The Representation of Causality and Causation with Ontologies: A Systematic Literature Review

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ABSTRACT

Objective: To explore how disease-related causality is formally represented in current ontologies and identify their potential limitations. Methods: We conducted a systematic literature search on eight databases (PubMed, Institute of Electrical and Electronic Engendering (IEEE Xplore), Association for Computing Machinery (ACM), Scopus, Web of Science databases, Ontobee, OBO Foundry, and Bioportal. We included studies published between January 1, 1970, and December 9, 2020, that formally represent the notions of causality and causation in the medical domain using ontology as a representational tool. Further inclusion criteria were publication in English and peer-reviewed journals or conference proceedings. Two authors (SS, RM) independently assessed study quality and performed content analysis using a modified validated extraction grid with pre-established categorization. Results: The search strategy led to a total of 8,501 potentially relevant papers, of which 50 met the inclusion criteria. Only 14 out of 50 (28%) specified the nature of causation, and only 7 (14%) included clear and non-circular natural language definitions. Although several theories of causality were mentioned, none of the articles offers a widely accepted conceptualization of how causation and causality can be formally represented. Conclusion: No current ontology captures the wealth of available concepts of causality. This provides an opportunity for the development of a formal ontology of causation/causality.

Keywords: causality, causation, ontology, knowledge representation

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INTRODUCTION

The relationship between cause and effect is one of the fundamental problems in the sciences. In the population health sciences, epidemiologists have discussed causality and causal inference to a great extent [1-3]. Despite the widely discussion of causes, it is not clear that epidemiologists are sharing the same concept. One way to share a common understanding of the structure of information among people and software agents is through the use of what is called an "ontology."

Ontology is a branch of philosophy concerned with the nature of what exists and the relations between entities [4]. In information science, the term has been adopted as the name for formal systems that provide definitions of entities in a given domain and allow informaticians to represent data and their interrelations semantically. In this way, ontologies can be used by computing algorithms to facilitate searching, querying, and/or reasoning about the data [5].

Ontologies describe reality using logical expression as well as plain English without the need to rely on human interpretations that are oftentimes very ambiguous. These descriptions allow information sharing between computer systems as well as humans to better understand the intended meaning of classes and properties within the framework, thus enabling knowledge reusability, integrability, and interoperability [6].

In order to clarify how the terms "causality" and "causation" are used in biomedical ontologies, we performed a systematic literature review. While it is not our intention to provide a novel theory or framework for causality representation, we want to provide a general synopsis on how "causality" and "causation" are conceptualized and ontologically represented. Thus, our focus will be on the nature of causation rather than on causal inference. This will be helpful in the development of a formal ontology for causality and causation. Thus, we wanted to address two questions: (1) How are causality and causation conceptualized (defined, described, and represented) in the health science publications that use ontology as a representational tool? (2) Are there well-developed frameworks that could be used to develop an ontology for causality?

The paper is divided as follows. In section 2, we explain each step of the methodology in detail. Next, we present the results of the retrieved articles in section 3. In Section 4, we discuss our results and the limitations of the literature review. Finally, we conclude and present ideas for future research in section 5. We use the term "causality" to refer to the general concept of a relationship between entities in which the cause makes a difference to the occurrence of the effect. We use "causation" to refer to the process that connects causes to their effects. We use "cause" to refer to the antecedent event in causal processes and "effect" to denote the event that defines the outcome of causal processes (Table 1).

Table 1. Glossary of terms

Term	Definition
Ontology	A data structure of: (1) unique identifiers representing types and natures of entity, (2) labels and meanings related to these identifiers, and (3) specified relationships between the entities [6]
BFO	Basic Formal Ontology (BFO) is an upper-level ontology that provides a structure for development by categorizing entities into two groups: continuants and occurrents [6]
BioPortal	Repository (portal) for the hosting and maintenance of biomedical-related ontologies [81]
Ontobee	A linked ontology data server for publishing and browsing biomedical ontologies in the Open Biological Ontology (OBO) Foundry [82]
OBO Foundry	Repository (portal) for the hosting and maintenance of 'gold-standard' ontologies, adhering to clearly defined principles of best practice [9]
Entity	A domain's object, attribute, or process represented in an ontology
Domain	A specified area of knowledge. For example, the domain of health science and medication adherence domain. In mathematics and computer science domains, it refers to the set of possible input values, and the range is the set of possible output values.
Triplets	An ontology model in which ontology consists of a set of three entities (subject, predicate, object) triplets that codifies a statement about semantic data (e.g., SARS-COV-2 causes COVID-19 disease) [83].
Protégé	Protégé is a free, open-source ontology editor and a knowledge management tool [84]
Causality	A general concept is that there is such a thing as a cause-effect relationship between entities, in which the cause makes a difference to the occurrence of the effect.
Causation	A process that connects causes to their effects.
Cause	An antecedent event in causal processes.

