Research Brief (Causal Investigations)

Synoptic Summary of the Historic National Academies Assessment of Frameworks for Causal Determinations

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Why This is Important:

The National Academies recently conducted a formal assessment of frameworks for causal determination and found that the currently-popular “statistical causal inference approach” (based on Potential Outcomes and Structural Causal Models) is incomplete and insufficient for causality assessments. The Report endorses a mechanistic view of causation and the need to recognize the importance of (1) mechanistic causal inference, (2) consideration of all forms of relevant evidence, and (3) adoption of a weight-of-evidence approach involving subject matter experts. This finding initiates a seismic shift in causal methodology of major importance to science.
(the full report can be found here: https://doi.org/10.17226/26612)

Abstract

In 2022, the National Academies of Science, Engineering, and Medicine conducted an evaluation of frameworks for causal determination. This Synoptic Summary seeks to make the findings of the National Academies Consensus Report more concise and make its relevance more apparent. It also links the Academies findings to more recent developments furthering the rollout of a new and expanded paradigm for causal investigations. This work is of major importance to all scientists because as Schwartz and Prins (2025) have pointed out,

> "Researchers should take debates about causal methods seriously because with or without our awareness, and with or without our consent, these debates shape the questions we ask, the methods we use, and the narratives we construct about our study results."

Keywords: causal investigations; causal inference; mechanistic causal investigations.

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1. Introduction

The purpose of this synoptic summary is to help spread important information relevant to the scientific enterprise of building causal knowledge and understanding. Despite the foundational importance of this objective for science, the literature on the subject has been largely separated into disconnected silos created by associated expertise. Making general statements about historical sources and traditions is exceptionally challenging given the vast literature. A paper by Holland and Rubin in 1987 opened with the following statement, which perhaps provides us with a perspective from the field of statistics.

> "Philosophical discussions of causality often emphasize the meaning of causation. Scientists are usually concerned with understanding causal mechanisms. Purely statistical discussions of causality are substantially more limited in scope, because the unique contribution of statistics is to measuring causal effects and not to the understanding of causal mechanisms or to the meaning of causation."

Philosophers, scientists, and statisticians, with individual exceptions, commonly differ in training, expertise, perspective, and interests. Each tends to be judged by their peers based on profession-specific training and norms and each is prone to use terminology that is specific to their fields. This means that the literature relevant to causal methodology lives in separate silos. This separation has played a critical role in the current state of flux in the literature on causal methods. The National Academies Consensus Report that is the focus of this summary (NASEM 2022) represents a potentially historic examination of frameworks for causal determination, which is the judgement as to whether available evidence of all types supports a causal claim. In this synoptic summary, select excerpts from the full report (which contains 187 pages) are first presented, followed by commentary intended to broaden the context of this material beyond the task of causal determination. Important ramifications of the NASEM Report are discussed in the final section.

2. Overview

This National Academies Report is important because it presents a contemporary state of the art comparative assessment of frameworks for causal determination. This central aspect of the report is of major and far-reaching interest to all branches of science and science methodology that deal explicitly with causality. It is necessary when reading the report, however, to be aware that the assessment was conducted within a specific context. The context is that the U.S. Environmental Protection Agency is charged with conducting Integrated Science Assessments (ISAs) on select pollutants and their potential causal effects on human health and "welfare" (impacts on soils, water, agriculture, forests, wildlife, human-made materials, atmospheric visibility, and climate). The USEPA (2015) has an established system for conducting ISAs and assessing causality that provides baseline context for the evaluation. The excerpts that follow do not provide a complete description of the ISA procedure but instead focus (as the Report does) on evaluating the causal methods literature. Described simply, the ISA is based on a protocol for reviewing all relevant scientific literature for a pollutant and assessing the evidence for causal determination. Evidence is integrated across scientific disciplines and study types and judged via collaboration among scientists from multiple disciplines so as to characterize the weight of evidence for causal relationships between the pollutant and various outcomes. Thus, causal determination is based on a weight of evidence approach that involves all relevant forms of evidence and expert judgment based on considerations that include consistency, coherence, biological plausibility, gradient relationship, strength of association, experimental evidence, temporal sequencing, specificity, and structure-function relationships.

