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Editorial

Research Hypothesis: A Brief History, Central Role in Scientific Inquiry, and Characteristics

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Abstract
Background: A well-constructed hypothesis is central to scientific knowledge, guiding the research process from a problem to its potential solution. This paper aims to provide a brief history of the scientific hypothesis, emphasize its central role in hypothesis-driven research, and outline the characteristics of a well-formulated scientific hypothesis.
Methods: We conducted a narrative review of philosophical and scientific literature to examine the evolution of hypothesis formulation within the hypothetico-deductive (HD) framework, with emphasis on Karl Popper's principles of falsifiability and deduction.
Findings: The HD method remains the cornerstone of scientific inquiry, with hypothesis formulation serving as a critical link between theory and empirical testing. The 5E rule, which is a framework that defines an effective research hypothesis as Explicit, Evidence-based, Ex-ante, Explanatory, and Empirically testable, ensures that hypotheses are clear, relevant, and actionable within scientific investigation.
Conclusion: Despite its importance, hypothesis formulation is often underemphasized in modern biomedical research, where many struggle to construct well-defined, testable hypotheses.
Keywords: Hypothesis, Research, History, Scientific method

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Introduction

Scientific research starts with the research problem,[1] an obstacle that must be overcome to achieve a goal.[2] This problem is refined into an answerable research question,[3] which offers a more detailed and focused expression of the problem[4] (see Table 1 for definitions). After formulating the research question, the path of the quantitative research process is determined by the research framework. There are two primary frameworks: hypothesis formulating and testing and model building.[5,6] This means that a research question can be transformed into a hypothesis for empirical and statistical testing or used to build a model that explains a data set.[5] Hypotheses are typically constructed by deduction through the hypothetico-deductive (HD) method in advance of the experiment from existing knowledge (theory-driven) and undergo falsification.[7] In some cases, hypotheses are generated from data/observations by induction, following the hypothetico-inductive (HI) method.[8] Conversely, models are created after data collection through induction (data-driven), relying on the observational-inductive (OI) method, where predictive power is emphasized by verification.[6,8] Thus, research frameworks can be categorized into hypothesis-driven methods (HD and HI) and non-hypothesis-driven methods (OI).[9,10] These methods reflect complementary scientific approaches developed and refined over different eras, with the HD method best formulated in the 1930s, the HI method in the 1970s, and the OI method in the 2000s[8] (Figure 1).

While related, the research problem, question, and hypothesis serve distinct functions in hypothesis-driven research.[11, 12] The hypothesis is derived from the research

Table 1. Definitions of key terms

Term	Definition
Scientific research	A systematic inquiry linking existing knowledge to the research question in an objective and testable way (scientific method) that solves the problems
Research problem	A hurdle with no acceptable solution available
Research question	A structured interrogative statement based on an unsolved problem, which the researcher tries to answer through the study
Hypothesis	A logical construct interposed between a problem and its potential solution, playing a central role in acquiring scientific knowledge
Deduction	A top-down logical approach that infers specific conclusions from general principles or theories, often referred to as theory-driven reasoning
Hypothetico-deductive method	A hypothesis-driven approach that formulates hypotheses by deduction from theories and makes predictions followed by empirical testing: if (hypothesis)… and (test)… then (expected result)… but (observed result)… therefore (conclusion)
Induction	A bottom-up logical approach that derives general principles or theories from specific observations or data, commonly known as data-driven reasoning
Hypothetico-inductive method	A data-driven approach that formulates hypotheses by induction from data/observations and makes predictions followed by empirical testing
Observational-inductive method	A non-hypothesis-driven approach that builds a model that explains a data set, and the predictive power of the model is emphasized by verification
Null hypothesis	A statement that assumes no effect, difference, or relationship exists between groups or variables, serving as the default position tested against the alternative hypothesis
Alternative hypothesis (or research hypothesis)	Represents the effect of the intervention that researchers aim to detect, and it should reflect a plausible and meaningful difference.
HARKing	"Hypothesizing After the Results are Known" is a questionable research practice of creating or modifying hypotheses after seeing the results; HARKing leads to hypotheses that are always confirmed (precludes falsification) and reduces the replicability of published effects

