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REVISITING HILL'S CRITERIA: BRIDGING HISTORICAL FOUNDATIONS AND MODERN EPIDEMIOLOGICAL CHALLENGES

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PONOVNO RAZMATRANJE HILOVIH KRITERIJUMA: POVEZIVANJE ISTORIJSKIH OSNOVA I SAVREMENIH EPIDEMIOLOŠKIH IZAZOVA

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ABSTRACT

Causal assessment is a cornerstone of epidemiological research, providing a framework for understanding the relationships between exposures and health outcomes. In his seminal 1965 paper, Sir Austin Bradford Hill proposed nine criteria to guide the evaluation of causal associations. These criteria - strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy – continue to serve as foundational principles in modern epidemiology. However, the application of these criteria has evolved significantly in response to advances in scientific knowledge, statistical methodologies, and data availability. This paper revisits Hill's criteria within the context of contemporary challenges and opportunities in public health research. It explores the nuanced interplay between causality and risk quantification, particularly in chronic and multifactorial diseases where direct causation is elusive. Through historical and modern examples, the paper illustrates the enduring relevance and adaptability of Hill's framework. Additionally, the discussion emphasizes the importance of experimental and observational designs, the integration of advanced analytical techniques to emulate randomized trials, and the need to balance adherence to established principles with openness to novel discoveries. By revisiting Hill's criteria, this work underscores their continuing utility in navigating the complexities of causality in a rapidly evolving scientific landscape.

Key words: *epidemiology; causality; association; risk assessment.*

SAŽETAK

Procena uzročnosti ima suštinski značaj za epidemiološka istraživanja i pruža okvir za razumevanje odnosa između izloženosti i zdravstvenih ishoda. U svom čuvenom radu iz 1965. godine sir Ostin Bradford Hil predložio je devet kriterijuma za procenu uzročno-posledičnih veza. Ovi kriterijumi – jačina veze, konzistentnost, specifičnost, vremenska povezanost, biološki gradijent, prihvatljivost, koherentnost, eksperiment i analogija – i dalje predstavljaju osnovne principe moderne epidemiologije. Međutim, njihova primena znatno se razvila u skladu s napretkom naučnih saznanja, statističkih metoda i dostupnosti podataka. Ovaj rad ponovo razmatra Hilove kriterijume u kontekstu savremenih izazova i mogućnosti u istraživanjima javnog zdravlja. Istražuje suptilne veze između uzročnosti i kvantifikacije rizika, posebno kod hroničnih i multifaktorskih bolesti, gde je direktna uzročnost teško dostižna. Kroz istorijske i savremene primere, u radu se ilustruje trajna relevantnost i prilagodljivost Hilovog okvira. Osim toga, naglašava se značaj eksperimentalnog i opservacionog dizajna, integracije naprednih analitičkih tehnika za simulaciju randomizovanih ispitivanja, kao i potreba za balansiranjem između pridržavanja utvrđenih principa i otvorenosti prema novim otkrićima. Ponovnim sagledavanjem Hilovih kriterijuma, u ovom radu se ističe njihova korisnost prilikom snalaženja u složenim uzročnostima u brzo razvijajućem naučnom okruženju.

Ključne reči: *epidemiologija; uzročnost; povezanost; procena rizika.*

INTRODUCTION

In the dynamic landscape of modern epidemiology, we navigate the complex relationships between exposure variables and health outcomes. The "Bradford Hill criteria" are not just historical relics but a vital guide in understanding causality. Originally unveiled nearly six decades ago, they not only gave a biomedical lens upon epidemiological research but have also seamlessly woven themselves into the fabric of contemporary textbooks and data interpretation (1).

Modern research sometimes struggles to distinguish association from causality, creating challenges in biomedical studies. In biomedical research, our aim is to discover and establish the truth. However, the pursuit of truth in modern medicine is often clouded by various types of biases and confounding factors, many of which we may not even be aware of, exerting influence on the outcomes of our work.