3. Excerpts from the Academies Report

THE TASK

"The EPA Office of Research and Development requested the National Academies of Sciences, Engineering, and Medicine (the National Academies) to consider existing frameworks and new advances and tools for integrating, documenting, and evaluating scientific evidence for assessing causality of health and [environmental] welfare effects, describe how EPA's methods for classifying the weight of evidence for causation (i.e., what EPA terms 'causal determinations') might be refined, and make recommendations related to the development and use of a future causal determination framework." ... "Furthermore, the committee was asked to consider whether a single framework and set of practices is appropriate for assessing causality for both health and [environmental] welfare effects." ... "In addition to the current causal determination framework [used by the EPA], the committee reviewed nine other frameworks that are or have been used for determining causal relationships, or include major aspects of that process."

"The criteria pollutants [of concern in this report include] ... carbon monoxide, lead, oxides of nitrogen, particulate matter, ozone and related photochemical oxidants, and sulfur oxides." "Health effects are those adverse impacts on human health; welfare effects include impacts on soils, water, agriculture, forests, wildlife, human-made materials, atmospheric visibility, and climate."

COMMITTEE COMPOSITION

"The committee includes researchers and practitioners with expertise in atmospheric sciences, statistics and biostatistics, epidemiology, biogeochemistry, toxicology, exposure science, dosimetry, public health, terrestrial and aquatic ecology, and regulatory decision making for air pollution control."

DEFINING CAUSAL EFFECTS: POTENTIAL OUTCOMES

"Evaluation of causality implicitly involves comparing outcomes under two or more hypothetical states of the world. The defining feature of those worlds is a hypothetical intervention on the proposed causal factor of interest. For example, when considering a proposed causal factor (such as exposure to a pollutant of a specific concentration), one hypothetical world is that in which every unit in the population is subject to the intervention (exposure to the pollutant) versus another hypothetical world in which no unit in the population is subject to the intervention. In the statistical literature, the outcomes in these hypothetical worlds are known as "potential" outcomes, and where in a particular dataset one will be observed for each unit; the other is unobservable and termed 'counterfactual'" ... "A causal effect, defined as a property (summary) of the distribution of potential outcomes (e.g., the difference in means), is identified if it can be uniquely computed from the distribution of observed variables, using a set of well-articulated causal assumptions encoded in a causal model (... Pearl 2009)."

EVALUATING CAUSALITY THROUGH MECHANISTIC UNDERSTANDING

"The above description defining causal effects does not require any knowledge of why such effects occur. An alternative approach to causality is known as 'mechanistic causality.' Mechanistic causality requires an understanding of the causal mechanism—that is, all the steps underlying an observed association need to be explicit and have a genuine explanation (Campaner, 2011). To achieve mechanistic knowledge is to be able to determine not only that some factors contribute to some effects, but also how they contribute, revealing the continuous and dynamic processes linking causes with their effects. A mechanistic perspective on causality holds that a causal relationship can be revealed through identification of the specific mechanisms that describe how a given cause affects the study outcome. More detailed definitions and discussion of variations of this approach can be found in Salmon (1984), Glennan (1996), and Machamer et al. (2000). Writing from a classical physics perspective, Glennan (1996) defined mechanisms as 'complex systems whose internal parts interact to produce a system's external behavior,' arguing that "events are causally related when there is a mechanism that connects them. A major part of establishing causality includes some aspects of mechanistic understanding. Knowledge of underlying mechanisms, however imperfect, can help clarify which apparently causal relationships are plausible and potentially relevant. For example, mechanistic understanding can help inform how causal effects should be defined (e.g., the appropriate time lag between the exposure of interest and the outcome of interest), and how well one can learn about the causal relationships of interest (e.g., to help understand how plausible the underlying assumptions of studies are, such as whether confounding is sufficiently dealt with). Perfect knowledge of all mechanisms involved in all the effects of air pollution on public health or welfare is currently (and may always be) unattainable."

CAUSAL MODELS

"A concept that brings together the ideas of mechanistic causality and the definition of causal effects as defined using potential outcomes are 'causal models.' Causal models—which aim to establish an understanding of causal effects in part through the clear articulation of causal assumptions—must be distinguished from purely statistical models."