Term	Definition
Effect	An event that defines the outcome of causal processes.
Web Ontology Language (OWL)	A language for defining and instantiating Web ontologies [85].

MATERIALS AND METHODS

Data Source

We conducted this systematic review following the Procedures for Performing Systematic Reviews [7] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8]. Two search strategies were used to retrieve the relevant publications. (1) Electronic Databases: PubMed, Institute of Electrical and Electronic Engendering (IEEE Xplore) Digital Library, Association for Computing Machinery (ACM) Digital Library, Scopus, and Web of Science databases were searched for items published between January 1, 1970, and December 9, 2020. Reference lists from all included studies were searched for potentially relevant studies as well. We included conference papers as some ontology frameworks could only be identified in gray literature. (2) Ontology repositories: OBO Foundry [9], BioPortal [10], and Ontobee [11] were navigated to retrieve published ontologies. However, for an ontology from ontology repositories to be considered for inclusion, a publication in a peer-reviewed journal and/or conference proceedings was required.

Search Strategy

We followed the Cochrane Handbook for the search strategy to maximize literature retrieval [12]. We utilized "OR" to combine our search terms and amended the search command by utilizing the truncation function "*". When used within a search term (e.g., “caus*mod”), this placeholder function allows databases to retrieve words that include the letters before and after the asterisk and any combination of characters in lieu of the asterisk (e.g., cause model, causal model, causation model, and so on). Two different research concepts were used: (1) Cause: It has many related MeSH descriptions in clinical and epidemiology; however, the following terms are semantically selected: “causality,” “causation,” “causal mechanism,” “causal explanation,” “pathogenesis,” “pathogenic mechanism,” “pathogenetic mechanism,” “etiology,” and “etiopathogenesis.” (2) Ontology: No MeSH terms were detected, but the following terms are used: “ontology,” “ontology-based model,” “ontological approach,” “ontological framework,” “ontology representation,” and “formal representation.” The search strategy is provided in the supplementary material (Supplement Table 1).

Inclusion Criteria

We selected papers that were based on research and not merely a report or discussion of an existing model. We further restricted the search to studies that formally represent causality and/or causation in the biomedical domain using ontology as a representational tool. We excluded proposed (future) ontologies, studies on diseases without reference to etiology, publications on causality in areas other than biomedicine, studies that address data mining, gene annotation, and prediction using ontologies, ontologies that were inaccessible, not written in machine-readable languages such as Ontology Web Language (OWL), or not published in a peer-reviewed journal and/or conference proceedings.

Data Extraction and Synthesis

Our data extraction and synthesis goal was to record all important data obtained from the primary papers accurately. Thus, two authors (S.S. and R.M.) independently screened the title and abstract and reviewed the full text between October 2020 and March 2021, following the inclusion and exclusion criteria. As some information was not explicitly mentioned and reaching the author(s) was impossible, assessing the agreement between measures was essential. Thus, a test-retest process [13] was performed to measure intra-rater reliability, in which each researcher performed a second extraction from a random selection of five primary studies at a different point in time to check data extraction consistency and accuracy. The correlation between the two sets of results was calculated using intraclass correlation coefficient (ICC), in which values less than 0.5 represents poor reliability, between 0.5 and 0.75 indicates moderate reliability, between 0.75 and 0.9 reveals good reliability, and greater than 0.90 is indicative of excellent reliability [13]. The results unveiled no inconsistencies (ICC >0.90). In addition to measuring intra-rater reliability, we calculated the inter-rater reliability (IRR)—the agreement between the measurements obtained by the two evaluators (S.S and M.R.). The Cohen kappa (κ) statistic was used to test for Inter-Rater Reliability (IRR) with values ≤ 0 indicating no agreement, 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement [14]. Discrepancies were resolved by discussion until consensus was reached and/or by consulting a third reviewer (OD).

Data were extracted according to a predefined extraction form (Supplement Table 2). This form allowed us to record full details of the included studies and to be specific about how each of them addressed our research questions. In addition, the reasons for exclusion were recorded. Each ontology was downloaded in Protégé [15] and checked for logical consistency by performing classification with the HermiT reasoner [16]. HermiT can determine the consistency of any given ontology and identify the subsumption relationships between its classes [17]. This reasoner is based on a hypertableau calculus which provides more efficient reasoning than previously-known algorithms [16]. The central aspect of this algorithm is that it is less non-deterministic than other existing tableau algorithms and can classify ontologies that no other reasoner can currently process in a fast manner [17].