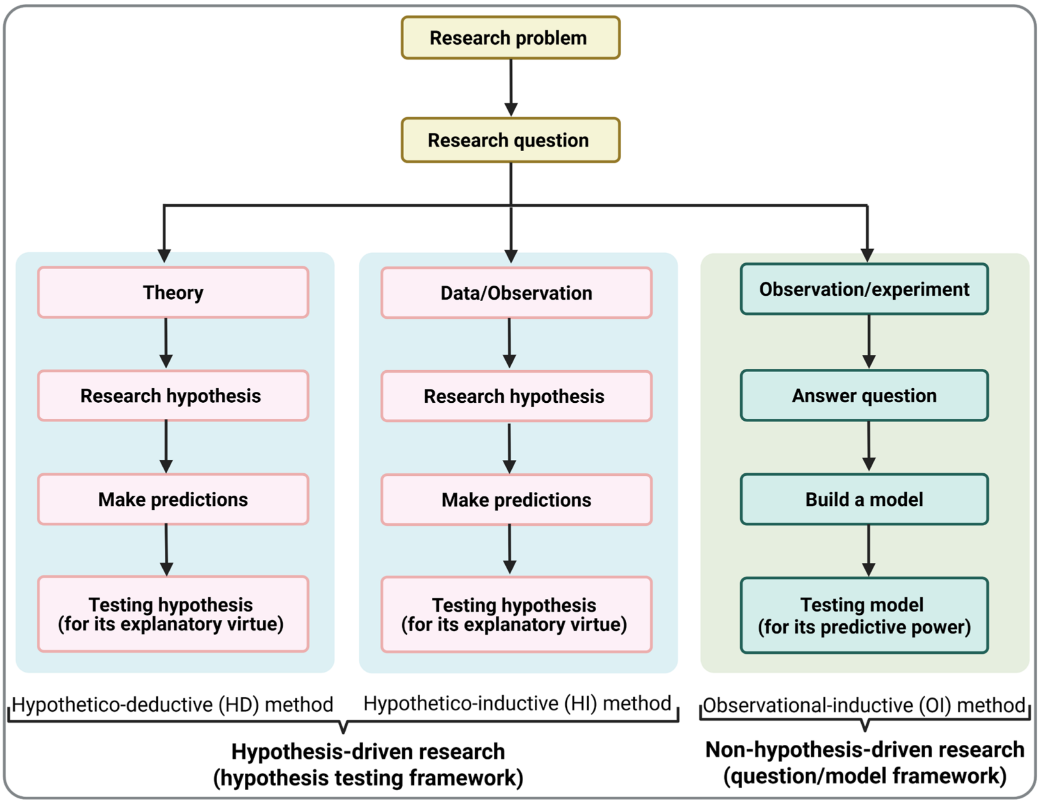

Figure 1. Hypothesis-driven and non-hypothesis-driven frameworks of quantitative research. The scientific inquiry may be framed around a hypothesis, which is constructed from theory (the hypothetico-deductive [HD] method) or data/observation (the hypothetico-inductive [HI] method) or framed around the question, which is answered by observation/experiment (the observational-inductive [OI] method). Not shown in the figure is that a research problem may raise several research questions, and a single research question can suggest several hypotheses. Created with BioRender.com

question and informs the experiments designed to answer that question.[11] A research question raises ideas about how certain concepts may be related, while the hypothesis is a predicted, evidence-based answer to that question.[13,14] Hypotheses also satisfy the validity criterion, meaning they must reflect the truth of a knowledge claim about reality.[12] A well-formulated hypothesis has moderate initial validity, neither too low to prevent hypothesis formation nor too high, indicating the problem has been sufficiently studied.[12] In contrast, research questions and problems are not directly testable and do not require the validity criterion.[12,15] It would be ideal to present the research question as a hypothesis,[16] and the HD method is preferred when there is enough evidence to make a non-trivial hypothesis.[17] Experimental, analytical observational, and candidate gene association studies are hypothesis-driven.[3] However, for purely descriptive studies, systematic reviews, and genome-wide association studies (GWAS), hypotheses cannot be formulated, and these studies are known as non-hypothesis-driven studies.[3,18] In addition, hypotheses are formulated when there is enough information about the problem[19]; in areas where little is known, hypothesis development may not be feasible.[18] Thus, all research projects have a question, but not all have a hypothesis.

The hypothesis is the most powerful tool invented by human beings to achieve dependable knowledge.[20] It serves as the working instrument, tentacles of theory, and a means for seeking solutions to human problems.[20] The research hypothesis acts as a pointer to valuable knowledge[12] and directs thinking toward problem-solving.[20] It has been stated that without hypotheses to be tested, science would be prone to stamp collecting.[18] The central position of the hypothesis in acquiring scientific knowledge is evident from this sentence: "There is no science without hypothesis".[21]

Although the hypothesis is one of the most powerful tools for achieving dependable knowledge and is crucial in experimental studies, it has received less attention in contemporary biomedical research.[15, 22] Researchers often fail to craft testable hypotheses or formulate them poorly, leading to studies with weak or non-testable hypotheses.[23-25] This is problematic, especially since many funding calls are for hypothesis-driven research proposals,[26] and papers with clear mechanistic hypotheses tend to be published in higher-impact journals.[18] Thus, this paper aims to provide a brief history of the scientific hypothesis, emphasize its central role in hypothesis-driven research, and outline the characteristics of a well-formulated scientific hypothesis.

Definition of hypothesis

The word hypothesis originates from the Greek word *hupothesis*, which combines *hupo* (meaning under) and *thesis* (meaning placing),[15] or *hypo* and *tithenai* (meaning to put),[27] which suggests a foundation or provisional supposition.[15,28,29] Another interpretation breaks it down into *hypo* (meaning under or less than) and *thesis* (meaning expressing a standpoint to be defended), which translates to "an idea with the lesser weight of prevailing views".[30] A hypothesis is a declarative sentence in which researchers predict the expected answer to the research question based on available knowledge and assumptions.[11,14,26,28,31,32] In essence, a hypothesis is a testable, tentative, and reasoned (but unproven) explanation for a problem or observed phenomenon based on partial evidence.[18,26,28,33-35] It provides a satisfying answer to the research question and serves as a statement that can be empirically tested.[36,37]

History of Hypotheses in Scientific Research

The historical evolution of scientific inquiry methods is illustrated in Figure 2, which highlights two main approaches. The first is the hypothesis-driven approach (HD and HI methods) that involves hypothetical reasoning from facts/observed to the unobserved.[38] It encompasses both deductive verification and deductive falsification and traces back to the 4th century BC with Aristotle, who emphasized the importance of deduction.[38,39] The second approach is the non-hypothesis-driven method or inductive generalization. This approach was introduced in the 17th century by Francis Bacon, who advocated for deriving general laws from repeated observations without relying on preconceived hypotheses.[40-42]

Hypothesis-Driven Approach

Aristotle first applied deduction in mathematics and philosophy, but its use was later extended to fields where hypotheses were tested empirically.[39] In the 16th century, Galileo Galilei used hypothesis as a premise (i.e., a starting point based on an unproven assumption) but did not formalize it as a methodology.[5] By the mid-17th century, scholars, including Rene Descartes, Robert Boyle, and Robert Hooke, advanced the use of hypothesis.[5, 9,38] Hooke notably highlighted hypotheses as tools to accelerate discovery by moving from known to unknown realms.[43]

After the dominance of Baconian-Newtonian observation-based inductive generalization, the HD method fell into disfavor by the 1720s to 1730s and 18th century,[38] when most scientists no longer used hypotheses.[9] Immediate successors of Newton believed his success came from avoiding hypothetical reasoning and relying on inductive generalization from experimental data.[38] However, by the 1740s-1750s, some scientists discovered this was not the case and began developing theories and hypothesizing unobserved entities to explain observed phenomena.[38] Georges LeSage helped restore the prominence of the hypothesis method, which became central to scientific inquiry through deductive verification by the late 18th century.[38]

In the 19th century, Jean Senebier endorsed the method of hypothesis in 1782 in his book on the scientific method,[38] while methodologists like Auguste Comte and Claude Bernard revived and emphasized the method of hypothesis over inductivism.[38] Bernard defined the scientific method as formulating and testing a hypothesis, emphasizing its obligatory for experimental reasoning.[7] The HD method was further advanced by William Whewell, William Stanley Jevons, and Charles Peirce.[7,44] It was used by Louis Pasteur and Gregor Mendel,[7] with

