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Perspective

Breakthrough Knowledge Synthesis in the Age of Google

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Received: 25 January 2020; Accepted: 28 February 2020; Published: 4 March 2020

Abstract: Epistemology is the main branch of philosophy that studies the nature of knowledge, but how is new knowledge created? In this perspective article, I introduce a novel method of knowledge discovery that synthesizes online findings from current and prior research. This web-based knowledge synthesis method is especially relevant in today's information technology environment, where the research community has easy access to online interactive tools and an expansive selection of digitized peer-reviewed literature. Based on a grounded theory methodology, the innovative synthesis method presented here can be used to organize, analyze and combine concepts from an intermixed selection of quantitative and qualitative research, inferring an emerging theory or thesis of new knowledge. Novel relationships are formed when synthesizing causal theories—accordingly, this article reviews basic logical principles of associative relationships, mediators and causal pathways inferred in knowledge synthesis. I also provide specific examples from my own knowledge syntheses in the field of epidemiology. The application of this web-based knowledge synthesis method, and its unique potential to discover breakthrough knowledge, will be of interest to researchers in other areas, such as education, health, humanities, and the science, technology, engineering, and mathematics (STEM) fields.

Keywords: knowledge synthesis; epistemology; breakthrough knowledge; domain-specific knowledge; web-based search; grounded theory; Bradford Hill criteria; association; causation; mediation

1. Introduction

Great minds throughout human history have endeavored to understand the nature of knowledge, which forms the subject of the branch of philosophy known as epistemology, a word that translates to understanding [1]. In his dialogue Theaetetus, written around 369 BC, the philosopher Plato originated a definition of knowledge as justified true belief [2]. Despite criticism by epistemologists and other philosophers, such as Gettier in 1963 [3], Plato's contribution to the definition of knowledge has endured to this day. But how is new knowledge created, especially in other branches and areas of philosophy, such as logic, education, and science? Sir Isaac Newton wrote in 1678, "If I have seen further it is by standing on ye shoulders of giants" [4]. Newton's statement implies that he discovered new knowledge by building upon prior knowledge discovered by others. More recently, researchers examining more than 28 million studies and over 5 million patents discovered that breakthroughs in almost all fields of knowledge are more likely to occur as large amounts of prior knowledge are mixed with current, extant knowledge, confirming Newton's observation [5].

The definition of breakthrough means to overcome a barrier, and breakthrough knowledge implies overcoming barriers to advance knowledge. One barrier to knowledge advancement throughout history has been a powerful status quo which resists novel ideas. For example, while conducting his scientific research at the University of Padua, Italy, Galileo Galilei complained in a letter to scientist Johannes Kepler in 1610 that "these philosophers shut their eyes to the light of truth" [6].

The philosopher Thomas Kuhn [7] later described how most advances in scientific knowledge involve incremental changes within the conventional paradigm. Kuhn further noted how scientific revolutions occur periodically as new knowledge breaks through conventional barriers and causes a disruptive shift in the reigning paradigm. Another historical barrier to the advancement of knowledge occurred throughout Europe in the Middle Ages, when recorded information was owned exclusively by elite sectors of society, usually the clergy and members of academia. As knowledge spread with the advent of the printing press, the power of the Catholic Church was reformed, and the printing press had an influential effect on the Renaissance and the Scientific Revolution [8]. Since then, modern society has witnessed a relentless movement toward the democratization of the public's access to knowledge, especially in the age of digital technology.

Using today's web-based interactive tools such as Google's ubiquitous search engine and online databases, students, educators, practitioners, research scientists and inventors have an unprecedented opportunity to discover breakthrough knowledge by synthesizing current and prior knowledge available online. As academic libraries have digitized much of their content, no longer must students, practitioners, and researchers descend into the dark and dusty basements of institutional buildings seeking microfiches of archived literature. And yet, despite advances in accessing information online, a coming revolution in breakthrough knowledge appears to lie beyond the horizon. Students seeking new knowledge may feel hopelessly overwhelmed as they are bombarded with an overload of redundant online information [9], much of it of questionable veracity. In a quest to discover breakthroughs, research scientists may lack the advantage of leveraging online information search tools [5], inhibiting their capacity to step outside their disciplines and generate innovative, novel theories with the potential to produce a revolutionary paradigm shift in scientific concepts and practices [7]. The aim of this perspective article is to introduce concepts of researching and writing a web-based knowledge synthesis, which is intended to empower researchers across diverse disciplines with the skills to discover breakthrough knowledge in the age of Google.