Causality-related terms were represented manually in triplet structure (Table 3), as in "subject, predicate, object" [18]. Subject and object were further specified whether they were classes (i.e., entities) or individuals (i.e., instances of classes). This structure allowed us to know which part represents the class, which part is the relation, and which is the instance. The subject (i.e., domain) can be a cause (e.g., SARS-COV-2) or effect (e.g., Covid-19 disease). Predicate, i.e., property or indicator verb of causation, defines the type of relationship that exists between the subject and object (e.g., caused by, causes). The object (i.e., range) is an entity or value that describes the subject through the relation that connects them. The object is similar to the subject in that it can represent cause or effect. The object of one triplet can become the subject of another triplet or vice versa (figure 1).

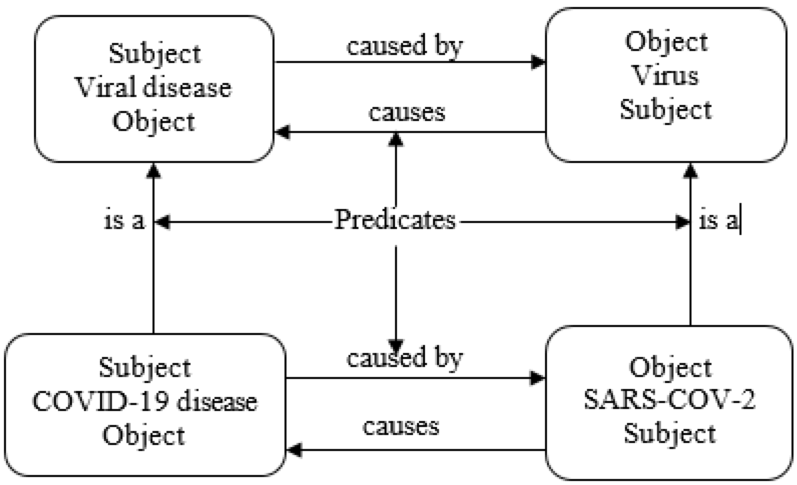

Figure 1: Example of graphical representation of a triplet structure with subjects, predicates, and objects

Due to the vast heterogeneity in study methodology, settings, ontology types, and outcomes, a quantitative data synthesis using a meta-analytic approach is not feasible. Therefore, eligible studies were evaluated in a narrative format using some statistical analysis when feasible.

Quality Assessment

Two authors (SS, RM) independently assessed the likelihood that the selected articles will add value to this review using a checklist of 23 quality criteria. Fourteen criteria were adapted and modified from [7,19-24], and the remaining criteria were added by the authors according to this review's topic and scope. The criteria are specified in Table 3. We were mainly interested in evaluating the quality of reporting and documenting of each primary study, the degree of reusability of the developed ontologies, the extent of covering methods and evaluation, and the quality of representing the usefulness of the finding to the research community and practice. We devised a three-grade scale to score the quality criteria, either as "yes," "to some extent," or "no." We added the answer "to some extent" to give some credit to the limited information available in some papers that helps answer the assessment questions. We assigned a numerical value to each quality assessment question (yes = 1, no = 0, and to some extent = 0.5). We calculated a "quality assessment score" for each study by summing up the scores for all questions for that study. We then divided the total score for each study by the total number of items and multiplied by 100. To create the overall quality grades, we used the following definitions: high quality for studies scored between 80-100%; medium quality for studies scored between 50-80%; low quality for studies scored between 0-50%.

The quality assessment of studies was done in parallel with data extraction. The Cohen kappa (κ) statistic was used to test for Inter-Rater Reliability (IRR) with values ≤ 0 indicating no agreement, 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement [14]. Microsoft Office Excel 2016 was used to test the IRR between the two reviewers. We did not plan to exclude any studies based on their quality scores alone, as they might cover essential knowledge related to causality and causation that might be worth considering even if they were poorly scored.

RESULTS AND ANALYSIS

Search Results

The search returned 8,480 articles via electronic databases and 21 articles from online medical ontology repositories. After removing duplicates, 4,304 remaining titles and abstracts were read by two reviewers (SS, RM). Based on the selection criteria, 661 articles were retained for a more detailed review. A full-text assessment of these studies led to the exclusion of 611 studies. The reasons for exclusion are depicted in the flow diagram (Figure 2). A total of 50 articles met all of the study inclusion criteria. The kappa statistic for the title and abstract screening was 0.78 (substantial agreement) for the first round and 0.89 (almost perfect agreement) for the second round. For the full-text screening, it was 0.75 (substantial agreement) in the first round and 0.91 (almost perfect agreement) in the second round before the consensus agreement was reached. The PRISMA process was followed and is outlined in Figure 2.