MANIPULATIVE CAUSATION

"When developing a causal model, researchers may seek to evaluate how a proposed causal effect (e.g., an exposure, a regulatory intervention, a particular set of conditions) will potentially impact the outcome of interest. Under this potential outcome framework, when determining whether a given event has a causal relationship with an outcome, such as the event leading to a higher probability of experiencing the outcome, researchers need to specify that actual or hypothetical event. In the manipulative view of causation, researchers are further required to specify a feasible event, that is an intervention that can actually be manipulated (i.e., interventional cause) that would bring about the potential outcome of interest, and only events that are manipulable can be deemed as interventional causes."

Useful Definitions

"Causal inference. The process of estimating, after having postulated a causal model, the effect of a cause on an outcome (health or welfare) from a randomized or observational study (Pearl, 2009). Common approaches include counterfactual causal inference, manipulative causal inference, and mechanistic causal inference."

CONCLUSION

"*Conclusion: A single study will rarely definitively and comprehensively address issues associated with the determination of causality that are examined in ISAs [Integrated Causal Assessments]. A weight of evidence approach—combining assessment of study quality with expert judgment—allows EPA to draw conclusions that integrate scientific findings across multiple study designs and disciplines ... Increased transparency in how evidence is integrated would improve confidence and understanding of ... causal determinations and other conclusions.*"

4. Commentary – Limitations of the National Academies Report

Comment 1: An important strength of this report is its creation by a diverse set of researchers and practitioners. The Committee is to be applauded for reaching key points of consensus that considered the relevant contributions of scientific and statistical perspectives for causal determination. Conspicuous, yet also instructive, is the disparate presentations from statistical and scientific viewpoints in individual sections. This should not be surprising given the active interest during the past four decades in statistical/counterfactual causal inference during which that literature has developed in relative isolation from scientific opinion.

Comment 2: The Report's consideration of philosophical sources contributed importantly to making the point that causation can be studied directly through examination of the underlying mechanisms. Less well represented in the Report is the substantial growth in literature during the past two decades on this topic clarifying the fundamental role of mechanistic causation in expanding the domain of causal methodology. The literature related to accumulated causal knowledge and causal investigations, critical to the advancement of science, remains isolated in neglected silos in the literature. Important sources that should be widely studied include the updated treatment by Craver et al. (2026) discussing the fundamental principles behind mechanistic causal investigations and describing the growing consensus surrounding the mechanistic view of causation.

Comment 3: The Report's section describing manipulative causal inference strongly reflects the statistical perspective developed from randomized experiments. The description in this section fails to mention the wide use of non-randomized controlled manipulations where a manipulation targets a known mechanistic component, and the effect reverses when the manipulation is reversed. Such manipulations provide strong evidence of causation, often stronger than statistical counterfactual methods because they test the productive activities of the mechanism itself and, importantly, readily achieve repeatability. This approach is widely used throughout physiology, biochemistry, neuroscience, and molecular biology (e.g., Suda et al. 2025). Given the EPA's interest in informing regulation of criteria pollutants for human health, this would seem like an important omission.

5. Commentary – Implications of the National Academies Report

Comment 4: The findings of the Report have major implications for the causal methods literature. It is easy to see the finding from the Report as a strong argument for a replacement of the widely used phase "causal inference methods" with more specific terminology that avoids semantic overreach. Reference to "counterfactual causal inference", "mechanistic causal inference", and "manipulative causal inference" are specifically mentioned. This set of distinctions not only provides a more accurate label for the Potential Outcomes and Structural Causal Models (counterfactual) approaches but also points to a plurality of valid methodological approaches for causal studies. Given that Holland and Rubin (1987) knowingly used the label "causal inference" for counterfactual statistical causal inference and that overly broad label has been adopted by all those who have followed is highly problematic.

Comment 5: The Report's declaration that, "A causal effect [is] defined as a property (summary) of the distribution of potential outcomes (e.g., the difference in means [between exposed and non-exposed sets of individuals])" points to a major limitation to the larger objective of causal determination. Counterfactual causal effects provide answers to the dataset-specific question, "What happened as the result of an exposure or intervention?" while causal determination addresses the question, "Is there a mechanism in the real world by which we can expect an exposure will lead to some influence in the future?" When the structures and processes that compose the mechanism are known, we possess repeatable knowledge that is independent of individual datasets and events.