Many diseases involve multiple factors, and causation is interpreted differently across scientific fields. Exploring the various causes of an illness is rewarding, as understanding the various risk factors is crucial for identifying opportunities for prevention and developing strategies to reduce the burden of disease. Bradford Hill's seminal paper introduced nine criteria to guide the

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evaluation of causal relationships, including strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy (1). Despite the passage of six decades since its publication (1), epidemiologists now tackle a spectrum of multivariate, multistage, and multi-level research questions, employing evolving statistical methods and actively engaging in interdisciplinary studies. In this evolving landscape, the focus shifts from seeking discrete causes to identifying a network of interconnected and often interacting factors influencing disease risk. This complexity adds layers of intricacy to the assessment of causality. In such a complex system of mingled networks involving various elements, factors, "causes," intricate interrelationships that we can both predict and not predict (essentially defining the world we live in), we must ponder what causality is, how we define it, and what truly constitutes a causal factor. This paper explores the evolution of causality assessment in epidemiology, focusing on the enduring relevance of the “Bradford Hill criteria” and their application in contemporary research.

CAUSE, CAUSALITY

Understanding causality is fundamental to epidemiology. For centuries, philosophers have engaged in a discourse exploring the nature of causality. As the Susser says “A cause is something that makes a difference” (2). For a clearer and simpler understanding in the fields of medicine and public health, it appears reasonable to adopt a practical concept of causality.

One of the early definitions of causality comes from *Abraham Lilienfeld* in 1957, who stated: "A factor may be defined as a cause of a disease if the incidence of the disease is diminished when exposure to this factor is likewise diminished."(3). In an ideal scenario, epidemiologists and all scientists aspire to straightforwardly define and prove that Factor A causes Outcome B. Such simplicity in establishing causation, as mentioned, appears more attainable when dealing with infectious diseases, although even in such cases, a nuanced and well-founded discussion remains possible. As evidence of this, we can turn to Koch's postulates from as early as 1877. Defined by Robert Koch under the influence of his mentor *Jacob Henle*, these postulates attribute a causal role to exogenous pathogens in the context of infectious diseases (4, 5). Although all four postulates were acceptable and applicable in their time, aligning with the prevailing biological knowledge, it's evident that we have since exceeded those understandings. Nevertheless, they served as a crucial starting point and a springboard for further scientific progress.

Biological plausibility

Biological plausibility is one of Hill's most debated criteria due to its dependence on current knowledge. In the context of biomedical advancement, Hill himself acknowledges biological plausibility as unachievable - (1). Strictly following Hill's argument could slow the progress of new knowledge. Consider *John Snow*, who, by daring to challenge the prevailing miasma theory, was able to conclude that water was the source of cholera (6). If *Alphonse Laveran* and *Robert Ross* had not challenged old theories, we might still misunderstand the true causes of malaria (7,8). Robert Ross established the role of mosquitoes in transmission, replacing the previously held belief in ‘mala aria’ or bad air (9), allowing us to move beyond outdated theories and uncover the true causes of this disease. We can only imagine the discoveries that lie ahead in the future, wondering whether, from the perspective of scientists two to three centuries from now, we might appear as unenlightened and deprived of knowledge as we perceive the people and the world from two to three centuries ago. Another excellent example where strict adherence to this criterion might have obstructed a breakthrough discovery is the work of *Marshall* and *Warren*, who identified a spiral-shaped bacterium (*H. pylori*) as the causative agent of peptic ulcers (10). Until then, it was widely believed that no organism could survive in the harsh acidic environment of the stomach.

In the context of biological plausibility, potential limitations can also arise from the beliefs of investigators (11,12). When we stand at the boundary between the known and the unknown, our prior knowledge can shape convictions that may prevent us from exploring the direction of the unknown and the seemingly impossible.