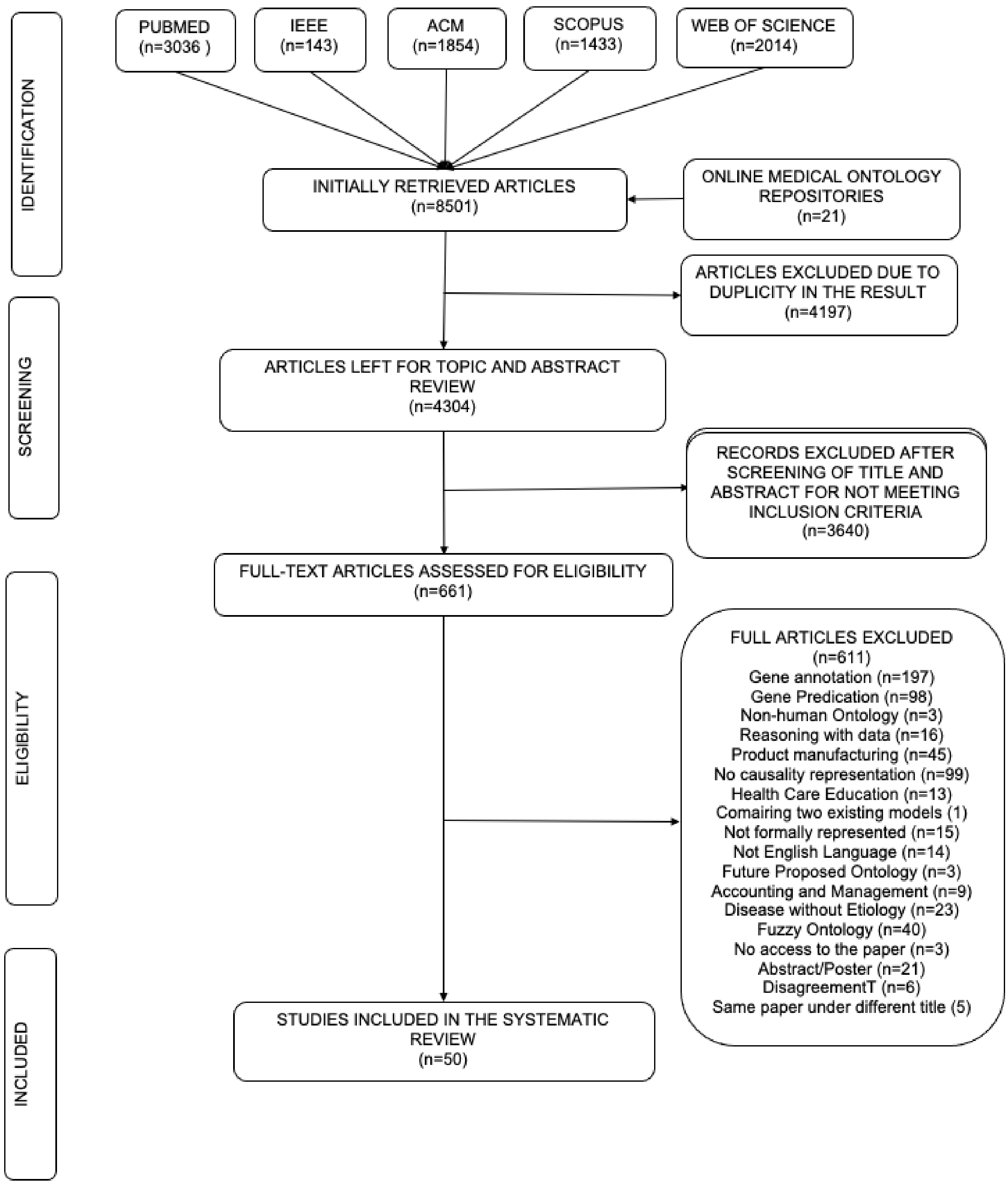

Figure 2. Flow diagram of search for and selection of relevant publications

Study Characteristics' Results

A summary of the general characteristics of included articles is shown in Table 2. A full description of the 50 included articles is available in Supplement Table 2. Publication years ranged from 2003 to 2020, with an overall increase in articles published more recently. Only slightly more than half of the included publications were peer-reviewed (58%, 29/50). With respect to the different targeted disorders, nervous system (neurological) disorders were most frequently represented (14%, 7/50, e.g., Alzheimer's disease). The dominant type of ontology was domain type ontology (76%, 38/50), followed by application type ontology (14%, 7/50), and reference type ontology (10%, 5/50). Only 42% (21/50) of ontologies are accessible in one of the ontology repositories. The majority of studies used Web Ontology Language (OWL) to formally represent the domain knowledge (88%, 44/50), and 40 publications adopted Protégé to encode the domain-specific knowledge (80%, 40/50).