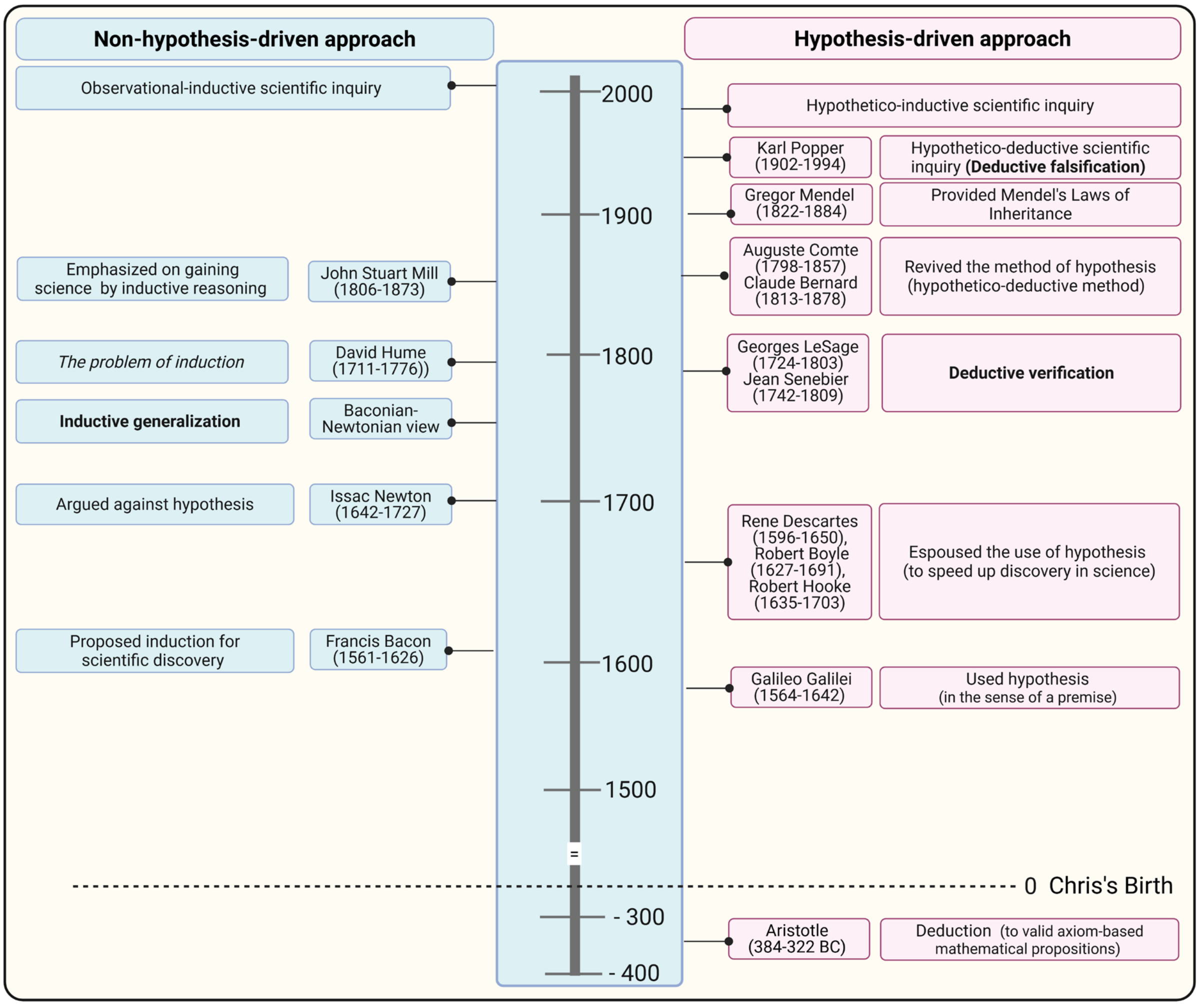

Figure 2. A historical overview of scientific inquiry methods. The figure illustrates the evolution of two primary approaches in scientific inquiry, hypothesis-driven and non-hypothesis-driven methods, across key historical periods, highlighting major milestones, including the development of inductive generalization, deductive verification, and deductive falsification, alongside influential scientists and paradigm shifts from antiquity to the present. See text for details. Created with BioRender.com

Mendel's work on inheritance is a classic example of hypothesis-driven research in biology.[45]

In the 20th century, philosophers such as Karl Popper and Carl Hempel advanced the HD method.[7,9] In the 1930s, Popper emphasized hypotheses as tools for falsification rather than verification.[6] He used hypothesis in the meaning that is used today and introduced critical rationalism, defining scientific hypotheses as those that are testable and potentially disprovable, contrasting Hempel's focus on verification.[8, 46] This principle of deductive falsification became the foundation of modern scientific inquiry.[5,39] By then, hypothesis-based science had become central to research,[9, 44] especially in biology, which shifted from descriptive to hypothesis-driven methods.[47] In the 1970s, the HI method gained prominence in fields where controlled experiments were difficult, but theory and observation remained balanced.[8]

Non-Hypothesis-Driven Approach

In the 17th century, Francis Bacon criticized Aristotelian deduction and advocated induction as the foundation of scientific discovery.[42] Bacon's method involved (1) collecting facts through observation and active experimentation and (2) using inductive reasoning to derive general conclusions from those facts systematically.[48] Although a controversial issue, Isaac Newton, despite his groundbreaking discoveries, shared Bacon's skepticism toward hypotheses,[6] famously stating, "*I frame no hypothesis*".[5] Both Bacon and Newton rejected bold conjectures[49] and suggested that investigators use induction (a direct root of observation to understanding[49]) from available evidence.[5,9] According to the Baconian-Newtonian view, science could proceed without hypotheses (although Bacon himself did not explicitly use the term hypothesis[6]), and the gradual accumulation of general laws by inductive methods was the only legitimate method for science, sometimes called inductivist orthodoxy.[38]