Comment 6: The conclusions from the Academies Report point to the fact that the Potential Outcomes and Structural Causal Model approaches represent evidential systems where the admissible evidence, evidential standard, and evidential processes are determined by statisticians. The approach endorsed by the Report is fundamentally different in that the admissible evidence is that judged to be relevant to the specific situation by scientists, the evidential standards are qualitative categories based on strength of evidence judged by scientists. It is fair to say that the Academies Report recommends a scientific system over a statistical system. This may be the first time such a direct judge has been made in recent times.

6. Beyond the National Academies Report

There now exists a description of an integrative Multi-Evidence Paradigm for Building Causal Knowledge (MEP; Grace 2024) that is compatible with the findings from the National Academies Report, though it was developed independently (Fig. 1). This paradigm has been directly compared to the so-called statistical Causal Inference Paradigm (Grace et al. 2025a). The paradigm has been supported by explicit demonstrations of mechanistic causal inference as well (Grace et al. 2025b).

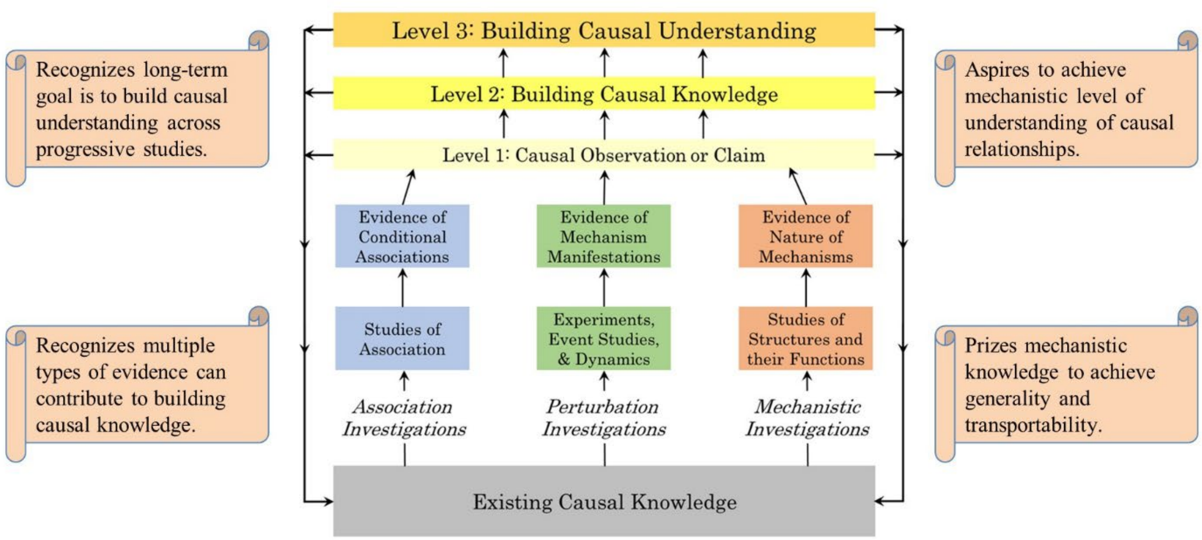

Figure 1. Representation of the Multi-Evidence Causal Investigation Paradigm (MEP; modified from Grace, 2024). Two of the most important features of this paradigm that contrast it with statistical approaches to causal inference are: (1) its expanded focus that includes the long-term goal of building causal knowledge and (2) its recognition that there are multiple forms of evidence that contribute to building causal knowledge, including a key role for mechanistic investigations.

The MEP goes far beyond the realm of causal determination considered by the National Academies Report. Perhaps most important is its long-term focus on developing causal understanding of phenomena by building causal knowledge across studies. To facilitate this later process, formal procedures are developed and demonstrated. Principles and illustrations for real-world causal investigations are now being developed (Grace 2026a), which fills in vital information related to where causal studies are meant to take us.

