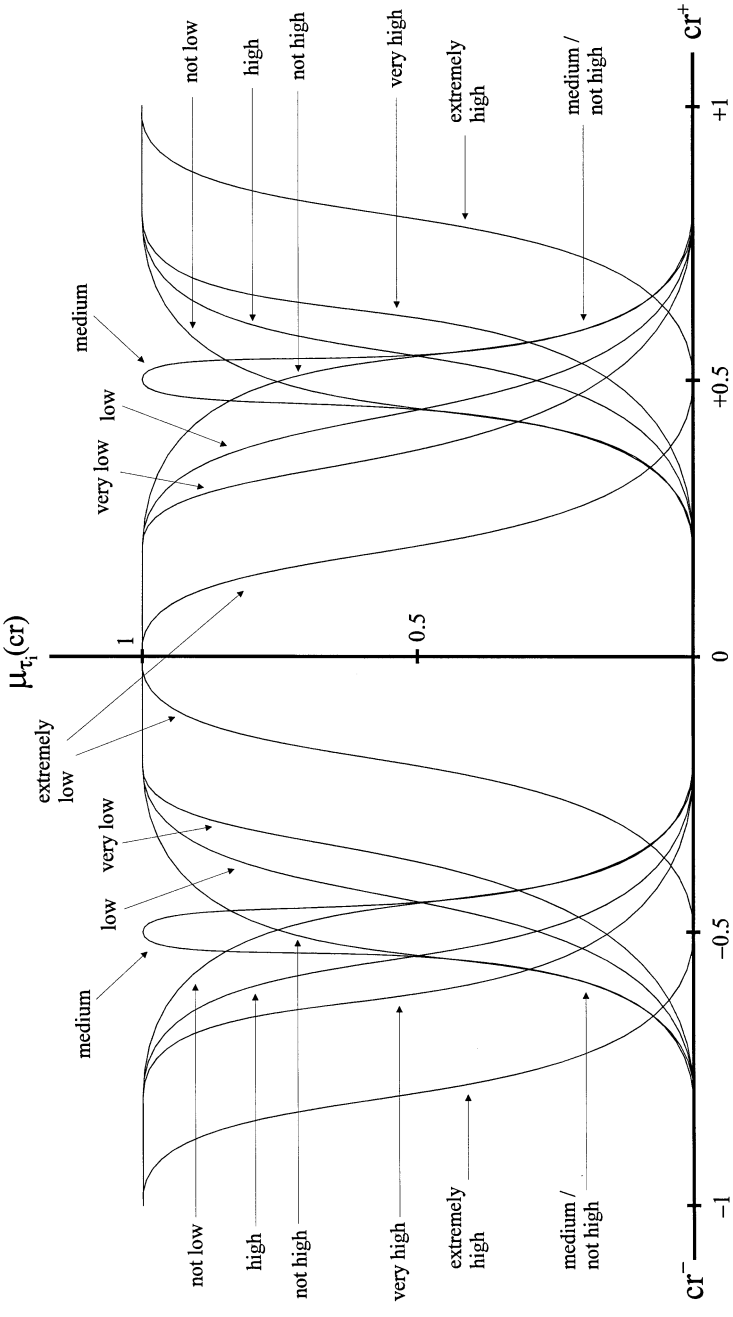

Fig. 7. A summary visualization of positive and negative fuzzy causal relevances *low*, *high*, *not low*, *not high*, *very low*, *very high*, etc. One may of course also consider additional values such as *not very high and not very low*, and the like. But we have tried to keep the present figure readable.

$\mu_{\text{high}}: [-1, +1] \rightarrow [0, 1]$.

We will thus obtain 'high, positive causal relevence' and 'high, negative causal relevance' as fuzzy sets, e.g.

causally highly positively relevant

$= \{(1, 1), (0.8, 1), (0.6, 0.8), (0.5, 0.3), (0.2, 0)\}$.