2. Synthesis

The traditional use of the word art means skill [10]. The art or skill of knowledge synthesis relies on the ability to retrieve information from peer-reviewed studies and form an academic literature review, which provides more than an annotated bibliography of summaries [11]. A synthesis, the assembly of parts into a new whole, organizes and interprets the concepts, connections, controversies and constraints of a body of literature, filling in gaps and generating new insights, perspectives, directions and novel explanations about the research topic. Table 1 lists over two-dozen types of knowledge synthesis methods [12].

Table 1. Knowledge synthesis methods.

Knowledge Synthesis Method	Author
Bayesian meta-analysis	Sutton [13]
Content analysis	Stemler [14]
Critical interpretive synthesis	Dixon-Woods, [15]
Cross-design synthesis	Droitcour [16]
Ecological triangulation	Banning [17]
Framework synthesis	Pope [18]
Grounded theory	Strauss [19]
Interpretive synthesis/Integrative synthesis	Noblit, [20]
Meta-ethnography	Noblit [20]
Meta-interpretation	Weed [21]
Meta-narrative	Greenhalgh [22]
Meta-study	Paterson [23]
Meta-summary	Sandelowski [24]

Table 1. *Cont.*

Knowledge Synthesis Method	Author
Meta-synthesis	Sandelowski [25]
Mixed studies review	Pluye [26]
Narrative review/summary	Dixon-Woods [27]
Narrative synthesis	Popay [28]
Qualitative cross-case analysis	Yin [29]
Qualitative meta-synthesis	Jensen [30]
Qualitative systematic review/evidence synthesis	Grant [31]
Quantitative case survey	Yin [32]
Realist review/synthesis	Pawson [33]
Textual Narrative synthesis	Lucas [34]
Thematic analysis	Mays [35]
Thematic synthesis	Thomas [36]

Note: Table based on Kastner et al. [12].

Other terms for knowledge synthesis include research synthesis, evidence synthesis, and scientific synthesis. Syntheses can integrate current knowledge to inform policy and best practices, as in systematic reviews and meta-analyses, or syntheses can create new knowledge by combining evidence from a wide variety of sources [37]. The latter type of synthesis for new knowledge generation at the source of the flow of scientific information, from theory to practice, is the topic of this perspective article. The term emerging synthesis has been used to describe the ongoing evolution of newer types of synthesis method in which a wide diversity of quantitative and qualitative findings, data, and research designs are combined together to contribute new knowledge and theory to a research area [38].

Explanatory theories that explain causes and effects are qualitatively different from descriptive theories that categorize, organize, and describe phenomena [39]. Hjørland's domain-analysis is an example of a descriptive theory used in library science to organize knowledge according to the specific contents of information within a knowledge domain [40]. I propose that differences between explanatory and descriptive theories are similar to differences between explanatory and descriptive knowledge syntheses. For example, in addition to its use in systematic reviews and meta-analyses, descriptive knowledge syntheses categorize and organize information in taxonomies, ontologies, encyclopedias, databases, library systems, and complex networks. Furthermore, data mining methods have been used to predict new information in complex networks, such as the prediction of paired protein interactions in a protein database, and the prediction of interactions within social networks [41]. However, these methods have limitations. Interactive predictions in social networks, based on observed structural patterns, were shown to have a low rate of correctness [42]. In addition, the method for predicting protein interactions, based on classification of interaction types, does not explain how predicted interactions function, which must be determined with follow-up studies [43], On the other hand, explanatory knowledge syntheses logically combine concepts to infer new explanatory theories and hypotheses which may lead more directly to new explanatory knowledge.

3. Synthesis in Education

Knowledge synthesis is not only an important theoretical concept in the philosophy of knowledge; it plays a role in the philosophy of science, where it also serves as a practical research method, and it is a valued concept as well in the philosophy of education. Teaching the skills necessary for researching and writing knowledge syntheses is an important educational objective. The ability to synthesize material begins as an academic skill developed in secondary school and post-secondary school [44]. Bloom's original 1956 taxonomy of educational objectives included synthesis, the ability to assemble parts into a new whole, along with other educational objectives, such as knowledge, comprehension, application, analysis, and evaluation [45]. A revised version of Bloom's taxonomy, Figure 1, advanced synthesis to the highest educational level as part of Creating [46].