In the 18th century, the Baconian-Newtonian observation-based inductive generalization faced criticism from David Hume, who raised the *problem of induction*, arguing that

that rejects the idea that past experiences can be used as proof for future outcomes[5,49] and challenging probability as a rationale for inductive reasoning.[6] In the 19th century, John Stuart Mill, a follower of Bacon, emphasized gaining knowledge through inductive reasoning based on unbiased observation.[7,44,50] In the induction proposed by Bacon and Mill, observations are made without prejudice, a concept known as the *inductionist canon*.[7] In the 21st century, the -*omics* revolution, incorporating nontargeted measurements of a large number of items, renewed interest in data-based induction, mirroring Bacon's vision.[44] This modern iteration of induction, known as *knowledge discovery in databases* or *data mining*,[45] is particularly applicable in fields like space science, where direct hypothesis testing is often impractical. This data-driven inductive approach, sometimes called the OI framework, aligns with Bacon's idea of systematic discovery through the analysis of vast amounts of observational data.[8]

Today's Scientific Method

Science is a less fallible form of knowledge acquired through a specific method known as the scientific method,[51] which serves as the principal methodology[52] and cornerstone[53] of scientific inquiry. In hypothesis-driven methods, hypotheses may be deduced from theory (HD method) or induced from data/observation (HI method).[8,45] Other dimensions of the scientific method pursue a direct route from observation to understanding[49] or from data to knowledge,[45] including data-mining-based induction and allochthonous reasoning (i.e., the use of mathematical and computational modeling in biology for knowledge acquisition),[44] which complement hypothesis-driven approaches.[45] Today, both hypothesis-driven and non-hypothesis-driven methods are integral to scientific inquiry,[5] though some argue that "making hypotheses remains an indispensable component in the growth of knowledge".[49]

Hypothetico-deductive method of scientific inquiry

Traditionally, the HD method (the method of hypothesis or hypothesis-driven deduction) characterizes the scientific method[44] since it assumes that if both the initial axiom and observations are valid, the logical deduction must also be correct.[45] As the standard framework for science, the HD approach assumes that the universe is a rational place in which scientific questions have answers that are a handful of reasonable explanations.[37] The HD method moves from idea (knowledge) to data.[45] The scientific method, as outlined by the HD method[46] involves two main phases (Figure 3): (1) formulating hypotheses from theory by deduction and (2) testing them experimentally via observation and experiment.[7,54] In experimental studies, focused on mechanistic causes, the hypotheses are deduced about the natural world and empirically tested for verification or falsification. Then, using null hypothesis significant testing, it is ruled out that the conclusion is by chance, and results are generalized (by induction) to the population from which the sample was obtained.[28]

The HD reasoning in science is cast as if … (theory/hypothesis), and … (planned test), then … (expected result), because … (theoretical rationale), and … (observed results), therefore … (conclusion).[55] For example, suppose we have the research hypothesis: Administration of drug x (intervention), which inhibits β-cell apoptosis, to obese subjects (population) for six months (time) decreases the risk of diabetes (outcome) compared to placebo-treated obese subjects (comparator). According to the HD reasoning, this hypothesis is cast as *If* drug x decreases pancreatic β-cell apoptosis (theory), *and* we treat obese subjects with drug x (planned test), *then* the risk of developing diabetes in obese subjects is expected to decrease (expected outcome), *because* apoptosis of pancreatic β-cells is the major cause of developing diabetes in obese subjects (theoretical rationale), *and* results showed the reduced risk of developing diabetes in obese subjects (observed results); *therefore* the theory of reducing diabetes risk in obese subjects using drugs with antiapoptotic action on β-cells is not falsified.

Hypothesis-Based Predictions

The HD approach to the scientific method uses hypotheses to make predictions[46] about experiments.[56] These hypotheses, as creations of the mind,[50] provide a possible world that is compared to the real world through experimentation.[7] Predictions made by hypothesis are the potential outcome of a test that would support a hypothesis[18] and should be in the form of being subjected to empirical testing.[50] For example, suppose a researcher claims to have developed a formulation that increases energy expenditure by affecting mitochondrial carbohydrate metabolism. In that case, one might predict it would not affect red blood cells (lacking mitochondria) and have a more significant effect on heart cardiomyocytes, which contain a high density of mitochondria.

Empirical Testing of Hypothesis

In testing a hypothesis, researchers examine whether logically derived predictions made by the hypothesis align with empirical observations through experiment.[7,50] The constant dialogue between imagination (possible world created by hypotheses) and experiment (real world) advances science.[50] Based on experimental results, hypotheses are either confirmed (Hempel approach) or rejected (Popper approach).[8,46] The *modus tollens* (manner of taking away) a logical method for empirically testing and rejecting scientific hypotheses; if a necessary consequence (a prediction) of a hypothesis is false, then the hypothesis itself is false.[50] This rule of inference and conditional reasoning follows the structure: 1. if A then B, 2. not B, so 3. not A.[57,58] *Modus ponens* (1. if A then