Table 2. Study Characteristics

Category	Number (Percentage)
Publication type	
Peer-reviewed paper	29(58)
Conference paper	21(42)
Publication Year	
2000-2005	4(8)
2006-2010	9(18)
2011-2015	15(30)
2016-2020	22(44)
Domain category	
Nervous system (neurological) disorder	7(14)
Alzheimer's diseases (29%, 2/7)	2(29)
Epilepsy and Seizure	1(14)
Parkinson's Disease	1(14)
Non-specified mental disease	3(42)
Infectious diseases	7(12)
COVID-19	1(14)
Pneumonia	1(14)
Dengue Fever	1(14)
Schistosomiasis	1(14)

Non-specified infectious disease	3(42)
Endocrinology and metabolic disorders	4(8)
Diabetes Mellitus	2(50)
Lipoprotein dysregulation	1(25)
Pancreatic Lesions	1(25)
Hypersensitivity and Autoimmune Diseases	4(8)
Adverse reaction	2(50)
Allergy	1(25)
Rheumatoid disease	1(25)
Radiology	2(4)
Clinical pathway	1(2)
Non-Specified Chronic Disease	9(18)
Ontology Type	
Domain ontology	38(76)
Application ontology	7(14)
Reference ontology	5(10)
Ontology Representing Language	
Web Ontology Language (OWL)	44(88)
DOGMA	1(2)
Frame-CG (FCG)	1(2)
XML	1(2)
Ontology Editor	
Protégé	40(80)
WebKB	2(4)
Neo4j	1(2)
Hozo	1(2)
NS	5(10)
Upper-Level Ontology	
Basic Formal Ontology (BFO)	14(28)
Yet Another More Advanced Top-level Ontology (YAMATO)	2(4)
Descriptive Ontology for Linguistic and Cognitive Engineering	1(2)

(DOLCE)	
Domain Upper-Level Ontology (BioTop)	1(2)
NA	32(64)
Application Dependency	
Application Semi-Independent	32(64)
Application Knowledge Base	10(20)
Application-Independent	8(16)
Approaches to Identify Concepts	
Top-Down Approach (starts by modeling top-level concepts, which are then refined in the next step).	9(18)
Middle-Out Approach (starts with the certain middle-level concepts and then applies the bottom-up or the top-down methods appropriately as needed).	4(8)
Hybrid Approach (a combination of top-down and bottom-up strategies).	4(8)
Bottom-Up Approach (starts from the most specific concepts and builds a structure by generalization).	1(2)
NS	32(64)
Accessibility in Ontology Repository	
Accessible	21(42)
Inaccessible	29(58)
Using Existing Ontology	
Ontology Integration	26(52)
NS	24(48)
Ontology Building Method	
Authors' Engineering Methodology	10(20)
Principles of the Open Biomedical Ontologies (OBO) Foundry	4(8)
METHONTOLOGY	4(8)
Seven-Step Method	6(12)
Best Practices for Ontology Design	3(6)
NS	23(46)
Ontology Evaluation Approaches	
Application or Task-Based Evaluation	15(30)

Criteria or Used-Based Evaluation	12(24)
Gold Standard-Based Evaluation	6(12)
Data-Driven Evaluation	5(10)
NS	12(24)

NS=Not Specified

Quality Assessment Results

The quality assessment of the 50 reviewed papers is summarized in Table 3. Only 16 articles (32%, 16/50) were rated as high quality. Inter-rater agreement between the two assessors was almost perfect (k=0.895). All of the included papers clearly articulated their authors' aims, objectives, rationale, the domain of interest and had a well-written discussion and conclusion (100%, 50/50). The authors of the vast majority of the included papers specified their knowledge representation language (94%, 47/50) and the knowledge management tool (90%, 45/50).

Twenty-seven out of 50 papers contained information on the methods used for ontology development (54%), only 24 articles had a specific information regarding the ontology metrics (i.e., number of classes, properties, axioms, type of axioms, rules, individuals) (48%), 16 had a well-documented knowledge acquisition strategy (32%, 16/50), 38 had well-reported sources of gathered knowledge (76%, 38/50), and 19 had well-defined approaches to identify concepts (38%, 19/50). Only 42% (21/50) of ontologies are open and freely available in one of the online medical repositories. The rest was available only through request. Twenty-eight out of 50 ontologies had a well-organized, hierarchical structure (56%), including those developed based on foundation ontology (34%, 17/50). The remainder did not incorporate the properties or relationships between entities (44%, 22/50). Only six ontologies (14%, 7/50) included clear and non-circular natural language definitions for most of their entities. Most ontologies are built without foundational ontologies (64%, 32/50). However, half of them integrated some parts or full ontologies in their frameworks (52%, 26/50). Eight models (16%, 8/50) included a relation ontology (RO) model to represent the relationships among entities.