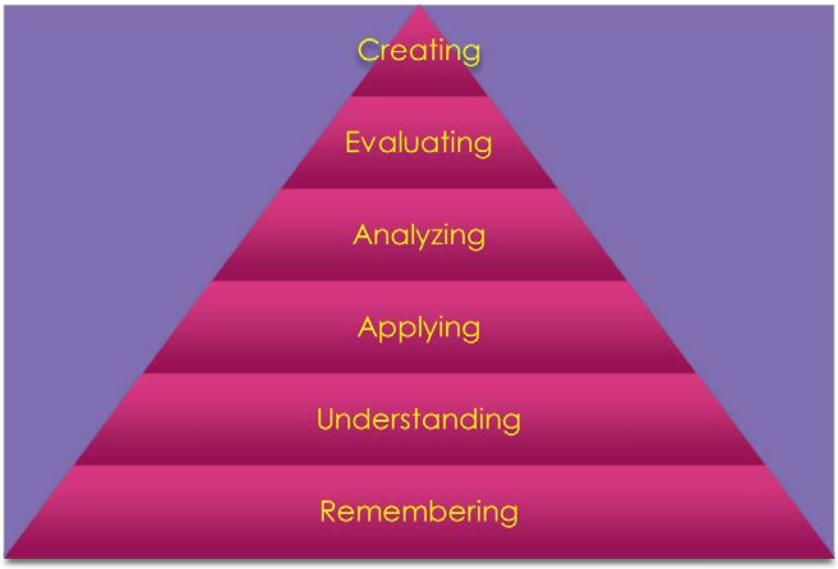

Figure 1. Bloom's taxonomy. Based on Forehand [46].

Training in synthesis skills should be acquired early in a researcher's career [47]. Today's evidence-based medicine is increasing the need for biomedical students to acquire research skills in information retrieval, critical judgment, statistical analysis, and writing [48]. Writing with rigorous analysis and logic is a critical professional skill required by most businesses, industry [49], and government agencies [50]. The National Commission on Writing in America's Schools and Colleges recommends that teachers encourage students to view writing as an enjoyable method for learning and discovery [51]—synthesizing new knowledge is a writing skill that can fulfill that recommendation by stimulating students with the excitement of exploration and discovery, leading to potential breakthrough knowledge. However, methods of synthesis writing must be developed to help students acquire proficiency in the skills of selecting, organizing, and associating information.

Recently, a method improved synthesis writing skills in students by employing note taking for information selection, and providing students with a graphic matrix organizer that presented information side-by-side to more easily draw associations between texts [52]. This method of teaching synthesis writing could be combined with use of web-based interactive tools in the classroom, which have been shown to enhance student engagement and improve learning experiences [53]. For example, web search engines could be used to teach students how to search, select, and synthesize online text sources in subject areas of interest to them. In addition to advancing keyboard, language and writing skills, students can practice skills to conduct online research which include forming a research question, locating online information, evaluating the information for selection, synthesizing the selected information, and communicating findings [54].

Another observation, relevant to the creative nature of synthesis in education, is the influential role knowledge synthesis plays in the development of the creative arts and humanities. For example, I propose that a composer synthesizes music out of musical components such as rhythm, timbre, pitch, and harmony. A painter synthesizes a painting out of form, texture, perspective, and color. A poet synthesizes a poem out of language, metaphor, and emotion. Artists often synthesize their style from the styles of the artistic giants who influenced them. Languages themselves are synthesized from other languages, social scientists such as psychologists and economists synthesize their work from the work of their predecessors (e.g., Freud and Marx), and so on. All fields in the arts and humanities have the potential to benefit from the knowledge synthesis methods described in this paper.

4. Synthesizing an Explanatory Theory

Psychologist Kurt Lewin proclaimed, “There is nothing so practical as a good theory” [55]. This perspective article’s method of knowledge synthesis borrows heavily from theoretical research methods such as grounded theory. Glaser and Strauss developed the grounded theory method to bring more rigor to qualitative research [56], although the methodological principles of grounded theory are also applicable to quantitative research [57]. The researcher’s overarching aim in grounded theory is to begin an investigation with a clean slate and inductively construct a new theory through an iterative process of comparative data analysis. With a new theory in hand, the researcher can encourage the development of hypotheses to experimentally test concepts deducted from the theory. Eventually, systematic reviews and meta-analyses can critically assess results of experiments and clinical trials testing the concepts. Interestingly, Ioannidis [58] suggested that the number of systematic reviews of clinical trials may be currently higher than the number of clinical trials, implying a greater need for theory synthesis at the source in the flow of new scientific information. Of relevance, the number of physician-scientists has also been on the decline over the past several decades, further highlighting the need to increase physician medical education in scientific thinking and biomedical research [59], including a need for education in knowledge synthesis and theory development.