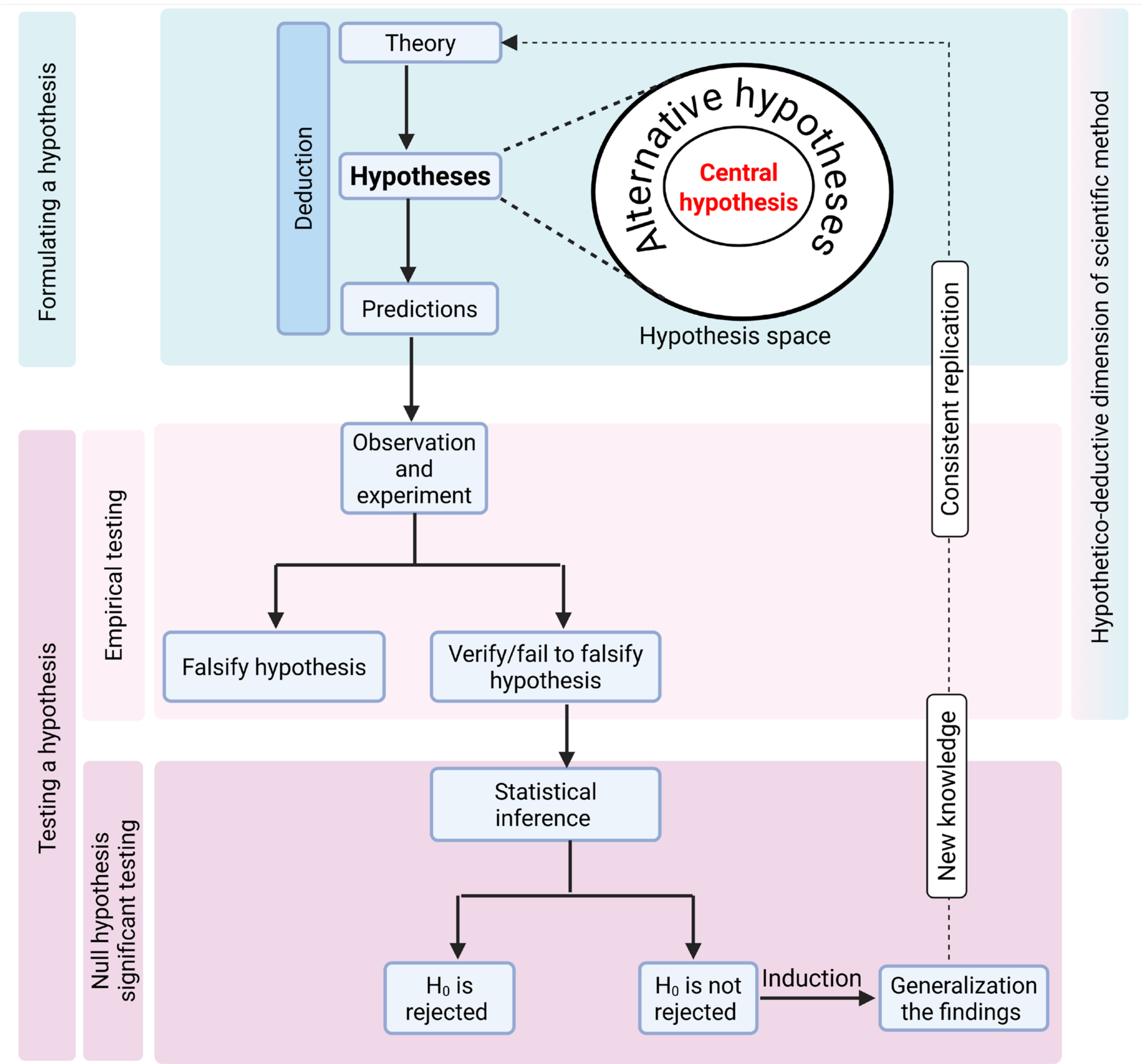

Figure 3. The central place of the hypothesis in the hypothetico-deductive method of scientific inquiry. The hypothetico-deductive method has two main steps: (1) formulating hypotheses from theory by deduction and (2) testing hypotheses. Central and alternative hypotheses, providing the hypothesis space, are formulated to answer a research question. In the first step, a working hypothesis or multiple working hypotheses (one of which may be considered the central hypothesis) are formulated based on the existing literature (theory). Based on the formulated hypotheses, some predictions are made about nature. In the next step, hypothesis-based predictions made in the possible world are empirically and statistically tested in the real world to reject alternative hypotheses and provide support for the central hypothesis. This new knowledge answers the research question, partially solves the research problem, and adds to existing knowledge to formulate new hypotheses. H_0, null hypothesis. Created with BioRender.com

B, 2. A, so 3. B) is another form of conditional reasoning for verifying some hypotheses.[58] Although verifiability, as defined by the Vienna Circle of the logical positivists, is less relevant in empirical hypothesis testing,[59] we often aim to falsify rather than verify hypotheses.[17] However, existential hypothesis (e.g., there are egg-laying mammals) are inherently verifiable not falsifiable.[60]

In Popper's HD approach to scientific inquiry, the disproof of hypotheses (falsification) generates knowledge[37] and empirical falsification is key criterion for demarcating empirical science from other forms of knowledge.[50] This preference for falsifiability over verifiability is due to the asymmetry between these two demarcation criteria: a universal statement can never be proven true by particular statements, no matter how numerous these may be; however, it can be proven false if it contradicts even one specific case.[7] Thus, while we can demonstrate the falsity of universal statements, proving their truth remains elusive.[50]

Statistical testing of hypothesis and inductive generalization

A hypothesis must be supported by empirical evidence to be valid.[28] However, measured experience can vary across time, place, and observers,[28] making it difficult to determine if observed differences are due to random variation or reflects true differences in the population.[28] To address this uncertainty, statistical hypothesis testing is employed[23] that analyzes samples to infer characteristics about the population from which the samples are drawn.[61] Null hypothesis significant testing (NHST) is the most commonly used method for statistical inference in scientific research.[23,62]

NHST involves two hypotheses: the null hypothesis (H_0), which is tested statistically, and the alternative hypothesis (H_1/H_A), also called research hypothesis.[62,63] Falsification requires researchers to propose opposing assertions for any single research question: H_1 that supports the hypothesis and H_0 that does not support the hypothesis.[28] This process resembles constructing "a straw man to be knocked down" and is termed the null (no difference) hypothesis.[28] The null hypothesis is framed by inserting a negative modifier in the research/alternative hypothesis[28] and is essentially a restatement of the research hypothesis, asserting no difference between groups.[11] The null hypothesis serves as the foundation of the statistical analysis,[11] suggesting that any observed differences are due to chance until proven otherwise by empirical evidence.[28] After establishing null and research hypotheses, NHST can be done to reveal whether the chance is (the null hypothesis is accepted) or not (the null hypothesis is rejected) an explanation.[28] Statistical analysis helps assess if there is enough evidence to reject the null hypothesis, which supports the research hypothesis rather than proves it.[23] Researchers determine whether to reject the null hypothesis based on the strength of the evidence[64] and rule out that the conclusion is by chance,[28] with non-significant results indicating no effect or a small effect obscured by chance.[65] For a hypothesis to be accepted as a theory (i.e., a hypothesis confirmed by further observation[29]) or a component of the theory,[28] it needs consistent replication and further observation (Figure 3).