The same kind of fuzzification applies to key notions of etiology, epidemiology, and clinical medicine such as indicator, risk factor, preventive factor, and protective factor. Each one of them may be fuzzily partitioned into different grades of strength, and these grades may be interpreted as labels for degrees of causal impact.

6. Conclusion

We have shown that *deterministic etiology* is empirically unproductive because the domains of health and disease are nearly void of deterministic cause-effect relationships. We have therefore proposed a concept of *probabilistic etiology* that also makes *fuzzy etiology* feasible. The concept proposed is part of a relativistic theory of causality that rests upon a syntactic solution to the venerable philosophic puzzle of causation. The sterility of perputal debates on causality is ascribed to the common Aristotelian view that the cause-effect relationship was adequately reflected by the two-place predicate 'A causes B'. We have recommended to conceive a third-place predicate instead, 'A causes B in C', where C is a reference class. This syntactic innovation enables us to define causation in terms of conditional probabilistic dependence and to put it in the algebraic frame of probability theory. We have shown that it is possible to reconstruct causal structures as algebraic extensions of probability spaces and thus to understand scientific etiology as an empirical application of probability theory to health and disease. Different types of causal notions (qualitative, quantitative, and comparative ones) have been constructed each one having its own, suitable domain of application. Among the interesting features of the theory are the following ones.

The causal notions we have proposed capture both positive causation (generating) and negative causation (preventing). They are amenable to algebraic calculation (causal algebra). The quantitative notion of causation measuring the causal impact makes it also possible to fuzzify causality. Thus, etiology becomes amenable to fuzzy theory.

The approach may be of assistance in medical knowledge engineering, pathology, nosology, epidemiology, and clinical decision-making. Dr G. William Moore (Chief Pathologist, Baltimore) brought it to my attention that "some concepts of medical etiology are of non-probabilistic nature, and are based upon years, even centuries, of interlocking tradition and experience. The established laws of physics, chemistry, and pathophysiology contribute at least as much as sequential probabilities to a concept of medical etiology. Two of the examples (the falling barometer as a spurious cause of thunderstorms, and smoking as a cause of lung cancer) beg for

some allusion to the laws of nature. In the lung cancer example, our concept of causality is not based solely upon the observation that many smokers get lung cancer, but also upon concepts that smoke is inhaled down the tracheobronchial tree, nicotine inhibits ciliary mobility and clearing from the surface respiratory epithelium, the remaining tars stimulate squamous metaplasia, and eventually atypical squamous metaplasia followed by dysplasia, whose cells have no cilia, and thus further aggravate the positive feedback of uncleared, carcinogenic tars, which select cell-lines with certain oncogenes, etc., etc. Even if we knew the probability (or only the fuzzy rank-order) of these events, we wouldn't know how to structure the relationships among the events in a manner that captures the centuries of experience and investigation with anatomy, physiology, pathology, etc. Likewise, the falling barometer is not a cause of thunderstorms, quite apart from its time-sequence relationships, because such an assertion would violate our sense of theory in geophysics and meteorology''.

Acknowledgements

I thank Inge Holtkamp, Daniela Imping, Hannelore Petry, Margret Titze, and Georg Karrasch for their diverse managerial assistance, my son Manuel for drawing the figures of this paper, and my son David for helpful suggestions in fuzzyfying causality. Special thanks are due to Dr G. William Moore (Baltimore) for valuable criticisms and suggestions.