Researchers most often use grounded theory as a method to analyze, compare, and combine concepts from original data, but Wolfswinkel et al. proposed that grounded theory may also be used to conduct a rigorous literature review in which concepts from published research findings themselves are the data [60]. Reviewing literature in this manner is particularly useful for synthesizing new knowledge from current knowledge—similar to thematic synthesis [36], a qualitative method that combines thematic analysis with meta-ethnography across multiple studies. An important difference is that the method proposed by Wolfswinkel et al. is a mixed method that combines both qualitative and quantitative research.

The following is an example of how I used a grounded theory approach to conduct a web-based synthesis in the field of epidemiology. I was interested in exploring online research literature investigating the association of phosphate toxicity with cancer [61]. The literature was reviewed using keyword searches in Google, Google Scholar, and other scholarly online databases, and all relevant studies associating phosphorus, tumorigenesis, cancer, etc. were identified. In addition to searching with keywords, I searched references cited in studies, which is known as citation analysis; a very useful method for evaluating a study’s impact in a research area [62]. For example, The Hallmarks of Cancer [63] is an influential study often cited by other studies in a literature review of cancer research.

Included in my synthesis were studies selected from the fields of basic research, clinical research, and epidemiological research; the designs of the selected studies included case studies, cohort studies, laboratory animal experiments, in vitro studies, systematic reviews and meta-analyses. My investigation followed the evidence without boundaries, and my final synthesis was written in the form of a narrative review. Although many speculations, hypotheses, and explanatory theories were proposed by authors of the studies selected for my synthesis, I analyzed only concepts from the objective findings of the selected studies in order to foster a new grounded theory. The rigorous evidence-based grounded theory method helped assure the high internal validity of the synthesis, i.e., the analyzed concepts were based on trustworthy peer-reviewed findings rather than speculation. As concepts from the reviewed literature were analyzed and compared, certain themes began to emerge from the data which were eventually linked together into a cohesive theory that explained how phosphate toxicity from dysregulated phosphorus metabolism stimulated cancer cell growth. Interestingly, this inferred knowledge challenged several of the hypotheses proposed in The Hallmarks of Cancer. For example, evidence from my synthesis supported the concept that cancer cell growth is dependent on exogenous growth-rate factors, challenging the concept that cancer cells independently stimulate themselves to grow autonomously.

5. Domain-Specific Knowledge

To extend current knowledge into new knowledge using the synthesis method introduced in this perspective article, possessing a solid foundational base of expert knowledge in one's field, called domain-specific knowledge [64], is vital. Most narrative reviews are written by experts [65], and research in memory and learning has revealed some important clues about how expertise is acquired. Practicing repeated retrieval of memorized information over a period of time strengthens knowledge storage and recall from long-term memory, developing the kind of deep learning possessed by experts which enables them to comprehend complex concepts, solve difficult problems, and infer new associations [66]. This finding implies that knowledge synthesis can be strengthened by repeated readings and practiced memory recall of relevant selected literature that lies outside the scope of one's domain-specific knowledge. Nevertheless, opportunities to form novel, potentially ground-breaking transdisciplinary theories and theses appear remote unless one is willing to investigate research outside of one's domain of expertise during the process of new knowledge synthesis.

Logan [67] criticized the disconnect between specialized knowledge and meaningful context, quoting Konrad Lorenz:

"Philosophers are people who know less and less about more and more, until they know nothing about everything. Scientists are people who know more and more about less and less, until they know everything about nothing."

In other words, a proper balance of both knowledge depth and scope is necessary for meaningful context and new knowledge synthesis. Research confirms that boundary-spanning knowledge search methods, which expand beyond one's domain-specific range, promote the discovery of new pathways and new combinations of knowledge that lead to breakthroughs [68]. For example, based on my web-based synthesis of phosphate toxicity and cancer, my awareness of the efficacy of a reduced-phosphate diet to treat chronic kidney disease patients led to a boundary-spanning proposal to test a similar phosphate-reduced diet as a novel intervention for cancer prevention and treatment [69].