Temporal association

Temporal association is essential for causality, emphasizing that the cause must come before the effect. In the discourse on what seems ostensibly straightforward, a consensus has eluded us when it comes to defining a cause. Hence, Hume wisely says: "…we may define a cause to be an object, followed by another, and where all the objects similar to the first are followed by objects similar to the second." (13). In his alternative definition of cause, Hume articulates: "Or in other words where, if the first object had not been, the second never had existed." (13,14). This aligns with the fundamental principles of causation, emphasizing not only the sequential relationship but also the necessity of the presence of the cause for the occurrence of the effect. This serves as a compelling introduction and inherently echoes what Hill defined in 1965 as another one of his criteria - temporality, prompting the question: “which is the cart and which is the

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horse?" (1). This temporal aspect appears quite logical, but it can be a misleading factor in the case of slowly progressing diseases. Advanced methods have shown temporal links between causes and effects, even when they are not obvious. *Fedak et al.* provide an excellent example illustrating the proof of temporal instances in studies measuring arsenic levels in hair and nails as markers of past arsenic exposure (15). The duration of exposure also plays a significant role, suggesting that in some cases, there might be a limit or a cut-off point in the length of time. For instance, exposure up to a certain duration may not lead to the occurrence of a disease, while surpassing that threshold could result in the manifestation of the disease. Therefore, the length of temporal exposure is something we must also consider when attempting to identify and define the cause, which, quite often, can be challenging to delineate within strict pre-established frameworks.

Biological gradient

The biological gradient or dose-response relationship helps quantify the strength of causation (1). Certainly, the dose-response relationship is crucial in causality, as defined by Hill. We anticipate that with an increase in the dose of the exposed agent, the corresponding effect of that agent should also rise. What makes epidemiology a fantastic science, practically enabling us to see the bigger picture, is its ability to reconcile the irreconcilable. Doll and Hill exemplified this when investigating the link between smoking and lung cancer. In addition to categorizing physicians as smokers and non-smokers, they further classified smokers based on the number of cigarettes smoked daily. They went one step further, recognizing that it wasn't sufficient to only consider smoking status; the duration of smoking history was also a crucial factor (16). These classifications allowed for a clear demonstration of the biological gradient, showing how both the intensity and the duration of smoking increased the risk of developing lung cancer. Hill's postulate of the biological gradient serves as an excellent example of quantifying an infectious agent, the required dose needed to cause disease, and the severity of the disease depending on the dose of the infectious agent. A perfect and currently relevant example of this is SARS-CoV-2, the agent responsible for COVID-19. Numerous studies have explored the infectious dose required to initiate the disease (17, 18). Furthermore, the severity of COVID-19 has been shown to depend on various factors, including the infectious dose, highlighting the importance of understanding the biological gradient in the context of this pandemic. Hill's criterion of biological gradient is well illustrated by the relationship between repetitive head impacts and chronic traumatic encephalopathy (CTE). Studies have shown that the risk of developing CTE increases with the cumulative number of head impacts sustained over time, highlighting how greater exposure leads to a higher likelihood and severity of disease (19).

This is undoubtedly one of the criteria given particular consideration during vaccine development. Careful thought is given to determining the appropriate content of microorganisms, microbial components, or specific antigens to elicit an adequate and protective immune response. One historical example is Jonas Salk, who, during the development of an influenza vaccine, experimented with varying quantities of calcium phosphate-adsorbed influenza virus to determine the optimal dose needed to provoke a sufficient and protective immune response (20).

In the context of the biological gradient, one of the pioneering researchers who utilized longitudinal study designs, Wade Hampton Frost, not only advanced our understanding of the biological gradient but also introduced a measure of the temporal gradient of exposure for each participant, creating the term person-time (21, 22). This concept revolutionized the quantification of exposure by integrating both duration and intensity into a single metric, laying the groundwork for more precise epidemiological analyses.