The majority of included ontologies were evaluated (76%, 38/50), either through software applications or use-case scenarios. Most of the authors of the included articles (82%, 41/50) offered a special recommendation for future work and improvement. Unfortunately, more than 64% (32/50) did not explicitly discuss their models' limitations. However, most ontologies were assessed as having a potential research impact (98%, 49/50).

Table 3. Quality assessment of included articles

Authors	**Q1** [24]	**Q2** [7]	**Q3** [19, 24]	**Q4***	**Q5** [24]	**Q6** [20, 24]	**Q7** [21, 24]	**Q8** [24]	**Q9***	**Q10***	**Q11***	**Q12***	**Q13** [24]	**Q14** [24]	**Q15** [24]	**Q16** [24]	**Q17** [20]	**Q18***	**Q19***	**Q20***	**Q21***	**Q22** [21, 22]	**Q23** [23]	**Quality (Score)**
[25]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100 (23)
[26]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100 (23)
[27]	1	1	1	1	1	1	0	0	0	0	0.5	0	0	0	0	1	1	1	0	0	1	1	0	50 (11.5)
[28]	1	1	1	1	1	1	1	0.5	1	1	0.5	1	0	1	1	1	1	1	1	0	1	1	1	87 (20)
[29]	1	1	1	1	1	0	0.5	0.5	1	0	0.5	0	0	0	0	1	1	1	1	0	0	1	0	54 (12.5)
[30]	1	1	1	1	1	1	0.5	0.5	0	0	0.5	0	0	0	0	1	1	1	0	0	0	1	0	50 (11.5)
[31]	1	1	1	1	1	1	0.5	0	1	0	0.5	0	0	1	0	0.5	1	1	1	1	1	1	0	67 (15.5)
[32]	1	1	1	1	1	1	1	0	1	1	1	0	0	0	0	1	1	1	1	0	1	1	0	70 (16)
[33]	1	1	1	1	1	1	1	0	1	1	0.5	0	0	0	0	0.5	1	1	1	0	0	1	0	61 (14)

[34]	1	1	1	1	1	1	1	1	1	0	1	0	0	0	0	0.5	1	1	1	0	1	1	1	72 (16.5)
[35]	1	1	1	1	1	1	1	0	1	0	1	0	0	0	0	0.5	1	1	1	0	1	1	1	67 (15.5)
[36]	1	1	1	1	1	1	1	0.5	1	0	1	0	1	1	0	1	1	1	1	1	1	1	1	85 (19.5)
[37]	1	1	1	1	1	1	0.5	0	0.5	1	0.5	0	0	0	0.5	1	1	1	1	0	1	1	0	65 (15)
[38]	1	1	1	1	1	1	1	0.5	1	0	0.5	0	0	0	0	1	1	1	1	0	1	1	0	65 (15)
[39]	1	1	1	1	0	0	1	1	1	0	1	0	0	1	0	1	1	1	0	0	1	1	0	61 (14)
[40]	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	1	1	1	87 (20)
[41]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	0.5	1	1	1	0	1	1	1	85 (19.5)
[42]	1	1	1	1	1	1	1	0.5	1	0	0	0	0	0	0	0	1	1	1	0	1	1	0	59 (13.5)
[43]	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	0	1	1	0	78 (18)
[44]	1	1	1	1	1	1	0.5	0	1	1	1	0	1	0	0	0.5	1	1	1	1	1	1	0	74 (17)
[45]	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	1	1	1	0	83 (19)
[46]	1	1	1	1	1	1	0	0	0	0	0	0	0	1	1	1	1	1	1	0	1	1	0	61 (14)