6. Association, Causation, and Mediation

An essential function of scientific inquiry is the ability to recognize patterns that connect discrete pieces of data and provide new meaning to the investigation [70]. Connecting pieces of evidence together in a synthesis is analogous to assembling pieces of a jigsaw puzzle to create a coherent big picture. The graphical abstract in Figure 2 uses the analogy of a jigsaw puzzle to illustrate how current, prior, qualitative, and quantitative knowledge are pieced together from various domains during knowledge synthesis. This section of the article provides an elementary explanation of relationships by which research concepts are logically combined during synthesis into new knowledge. The strengths and weaknesses of linked concepts can strengthen or weaken one's synthesis. I provide further examples from my web-based syntheses in the field of epidemiology, and the strengths and limitations of three common types of linked relationships are discussed: association, causation, and mediation.

6.1. Association

An association is a link between two items or variables. Sometimes the link may be coincidental or spurious and occur strictly by chance, and sometimes a link may be meaningful and occur with a higher probability than by chance alone. An example of a coincidental association is demonstrated by flipping a coin. The outcome of heads or tails is strictly a matter of chance, assuming you are using a fair coin. Even if turning up 99 heads in a row, the chance that the next coin flip will turn up tails does not increase; it still remains at approximately 50%. Betting that there is a meaningful association between the number of coin flips and the chances that heads or tails will turn up next is known as a gambler's fallacy [71].

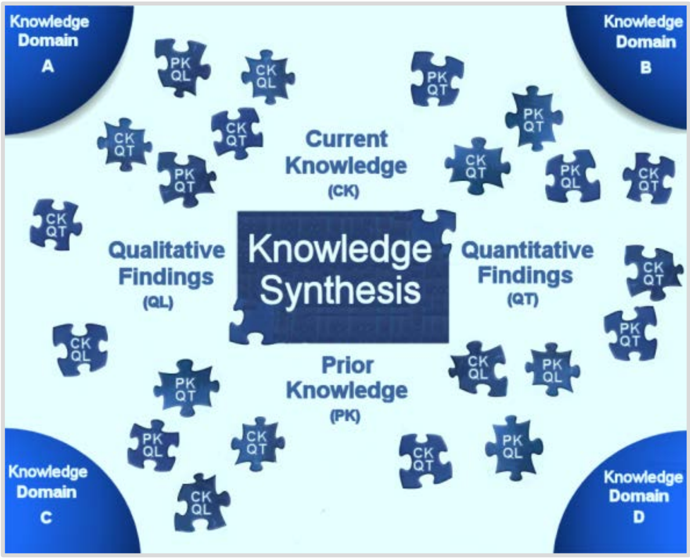

Figure 2. Graphical abstract. Like a jigsaw puzzle, pieces of knowledge are synthesized to form a coherent picture of new knowledge.

When associating concepts in a synthesis, the aim is to form a relationship in which the variables are meaningfully associated—as one variable changes, the associated variable also changes to some degree, known as covariance. But this does not necessarily mean that one variable is causing the other to change. Let us say the average person gets two colds a year and also takes vitamin C supplements. You do not take vitamin C supplements, and you observe that you get more colds than the average person. You suspect that taking vitamin C supplements may be associated with a reduced number of colds per year. But even if you are able to confirm that these two variables are statistically associated, as claimed in advertising using results of a clinical study, you still may not know what is causing the association between the variables. Perhaps people who take vitamin supplements look after their overall health better than you, which could be a confounding factor that independently causes the same outcome of reduced colds; which brings us to the next section.

6.2. Causation

Causation is a type of association in which one item, an independent variable, directly causes an effect on another item, a dependent variable or outcome variable. The highest form of evidence demonstrating causation is the randomized controlled trial (RCT), but RCTs are not always practical or feasible in research settings. Bradford Hill suggested the criteria in the list shown below for inferring causation from observational evidence in epidemiology [72]:

1. **Strength of the association**: stronger associations are more likely causal.
2. **Consistency**: causal findings are similar across multiple studies.
3. **Specificity of the association**: a cause produces a specific result.
4. **Temporality**: the cause precedes the result.
5. **Biological gradient**: the quantity of the cause determines the result size.
6. **Plausibility**: the cause may be explained by current knowledge.
7. **Coherence**: the cause is a good fit with related knowledge.
8. **Experimental evidence**: the cause occurs under controlled conditions.
9. **Analogy**: the cause is observed under similar circumstances.