Characteristics of a good research hypothesis

A strong research hypothesis should be Explicit, Evidence-based, formulated before the experiment (Ex-ante), and possess Explanatory power while being Empirically testable. These qualities, summarized in the *5E rule* (Figure 4), are essential for creating an effective research hypothesis and will be discussed below.

Hypothesis should be explicit

In addition to referring to an important and insufficiently investigated part of knowledge,[12] the research hypothesis should be clear and unambiguous (i.e., specific),[19,28,66] stated as a declarative sentence containing at least a subject, a predicate, and a verb.[28] In addition, it should be constructed with the correct set of variables,[19] describe the variables,[36] and express the nature of the relationship between variables.[16,22,28,33,67] In many cases, the purpose of a hypothesis is to make an inference about one or more variables (e.g., the association between diet and hypertension).[28] For example, *"Higher than recommended value of dietary intake of added sugars for six months is associated with an increased risk of developing type 2 diabetes in adults aged 40-65 years,"* defines the exposure, outcome, population, time, and expected relationship. Conversely, "*Sugar affects diabetes*" is vague and lacks necessary details.

Hypothesis should be evidence-based (theory-laden)

Hypotheses should be based on original ideas[36] but must be logically backed (rationalized) by previous evidence (i.e., relevant observations), not mere speculation.[16,28,36,66] As Ormrod said[29]: "The most elegant scientific hypothesis is futile if it is not firmly rooted in fact." As a rule of thumb, a proposition not supported by a standard textbook needs evidence.[35] The evidence for a hypothesis

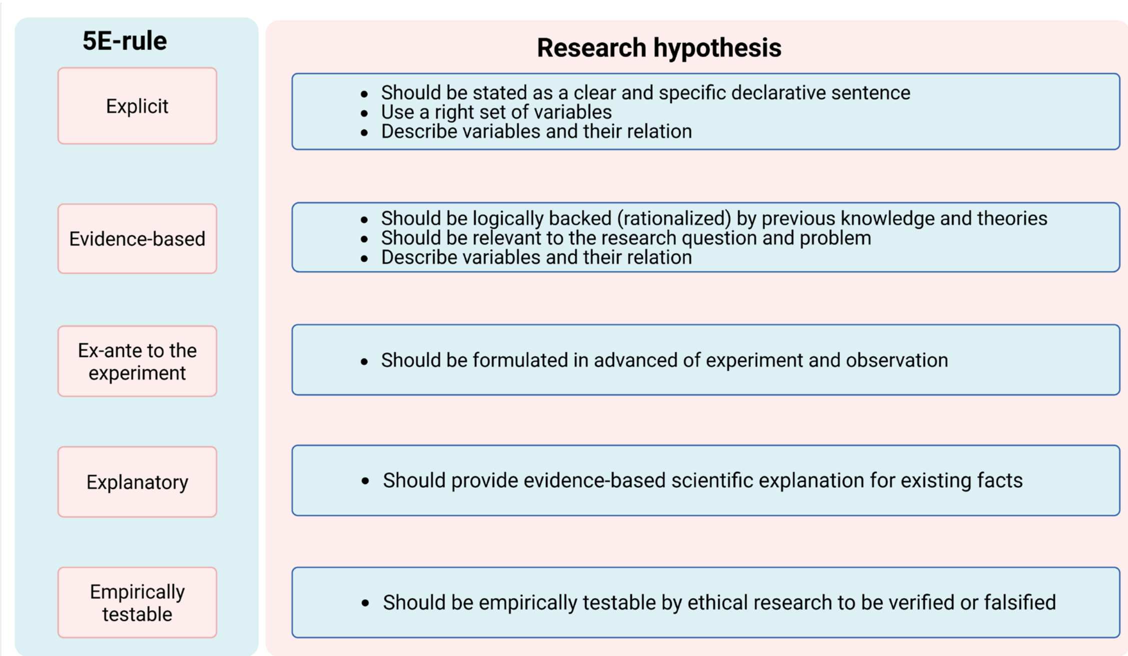

Figure 4. Characteristics of a good research hypothesis. Created with BioRender.com

must demonstrate the existence and significance of the problem, ensure the hypothesis is grounded on facts, verify the logical reasoning of the argument, and support the accuracy and reliability of the conclusion.[35] For the logical construction of a hypothesis,[68] it should relate to the research question,[30] address its content and scope,[28] and adequately answer it.[28] For example, the hypothesis that "*adults consuming less than 15 grams of fiber per day are at an increased 5-year risk of developing type 2 diabetes* compared to those *consuming more than 15 grams of fiber per day*" indicates its root in the literature. Conversely, "*wearing green socks prevents diabetes*" has no basis in established physiological mechanisms and is not backed by empirical evidence.

Hypothesis should be formulated ex-ante to the experiment

In quantitative research, hypotheses, referring to a prediction of study findings, should be formulated before a study begins (before the experiment) rather than derived from data afterwards.[5,33,36,63,66,69,70] The evidence for constructing a hypothesis (from the literature review) differs from the evidence for testing it (collected data).[71] Scientific hypotheses should be evaluated only after their formulation[22] as a priori hypothesis forces researchers to think in advance more deeply about various causes and possible study outcomes.[18,33] It is important that hypotheses are not altered post hoc to match collected data,[11] and exploratory testing of such post hoc hypotheses, known as hypothesizing after the results are known, or HARKing, should be avoided.[22] This means that we can choose any hypothesis before data collection but cannot change it after starting data collection.

HARKing, a questionable research practice,[22] involves altering hypotheses based on study results.[71] It includes two forms: (1) presenting a post hoc hypothesis as if it were a priori and (2) excluding a priori hypothesis.[71] The Texas sharpshooter fallacy or clustering illusion refers to HARKing.[71] It describes a scenario where a person shoots at a wall, erases the original target (excludes the priori hypothesis), and draws a new one (include the post hoc hypothesis) around random bullet clusters (his evidence), claiming success as a sharpshooter (researcher).[71,72] Coincidental clusters can appear in any data collection, so to achieve credible scientific results, targets should be pre-specified before data collection (i.e., the target should be painted before firing the bullets).[72]

HARKing harms science and impedes scientific progress by (1) leading to hypotheses that are always confirmed, hindering falsification, and (2) reducing the replicability of published effects since reported effects are unanticipated artifacts that are produced following p-hacking (massaging data to yield statistically significant results).[63,71] Searching data for significant results (data dredging) can also yield misleading outcomes[53] through chance alone.[63] HARKing is common among researchers, with a self-admission rate of 43%.[71] To combat data dredging, it is crucial to clearly define the study's objectives alongside a solid understanding of the scientific method.[53]

Hypothesis should have explanatory virtue

The research hypothesis should provide an evidence-based explanation for observed phenomena[73] rather than merely predict expected results.[18] It must have explanatory value, offering insights into why certain events occur.[50] For example, a hypothesis proposing that the effects of a particular drug vary by sex can help explain various observations regarding the drug's use in men and women.