[47]	1	1	1	1	1	1	0.5	0	1	0	0	0	0	0	0	0.5	1	1	0	0	1	1	1	57 (13)
[48]	1	1	1	1	1	1	0.5	0	1	0	1	0	0	1	1	0.5	1	1	0	1	1	0	0	65 (15)
[49]	1	1	1	1	1	1	1	0	0.5	1	1	0	1	0	0	1	1	1	1	0	1	1	0	72 (16.5)
[50]	1	1	1	1	1	1	0.5	0	1	0	0.5	0	0	0	0	1	1	1	1	0	1	1	0	61 (14)
[51]	1	1	1	1	1	1	0.5	0	1	1	1	0.5	1	1	0	1	1	1	1	1	1	1	0	83 (19)
[52]	1	1	1	1	1	0	0	0	0	1	1	0	1	1	1	1	1	1	1	1	0	1	0	70 (16)
[53]	1	1	1	1	1	1	0	0	1	0	1	0	1	0	0	1	1	1	1	1	1	1	0	70 (16)
[54]	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	0	87 (20)
[55]	1	1	1	1	1	1	0	0	0	0	1	0	1	0	0	0.5	1	1	1	0	0	1	1	59 (13.5)
[56]	1	1	1	1	1	1	1	1	1	0	1	0	1	0	0	1	1	1	0	0	1	1	1	74 (17)
[57]	1	1	1	1	1	1	1	0	1	1	0	0	0	1	0	0.5	1	1	1	0	1	1	1	72 (16.5)
[58]	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	1	1	1	87 (20)
[59]	1	1	1	1	1	1	1	1	1	1	0.5	0	0	0	0	0.5	1	1	0	0	0	1	0	61 (14)
[60]	1	1	1	1	1	1	0.5	0.5	1	0	0.5	0	0	0	0	0.5	1	1	1	0	1	1	0	61 (14)

[61]	1	1	1	1	1	1	0.5	0.5	0.5	0	0.5	0	0	0	0	0.5	1	1	1	0	1	1	0	57 (13)
[62]	1	1	1	1	1	0	1	0.5	0	0	1	0	1	0	0	0.5	1	1	1	0	1	1	1	65 (15)
[63]	1	1	1	1	1	1	0.5	0	1	0	0.5	0	0	0	0	0.5	1	1	0	0	1	1	0	54 (12.5)
[64]	1	1	1	1	1	1	1	0	1	0	0.5	0	0	1	1	0.5	1	1	1	1	1	1	0	74 (17)
[65]	1	1	1	1	1	1	0.5	1	1	0	1	0	1	1	1	1	1	1	1	1	0	1	0	80 (18.5)
[66]	1	1	1	1	1	1	0.5	0	0.5	0	1	0	1	1	0	1	1	1	0	1	1	1	1	74 (17)
[67]	1	1	1	1	1	1	0.5	0	0.5	1	1	0	1	0	1	0.5	1	1	1	1	0	1	0	72 (16.5)
[68]	1	1	1	1	1	1	0.5	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	89 (20.5)
[69]	1	1	1	1	1	1	1	1	1	0	1	0	1	1	0	0.5	1	1	1	1	1	1	1	85 (19.5)
[70]	1	1	1	1	1	1	1	1	1	0	1	0	1	0	0	0.5	1	1	1	1	0	1	0	72 (16.5)
[71]	1	1	1	1	1	1	1	1	1	0	1	0	1	1	0	0.5	1	1	1	1	1	1	0	80 (18.5)
[72]	1	1	1	1	1	1	1	0.5	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	89 (20.5)

[73]	1	1	1	1	0	1	0.5	0.5	1	0	0.5	0	0	1	1	0.5	1	1	0	0	1	1	0	61 (14)
	1	1	1	1	1	1	0.5	0.5	0.5	0	1	1	0	1	1	1	1	1	0	1	1	1	0	76 (17.5)
NO% (n)	0	0	0	0	4 (2)	8 (4)	10 (5)	46 (23)	16 (8)	64 (32)	10 (5)	84 (42)	52 (26)	50 (25)	64 (32)	2 (1)	0	0	24 (12)	58 (29)	18 (9)	2 (1)	66 (33)	
YES% (n)	100 (50)	100 (50)	100 (50)	100 (50)	96 (48)	92 (46)	54 (27)	30 (15)	74 (37)	36 (18)	60 (30)	14 (7)	48 (24)	50 (25)	34 (17)	56 (28)	100 (50)	100 (50)	76 (38)	42 (21)	82 (41)	98 (49)	34 (17)	
TSE% (n)	0	0	0	0	0	0	36 (18)	24 (12)	10 (8)	0	30 (15)	2 (1)	0	0	2 (1)	42 (21)	0	0	0	0	0	0	0	