6.3. Mediation

A mediator is a variable that lies between other variables within a direct causal pathway to an outcome variable. A directed acyclic graph (DAG) may be used to visually represent direct causal pathways between variables [73]. Acyclic means that a variable's causal pathway does not cycle back directly onto itself. Figure 3 is a DAG that shows a simple mediator causation pathway, based on Baron and Kenny, 1986 [74]. Note that confounders and effect modifiers lie outside the causation pathway in this model. For example, the independent variable may be replaced with an associated independent variable, a confounder, which causes the same effect on the outcome variable. An effect modifier may also change the outcome variable at the end of the causation pathway, as in the modifying effect of age and gender in the association of a risk factor with a disease. When inferring causation during a synthesis, possessing expert knowledge of the subject matter under investigation enables the identification of potential confounding factors [75], effect modifiers, and mediators. Research designs that include participant randomization and stratification of results can also assist in controlling the effects of confounders and effect modifiers.

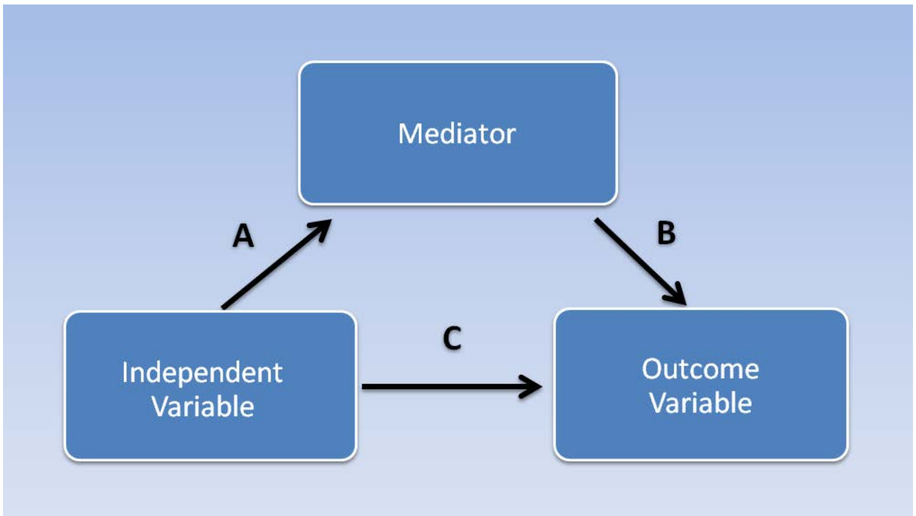

Figure 3. Mediation causal pathway. Causal path C runs from the independent variable to the outcome variable. Causal paths A and B run to and from the mediator, respectively, linking the independent and outcome variables. The absence of the mediator weakens path C, and if the path disappears altogether, the variables are linked indirectly through the mediator.

As causal diagrams have developed, indirect links between variables may be represented by a dotted line, and double-headed solid arrows may represent linked variables with an unspecified common cause [76]. I have also combined double-headed arrows with a dotted line (←------→) to represent variables linked indirectly with an unspecified common cause. When conducting a synthesis, the researcher may infer the mediating common cause that indirectly links two variables. To illustrate, low vitamin D levels in patients have been associated with a higher risk of cancer incidence [77]. Based on this association, some researchers have proposed that taking vitamin D supplements may prevent cancer, but recently published clinical trials of vitamin D supplements and cancer prevention do not support this causal inference [78–80]. Having coauthored a textbook chapter on the endocrine regulation of phosphate homeostasis [81], I have background knowledge of vitamin D's role in regulating intestinal absorption of dietary phosphorus—i.e., vitamin D levels are lowered if phosphorus serum levels rise too high, as in clinical and subclinical hyperphosphatemia. Synthesizing the link between lowered vitamin D and hyperphosphatemia with the link between hyperphosphatemia and tumorigenesis [61], I proposed that hyperphosphatemia is a common cause that mediates an indirect association between lowered vitamin D levels and increased cancer risk [69].

When selecting information during knowledge synthesis, conflicting material helps identify areas requiring further in-depth investigation. As demonstrated in the above example of vitamin D supplementation and cancer prevention, there may be additional factors that are missing which thwart the synthesis of a truer overall picture. To illustrate, in the allegory of six blind-men and the elephant, each blind man examined a different part of the elephant by touch: the tail, trunk, tusk, ear, leg, and side, and each man inferred a different description of the nature of an elephant as being like a rope, snake, spear, fan, tree, and wall, respectively. Although their tactile observations were accurate, the men were unable to discover the true overall nature of an elephant because they did not synthesize their findings into new knowledge.