References

[1] Buja LM. Does atherosclerosis have an infectious etiology? Circulation 1996;94:872–3.
[2] Glynn JR. Helicobacter pylori and the heart. Lancet 1994;344:146.
[3] Grayston JT, Campbell LA, Kuo CC, et al. A new respiratory tract pathogen: Chlamydia pneumoniae strain TWAR. J. Infect. Dis. 1990;161:618–25.
[4] Hesslow G. Two notes on the probabilistic approach to causality. Phil. Sci. 1976;43:290–2.
[5] Krantz DH, Luce RD, Suppes P, Tversky A. Foundations of Measurement, vol. 1. New York: Academic Press, 1971.
[6] Mackie JL. The Cement of the Universe. A Study of Causation. Oxford: Clarendon Press, 1974.
[7] Melnick JL, Petrie BL, Dreesman GR, et al. Cytomegalovirus antigen within human arterial smooth muscle cells. Lancet 1983;II:644–7.
[8] Mendall MA, Carrington D, Strachan D, et al. Chlamydia pneumoniae: risk factors for seropositivity and association with coronary heart disease. J. Infect. 1995;30:121–8.
[9] Miettinen H, Lehto S, Saikku P, et al. Association of Chlamydia pneumoniae and acute coronary heart disease events in non-insulin dependent diabetic and non-diabetic subjects in Finland. Euro. Heart J. 1996;17:682–8.
[10] Muhlestein JB, Hammond EH, Carlquist JF, et al. Increased incidence of Chlamydia species within coronary arteries of patients with symptomatic atherosclerosis versus other forms of cardiovascular disease. J. Am. Coll. Cardiol. 1996;27:1555–61.
[11] Reichenbach H. The Direction of Time. Berkeley: University of California Press, 1956.
[12] Ridker PM, Cushman M, Stampfer M, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. New Engl. J. Med. 1997;336:973–9.

[13] Sadegh-Zadeh K. Nosological and etiological problems of psychopathology. Paper presented at the Symposium, Karl Eduard Rothschuh 65 dedicated to Professor K.E. Rothschuh on the occasion of his 65th birthday. University of Münster Medical Institutions, Münster, 6th July, 1973. (In German.)
[14] Sadegh-Zadeh K. Problems of Causality in Clinical Practice. University of Münster Medical Institutions, 1979. (In German.)
[15] Sadegh-Zadeh K. Perception, illusion, and hallucination. Metamedicine 1982;3:159–91.
[16] Sadegh-Zadeh K. Foundations of clinical praxiology Part II: categorical and conjectural diagnoses. Metamedicine 1982;3:101–14.
[17] Sadegh-Zadeh K. Causal systems. In: Münstersche Beiträge zur Geschichte und Theorie der Medizin vol. 22. Tecklenburg: Burgverlag, 1984:17–22 (in German).
[18] Sadegh-Zadeh K. A pragmatic concept of causal explanation. In: Nordenfelt L, Lindahl BIB, editors. Health, Disease, and Causal Explanation in Medicine. Dordrecht: D. Reidel Publishing Company, 1984:201–209.
[19] Sadegh-Zadeh K. Fundamentals of clinical methodology: 1. Differential indication. Artif. Intell. Med. 1994;6:83–102.
[20] Sadegh-Zadeh K. Theory of Medicine. 1997 (in preparation).
[21] Sadegh-Zadeh K. Fundamentals of clinical methodology: 3. Nosology. Forthcoming in Artif. Intell. Med. 1998;14.
[22] Saikku P, Leinonen M, Tenkanen L, et al. Chronic Chalamydia pneumoniae infection as a risk factor for coronary heart disease in the Helsinki Heart Study. Ann. Int. Med. 1992;116:273–8.
[23] Salmon WC, editor. Statistical Explanation and Statistical Relevance. Pittsburgh: University of Pittsburgh Press, 1971.
[24] Simpson EH. The interpretation of interaction in contingency tables. J. R. Stat. Soc. Series B 1951;13:238–41.
[25] Suppes P. A Probabilistic Theory of Causality. Amsterdam: North-Holland Publishing Company, 1970.
[26] Thom DH, Grayston JT, Siscovick DS, et al. Association of prior infection with Chlamydia pneumoniae and angiographically demonstrated coronary artery disease. J. Am. Med. Assoc. 1992;268:68–72.
[27] Zadeh LA. The concept of a linguistic variable and its application to approximate reasoning—I. Inf. Sci. 1975;8:199–249.
[28] Zadeh LA. The concept of a linguistic variable and its application to approximate reasoning—II. Inf. Sci. 1975;8:301–57.
[29] Zadeh LA. The concept of a linguistic variable and its application to approximate reasoning—III. Inf. Sci. 1976;9:43–80.