This approach overlaps with the strength of association, another of Hill's criteria, which will be explored in detail later. Building on this principle of quantification, the concept of *person-time* has served as a fundamental indicator, merging the duration and quantity of exposure into a single parameter. For example, in the context of smoking status and history, the *pack-years* metric has become a critical tool for assessing cumulative exposure and its correlation with health outcomes (22). However, as with all criteria, there are exceptions that don't necessarily refute Hill's element outright but remind us to approach these relationships with a degree of caution and skepticism, ensuring that assumptions are supported by robust empirical evidence. Additionally, it is important to acknowledge that the relationship between dose and effect is not always linear, as certain factors may influence the response at different levels of exposure, leading to thresholds, plateaus, or even inverse effects in some cases.

Specificity

Another element in establishing causality is specificity, where one factor leads to one effect. When discussing diseases, exposure to a particular cause should result in the occurrence of a specific disease (1). Lilienfeld's investigation into the specificity of causes and effects initiates a profound inquiry. Through the dissection of these concepts, Lilienfeld prompts an observation of the complex relationship between causation and its resulting phenomena (23). This discourse thus far encapsulates

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Lilienfeld's commentary on the work of Yerushalmy et al. (24), where Lilienfeld distinguishes between the specificity of causes and effects, challenging conventional notions and prompting a contemplation of the complex relationship between causation and its resultant phenomena. Lilienfeld's perspective underscores the dynamic nature of causality, suggesting that the requisite level of specificity is contingent upon the observer's frame of reference.

When it comes to infectious diseases, the situation is relatively clear: we have microorganisms that cause specific diseases. For example, *Plasmodium* causes malaria (7, 8), *Bordetella pertussis* causes whooping cough, and the Ebola virus causes Ebola virus disease. However, even in this domain, there are various exceptions to the rule. While specificity suggests one cause leads to one effect, exceptions like *Streptococcus pyogenes* highlight the complexity of causality. The same microorganism can cause multiple types or forms of a disease. *Streptococcus pyogenes* serves as an excellent example of how a single microorganism can cause a variety of diseases. It is responsible for conditions ranging from mild infections, such as streptococcal pharyngitis, to more severe diseases, including scarlet fever, necrotizing fasciitis, and post-infectious complications like rheumatic fever (25). *Leishmania spp*. is another example of a microorganism that can cause multiple forms of disease. Depending on the species and host factors, it can lead to cutaneous leishmaniasis, characterized by localized skin lesions; mucocutaneous leishmaniasis, affecting the mucous membranes of the nose, mouth, and throat; or visceral leishmaniasis (kala-azar), a systemic and potentially fatal disease involving internal organs such as the liver and spleen (26). There are numerous factors, both known and unknown, that can influence which disease, and in what form, will manifest from these microorganisms. Proving many of these factors will need to pass through Hill's criteria. However, for some, a leap beyond the existing knowledge will be necessary, potentially challenging and overturning established understandings.

In modern times, the principle of specificity is approached with caution, indicating what could be termed as the multipotent specificity of a cause. We must always be mindful that in proving specificity, there is no influence from any other multipotent specific factor that could cloud our judgment. This primarily applies to chronic non-communicable diseases, where we can no longer speak of specific, concrete causes but rather of certain factors that influence the risk of disease development. These factors are categorized into modifiable and non-modifiable. For example, cardiovascular diseases, the leading cause of death globally (27), have numerous well-recognized risk factors (28). It has been definitively and clearly established that by eliminating or reducing these factors, we can lower the risk of developing the disease or its complications.