Mediation is also used in literature-based discovery, a synthesis method in which implicit knowledge is discovered from linking together separate bodies of literature [82]. For example, if concept A is related to concept B in one body of literature, and a separate body of literature relates the same concept B to concept C, transitive inference relates A to C, as shown in Figure 4. In this example, B acts as a potential mediator that causatively links two separate bodies of literature in a novel way to infer new knowledge.

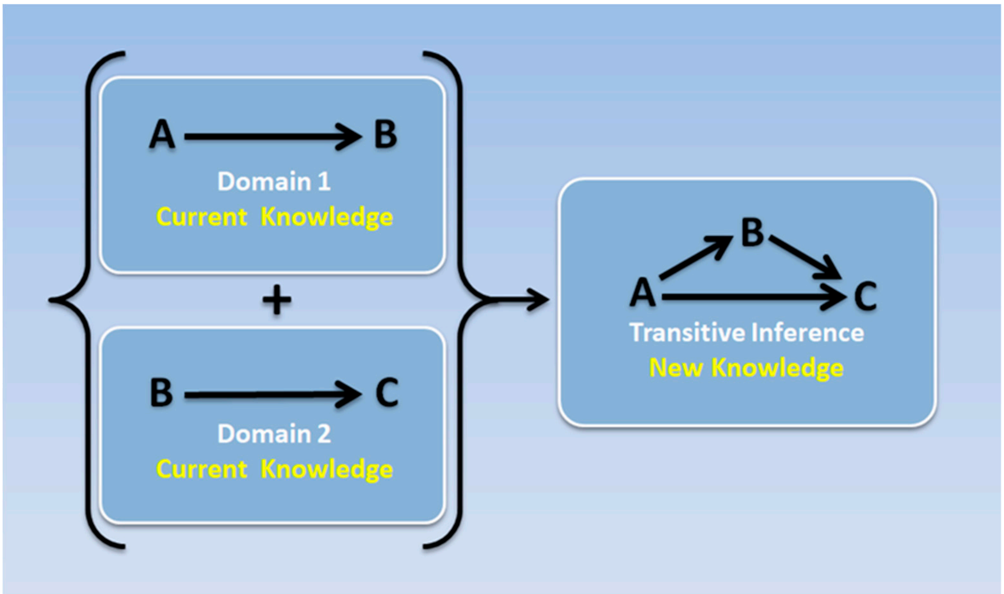

Figure 4. Transitive inference. A causes B in current knowledge domain 1, and B causes C in current knowledge domain 2. New knowledge is discovered when synthesizing domains 1 and 2 through transitive inference; i.e., A causes C, with B acting as a potential mediator.

I used transitive inference to propose an explanatory theory of how cholesterol oxidation products (COPs) are causatively linked to atherosclerosis [83]. I synthesized concepts from one body of research relating COPs (A) to defects in arterial cell membranes (B) with another body of research relating defects in arterial cell membranes (B) to atherosclerosis (C). In this case, defects in arterial cell membranes (B) acted as a mediator that linked COPs with atherosclerosis. This synthesis helped fill in some theoretical knowledge gaps in the potential cause and mechanism of atherosclerosis and strengthened the evidence for dietary prevention of atherosclerosis by avoiding COPs in thermally treated and processed animal-based foods that contain cholesterol.

7. Conclusions

Breakthrough knowledge has been shown to occur most often when prior knowledge is mixed with current knowledge. The art of discovering breakthrough knowledge in the age of Google involves writing web-based syntheses using interactive tools like online search engines and online databases.

Synthesis writing is an important educational objective. Grounded theory is a useful synthesis method to select, organize, analyze, and combine concepts from a mixture of research findings to infer an explanatory theory. Having domain-specific knowledge is important for synthesizing new knowledge and for identifying potential confounding factors, effect modifiers, and mediators when inferring a causal theory. I provided several examples of knowledge syntheses from my own published web-based syntheses in epidemiology, demonstrating how this novel method is readily available for use by researchers in other fields.

Funding: This research received no external funding.

Conflicts of Interest: The author declares no conflicts of interest.

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