Most recently there is interest in how causal methods might interface with Artificial Intelligence. A recent manuscript presents a conceptual outline for how causal methods will need to work with narrative descriptions of expert knowledge to achieve causal AI (Kungurtsev et al. 2025). The MEP appears to be well suited as the beginnings of a method that can contribute to the implementation of such an approach to causal AI.

7. Conclusions

The National Academies assessment of frameworks for causal determinations represent a correction to Holland and Rubin (1987)'s decision to describe the Potential Outcomes Model as a method for "Causal Inference" rather than (e.g.) "Statistical or Counterfactual Causal Inference". This mislabeling has spread without correction to the point that the argument is actively made by some and implied by many that mechanistic knowledge cannot be used for causal determination (VanderWeele 2016; Siegel and Dee 2025; Correia et al., 2026) despite direct proofs to the contrary (e.g., Grace et al. 2025b). Of greater potential consequence is the Report's finding that the Potential Outcomes Model (and by implication the Structural Causal Model) represents an incomplete and insufficient framework for causal investigations. Grace (2026a) has recently clarified that this limitation results from the fact that statistical models of causation are not compatible with the complexity of real-world causation but instead represent imagined-worlds where causation is reduced to overly simplistic causal effect estimates. Given the significance of the National Academy Report (and this Synoptic Summary), readers should share this information broadly to alert others to these issues.

References

1. Correia, H.E., Dee, L.E., Byrnes, J.E., Fieberg, J.R., Fortin, M.J., Glymour, C., Runge, J., Shipley, B., Shpitser, I., Siegel, K.J. and Sugihara, G., 2026. Best practices for moving from correlation to causation in ecological research. *Nature Communications*.
2. Craver, C.F. and Darden, L., 2013. *In search of mechanisms: Discoveries across the life sciences*. University of Chicago Press.
3. Craver, C., Tabery, J., and Illari, P. 2026. Mechanisms in Science. *The Stanford Encyclopedia of Philosophy* (Spring 2026 Edition), Edward N. Zalta & Uri Nodelman (eds.), URL = <https://plato.stanford.edu/archives/spr2026/entries/science-mechanisms/>.
4. Grace, J.B., 2024. An integrative paradigm for building causal knowledge. *Ecological Monographs*, *94*(4),p.e1628.
5. Grace, J.B., Huntington-Klein, N., Schweiger, E.W., Martinez, M., Osland, M.J., Feher, L.C., Guntenspergen, G.R. and Thorne, K.M., 2025a. Causal effects versus causal mechanisms: two traditions with different requirements and contributions towards causal understanding. *Ecology letters*, 28(4), p.e70029.
6. Grace, J.B. et al., 2025b. Causal interpretations in ecology can be based on mechanistic knowledge. *Journal of Ecology*, 113, 3084–3098.
7. Grace, J.B., 2026b. *Principles and Illustrations of Real-World Causal Investigations*. Research Brief G2026-1.Kungurtsev, V., Moore, L.C. and Krutsky, M., 2025. “Cause" is Mechanistic Narrative within Scientific Domains: An Ordinary Language Philosophical Critique of" Causal Machine Learning. *arXiv preprint arXiv:2501.05844*.
8. Holland, P.W. & Rubin, D.B., 1987. Causal inference in retrospective studies. *ETS Research Report Series*, 1987, 203-231.
9. Pearl, J., 2009. *Causality*, Cambridge University Press.
10. Schwartz, S. & Prins, S. J. 2025. *Causal Inference and the People's Health*. Oxford University Press.
11. Siegel, K. and Dee, L.E., 2025. Foundations and future directions for causal inference in ecological research. *Ecology Letters*, *28*(1), p.e70053.
12. Suda, H., Asakawa, H., Hagihara, T., Ohi, S., Segami, S., Hasebe, M. and Toyota, M., 2025. MSL10 is a high-sensitivity mechanosensor in the tactile sense of the Venus flytrap. *Nature Communications*, *16*(1), p.8280.
13. U.S. EPA., 2015. *Preamble To The Integrated Science Assessments (ISA)*. U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-15/067.
14. VanderWeele, T. J. 2016. “Commentary: On Causes, Causal Inference, and Potential Outcomes.” *International Journal of Epidemiology* 45: 1809–16.