Hypothesis should be empirically testable

Hypotheses must be empirically testable through ethical research.[19,28,36] Testability allows for examination via observation, experimentation, and analysis[28] to determine validity.[26,35] According to classic HD methods, scientific hypotheses should be falsifiable.[44] For example, claims about the number of chromosomes in angels are not hypotheses as they cannot be empirically tested.

Types of hypotheses

Hypotheses can be classified from various perspectives (Figure 5), including the origin of the hypothesis (deductive and inductive), scope (narrow and broad), number of variables (single variable, two variables, and multivariable), the relation between variables (associative and causal), and statistical types (null and alternative).

Deductive and inductive hypotheses

The origin of the hypothesis can stem from established theories (rationalist perspective), yielding a deductive hypothesis, or empirical events/data/observation (inductivist perspective), yielding an inductive hypothesis.[19,28] In quantitative studies, hypotheses are primarily deductive, developed from a theoretical framework that moves from general to specific.[28,36] While inductive hypotheses arise from observations,[19] they are influenced by existing theories since observations are theory-laden.[41] Thus, no scientist works without a preconceived plan.[7] In addition, observations are always more effective when channeled by hypothesis.[74]

Narrow and broad hypotheses

Hypotheses for new topics tend to be broad initially but become narrower with more literature.[22] Narrower hypotheses (e.g., a specific positive linear relation between x and y with a slope of 0.5) are more precise but less likely to be confirmed as true compared to broader ones (e.g., a relation between x and y).[22] Researchers should adhere to the Goldilocks principle when formulating hypotheses: too broad is excessive and not novel, and too narrow is unnecessary or wasteful; thus, hypotheses should be not

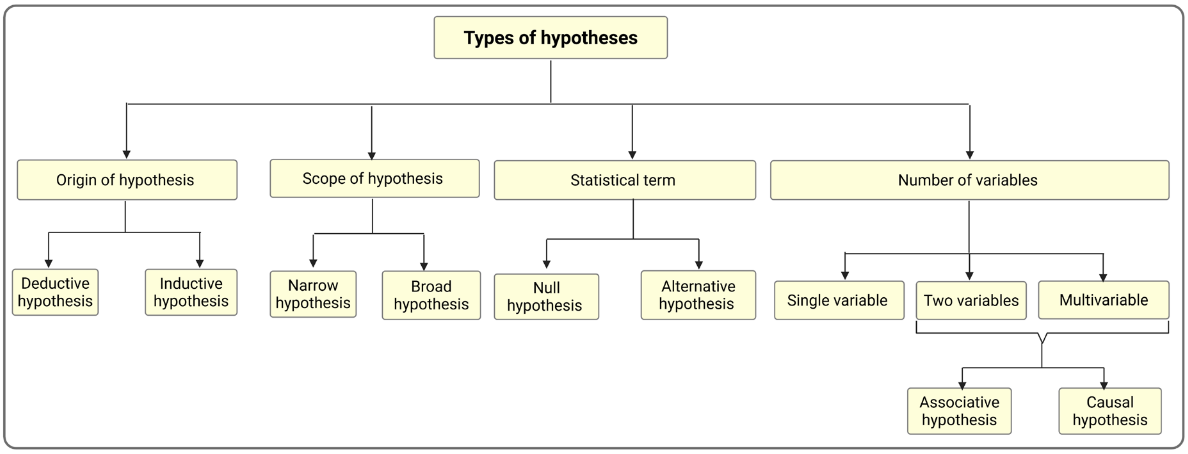

Figure 5. Types of research hypothesis. Created with BioRender.com

too broad, not too narrow.[22] A hypothesis must be narrower than current knowledge to ensure scientific novelty[22] but broad enough to navigate the hypothesis space effectively.[22] It should be noted that a broad hypothesis (e.g., testing whether one or both of two scales change after treatment), which allows for the evaluation of uncertainty, is different from a vague hypothesis (e.g., quantifying depression after treatment), in which the uncertainty is part of the interpretation of the hypothesis.[22]

Single and multivariable hypotheses

Some hypotheses involve a single variable (single variable hypotheses) to draw inferences about the population (e.g., assessing whether a mean differs from a specified value).[28] Others examine the relation between two (bivariate hypotheses) or more (multivariable hypotheses) variables.[28] The expected relationship may be predicted between a single independent and a single dependent variable (simple hypothesis)[36,63] or between two or more independent[36] and dependent[36,63] variables (complex hypothesis).

Associative and causal hypotheses

Hypotheses may be cast to propose an association between variables (associative hypothesis or hypotheses of association) or propose an effect of the independent variable on the dependent variable (causal hypothesis or hypotheses of difference).[28,36] Causal hypotheses (mechanistic hypotheses) are often used in preclinical research to define causes (explanation), while associative hypotheses, commonly found in clinical research, do not seek explicit explanations.[28]

Null and alternative hypotheses

Statistically, hypotheses are categorized as null and (research) alternative.[19] Null hypothesis (H_0 or H_N) indicates no effect (e.g., in clinical trials) or association between the studied variables and, in this sense, is also called nil hypothesis.[23] However, sometimes, the null hypothesis may not be nil (e.g., testing the observed correlation coefficient against a fixed value of correlation coefficient).[23] The alternative hypothesis (H_1 or H_A) represents the effect the researchers aim to detect, which should be a realistic reasonable difference.[64] Research (alternative) hypothesis can be non-directional ($A = B$) or directional ($A > B$ or $A < B$).[28] A non-directional hypothesis, or two-tailed hypothesis, indicates a relationship without specifying the direction, while a directional hypothesis, or one-tailed hypothesis, predicts a specific direction based on prior literature or experience.[28,33,36,63,70] The directional hypothesis is riskier since it is less likely to occur but is more convincing if confirmed.[33] Whether the directional or non-directional hypotheses is used depends on theoretical considerations.[28] Generally, a non-directional hypothesis should be used unless there is reasonable justification for using a one-sided hypothesis.[63] Suppose that a man approaches a street corner, a non-directional hypothesis predicts that he will turn to right or left, but a directional hypothesis would predicts he will turn to a specific direction (e.g., right). If he continues straight, neither hypothesis is supported.[33]