Consistency

Consistency refers to repeated observations of an association across different studies and settings (1). Consistency should not be mixed with replicability, which stands as one of the basics of experimental knowledge, and yet another of the Hill's criteria. This distinction, as noted by Susser, is essential, particularly considering past tendencies to overemphasize the principle of replicability (2). On the topic of consistency, a concrete example can be cited that expressively underscores this principle of causality. As Hill demonstrated, the Advisory Committee to the Surgeon-General of the United States Public Health Service accepted the association between smoking and lung cancer based on 29 retrospective and 7 prospective studies (1). Similarly, in the 21st century, with a remarkable depiction of consistency, we have demonstrated that the Zika virus is transmitted via sexual intercourse as well, not solely through mosquitoes as previously thought. From May 2011 to April 2016, multiple researchers across various parts of the world, under different conditions, arrived at the same conclusion: that the Zika virus can be transmitted via sexual intercourse (29–35). This ultimately led to the official recommendations by the Center for Disease Control and Prevention (CDC) regarding preventive measures related to sexual transmission of the Zika virus (36).

Analogy and coherence

Analogy involves drawing comparisons to known causal relationships to hypothesize new ones. Coherence suggests that causal relationships should align with existing knowledge (1). If every scientist were to adhere strictly to such predispositions, every attempt at breakthrough discovery would be doomed to failure, alongside the already mentioned principle of biological plausibility. Certainly, it's valuable to form assumptions and hypotheses based on analogy, however, not at the expense of adjusting the formation and testing of assumptions to avoid social condemnation and rejection, although and unfortunately this has often occurred. The principles of coherence and analogy have likely prevented unnecessary, futile, and unjustified research in many cases, potentially even safeguarding the health of potential participants. However, it certainly raises the question: Where is the boundary? How do we adhere to known frameworks while constantly making steps forward? Should we adapt like chameleons, boldly forging ahead regardless of consequences?

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Strength

The strength of association indicates the magnitude of the relationship between exposure and outcome. The strength of association is the first criterion mentioned by Hill in his seminal paper, where he cites the example of chimney sweeps and their increased risk of developing scrotal cancer (1). Hill emphasizes that a weak association may result from various factors, including the nature of the disease, host predispositions, the dose of the agent, or the influence of risk modifiers (1). Dismissing a hypothesis solely on the grounds of a weak association risks overlooking a causal relationship, which can have significant consequences in medicine and public health. Hill himself would not quickly reject a weak association without further investigation. However, it is well-established that an observed association, whether strong or weak, does not inherently indicate causation. Additionally, the observed association can often be hidden by various biases, such as selection bias, information bias, or confounding, further complicating the interpretation of the relationship (12). This underscores the importance of careful study design and robust analysis to discern the true nature of the association. To address these challenges, various statistical and methodological approaches have been developed to minimize the influence of confounding factors and biases. These methods aim to refine our understanding and provide a more accurate estimation of the strength of association. Techniques such as multivariable regression analysis, propensity score matching, stratification, and instrumental variable analysis are commonly employed to adjust for confounders and isolate the relationship between the exposure and the outcome. These advancements enable researchers to draw more reliable conclusions, even in the presence of complex underlying factors.

Experiment

Hill emphasized the importance of experiments in proving causality, though they are often limited in public health due to ethical constraints (1). This criterion suggests that if modifying exposure leads to changes in the outcome, it provides strong support for a causal relationship. Experimentation, such as through randomized controlled trials (RCTs), is often considered the gold standard for evaluating causal associations.

Hill acknowledged that experimental evidence is not always feasible, particularly in public health and epidemiology, where ethical considerations limit the ability to manipulate certain exposures. For instance, deliberately exposing individuals to harmful agents to observe outcomes is unethical. In such cases, observational studies with robust designs are necessary to complement experimental data. Moreover, with the arrival of large-scale observational datasets and advanced analytical techniques, it has become possible to emulate randomized trial data analysis (37). Therefore, we are continually developing various methods to maximize the potential of observational data, aiming to approximate the rigor of experimental evidence and establish true causal relationships (38).

CONCLUSION

Causality remains complex and elusive, but Hill's criteria provide a robust framework for evaluating relationships in epidemiology. Future advancements will depend on refining these methods and integrating new technologies.

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