Advantages for formulating the hypothesis

The HD approach to the scientific method emphasizes that hypothesis is obligatory for experimental reasoning.[7] Proponents of the hypothesis believe that the problem can only be scientifically solved if reduced to hypothesis form[12] and argue that hypotheses offer several benefits: (1) foster new scientific ideas[50]; (2) direct researchers on how to think about the problem, facilitating problem-solving[28]; (3) enhance understanding of the question and its related variables[33]; (4) enable evidence-based specific predictions based on previous knowledge[33] that can be tested[34,40]; (5) guide observation by suggesting what to observe[7,50]; (6) provide a basis for testing the statistical significance[19,75]; (7) force clarity and precision of thinking, provide mechanisms that have intrinsic value to humans, and increase the transferability of findings to new systems.[18]

Disadvantages of formulating the hypothesis

Despite advantages, formulating a hypothesis has some disadvantages: (1) it can suppress innovation[6]; (2) it may lead researchers to filter data through the hypothesis lens, rejecting contradicting evidence in favor of validating evidence[6]; (3) focusing on a single hypothesis (the method of working hypothesis) can introduce bias as investigators may be tempted to get the desired outcome and not focus on other important phenomena in the study[33]; (4) the researcher might accept small effect sizes that lack physiological relevance[6]; (5) big science (e.g., omics and mRNA sequencing) cannot be effectively framed with a hypothesis.[6]

Hypotheses in interdisciplinary research

The emergence of omics sciences (including genomics, proteomics, and metabolomics) challenges the orthodox hypothesis-driven method in medical science by large-scale exploration of biological systems.[76] Instead of testing predefined hypotheses, omics sciences generate data-driven insights through comprehensive molecular profiling, uncovering complex interactions and novel targets.[76] An example is GWAS, which "turns hypothesis-driven research on its head" by scanning the entire genome without *a priori* hypotheses about specific regions or variants, unlike traditional approaches that focus on predefined candidate genes in relation to a specific disease.[77,78] GWAS relies on the theory that "systematic genome-wide study of DNA variation in relation to disease can lead to the localization of causal genes".[78] Through genome-wide interrogation of genetic variation, GWAS are often described as "non-hypothesis driven" or "agnostic" approaches.[77,79] However, this label has been debated by some scientists, who argue that GWAS still rely on foundational assumptions, such as the "common disease/common variant (CD/CV) hypothesis" and the presumed role of independent single nucleotide polymorphisms (SNP) effects in genetic predisposition.[77] Candidate gene association studies (CGAS) use a deductive, hypothesis-driven approach to test whether specific genes are linked to disease risk.[80] This method focuses on predefined genomic regions, enabling targeted analysis of selected alleles, especially putative functional SNPs, within relevant study populations.[80] In summary, while original omics projects are often considered non-hypothesis-driven, the data generated from these studies can ultimately inform hypothesis-driven research, where explicit hypotheses are formulated to further explore and validate the biological mechanisms underlying complex diseases. The formulation of a hypothesis in this context can follow the *5E rule* discussed in section 6.

Multiple working hypotheses

The formulation of a single working hypothesis can lead to confirmation bias. To avoid this, multiple hypotheses- comprising a central hypothesis and alternatives- are constructed to answer a research question.[33,34,36] This approach provides a hypothesis space[22] that encompasses the subject on all sides[81] and brings up a set of rational hypotheses that offer complex explanations from different perspectives.[82] While the researcher intends to evaluate the central hypothesis using falsification or verification methods[22] that they think provides the best explanation of the observed phenomenon, alternative hypotheses can be rejected based on existing literature or assessed concurrently. This method of simultaneous multiple working hypotheses and disproof that provides a conclusion by exclusion (of alternative hypotheses) is secure and has been called strong inference,[81] reflecting the Popper instruction that science progresses by rejecting hypotheses.[34] For example, we know that the guanylyl cyclase (GC) enzyme catalyzed the conversion of GTP to cGMP, which is degraded to 5´-GMP by phosphodiesterase (PDE) enzyme. If investigating how drug X increases cGMP, possible alternative hypotheses include:[83,84] (1) Drug X inhibits PDE (e.g., sildenafil); (2) drug X stimulates GC (e.g., YC-1); (3) drug X produces metabolites (e.g., nitric oxide) that increases cGMP.

Using multiple-working hypotheses instead of single-working hypotheses reduces bias, increases reproducibility, and facilitates the discovery of mechanisms.[18] This approach allows for various plausible explanations, thereby preventing confirmation bias.[18] By avoiding attachment to a single idea, decreasing confirmation bias, and forcing one to think in advance, the method of multiple-working hypotheses improves research reproducibility.[18] Moreover, it transforms scientific discourse into a rational competition between ideas rather than an irrational argument among scientists.[37]

Conclusion

Research can be approached in two primary ways: hypothesis-driven or non-hypothesis-driven. As the principal methodology of scientific knowledge inquiry,[52] the scientific method has three main dimensions: The HD, HI, and OI approaches. Notably, the HD method is widely recognized as the standard and classic method of scientific inquiry. In the HD method, developing a research hypothesis is crucial, serving as a logical construct interposed between a problem and its solution.[28] In the HD method: (1) hypotheses are formulated from previous knowledge (theory) to explain a natural phenomenon; (2) Some predictions are made based on the hypotheses; (3) These predictions are tested by experiments/observations to be verified or falsified. Hypotheses that resist falsification following consistent replication can be added to science as theories. A good research hypothesis should be Explicit and Evidence-based, be formulated Ex-ante to the experiment, have Explanatory virtue, and be Empirically testable (the *5E rule*).

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