1=YES, 0=NO, 0.5=To Some Extent (i.e., TSE); * Authors of this paper; Q1: Is the ontology's full name, including the acronym reported? Q2: Are the aims and objectives of the primary study clearly stated? Q3: Is the rationale explicitly specified? Q4: Is the domain of the developed ontology mentioned? Q5: Is the knowledge representation language specified? Q6: Is the ontology editor or knowledge management tool reported? Q7: Are the methods and proposed techniques clearly explained? Q8: Are Knowledge acquisition documented? Q9: Are sources of the gathered knowledge reported? Q10: Do the approaches use to identify concepts specified? Q11: Does the ontology provide definitive and exhaustive classification of entities? Q12: Does the ontology include clear and non-circular natural language definitions for all/most of its entities? Q13: Are the ontology metrics specified (i.e., number of classes, properties, axioms, type of axioms, rules, individuals)? Q14: Did the study reuse/incorporate an existing ontology (full or part)? Q15: Is the model built based on a foundation ontology/upper-level ontology? Q16: Are the ontology relationships represented? Q17: Did the study discuss the resulted ontology? Q18: Is the article presented a conclusion related to the research aims and objectives? Q19: Is the ontology evaluation carried out? Q20: Is the ontology open, free, and universally implementable? Q21: Are the recommendations on future work and improvement specified? Q22: Are the contributions and potential research impacts specified and reported? Q23: Are the study's limitations explicitly discussed?

Causality Representation Results

Indicator Verb of Causality

One hundred thirty-one indicator verbs of causality were manually extracted from the selected ontologies and represented in Triplet form (Supplement Table 3). The majority of these relations are asserted between classes to provide a standardized vocabulary for knowledge bases. Representing the causality-related terms in triplet form was done to identify how ontologies link causes to their effects. Examples of these verbs are "cause", "is responsible for", "associated with", "induces", "is triggered by", "influences", "leads to", "has etiology", "may cause", "can cause", and "may effect". Causality also presents in the form of necessary and sufficient causes (e.g., Infertility due to extra testicular causes, as represented in [61].

Nature of Causality

Authors of most of the included papers did not specify neither the nature (i.e., what type of entity in reality) of the cause nor that of the effect (72%, 36/50). Moreover, 86% (43/50) do not provide a clear and non-circular natural language definition of cause and effect. For example, Chen and Hadzic [27] defined “etiology” as a subtype of the ontology class “lipoprotein,” which obviously does not make biological sense. Another example is that “allergen” is categorized as a subclass of “allergy,” which is also nonsensical [33]. Among those that defined the nature of cause (28%, 14/50), 85% (12/14) used BFO as an upper-level ontology to define the cause as in [25] in which etiology characterized as a material entity, and as in [72], in which cause (e.g., medical intervention) and effect (e.g., causal adverse event) are defined as processes.

Types of Causality Representations

We identified seven distinct but not mutually exclusive aspects of how causality was conceived and represented:

1. Association. Six articles (12%, 6/50) represented causality in the form of "A is associated with B." For example, Lin and Sakamoto [28] used the relation "associated-with" between genetic factors and disease in order to identify genetic susceptibility to human disease. Causal terminology is avoided and replaced by statistical terms (association as in correlation). Another interpretation of "association" would be simple co-occurrence without statistical connotation.
2. Determinism. Thirty articles (60%, 30/50) used an assertion of the form "if A, then B." For example, "radiation causes cancer", "treatment causes side effect" [49] and "herbs treat disease" [56]. The assumption seems to be that causation is like a natural law: whenever the cause occurs, it is safe to infer that the effect will occur.
3. Temporal order. Five articles (10%, 5/50) used the form "A causes B if A precedes B." Temporality is a necessary criterion for a causal association between an exposure and an outcome, in which a cause should precede its effect [46].
4. Disposition. The authors of seven articles (14%, 7/50) seemed to assume that causal relations are not dependency relations between entities (objects or events). Instead, causation is reflected in the circumstances in which objects express and generate

their powers. For example, adverse effects can be conceived as a disposition of a patient to adversely respond to exposure to a drug [25].

5. Causal chain. Two articles (4%, 2/50) structured causality as a series of events, each of which is caused by the immediately previous event, e.g., adverse series of events [71] or a pathogenetic process [70]. This view is reminiscent of the way causes of death are listed on death certificates and how causality is conceived in some legal contexts.
6. Influence. The authors of two articles (4%, 2/50) conceptualized causality as "process A influences (positively_influences, negatively_influences) the occurrence of B," such as in [31], in which the "nicotine_withdrawal positively_influences smoking_relapse" refers to a scenario in which an increase in withdrawal severity would tend to increase smoking relapse.
7. Production. The authors of three papers (6%, 3/50) used a representation in the form "A causes B if A produces B." For example [36,39], used "produces" and "triggers" to represent the concept of causality.

DISCUSSION

In this systematic review on the causality and causation representations using ontology as a representational tool, we reviewed and narrowed over 8480 records to a final set of 50 articles. Overall, we found that causality and causation have been conceived and represented in different and incompatible meanings. None of the existed ontologies appeared to provide the detail needed to adequately explain the exact nature of causality and causation in each context.

One of the most revealing findings from this systematic review was related to the nature of causation and causality. Several ontologies lacked semantic standards and were created de novo to represent this domain. These ontologies are information silos in the same way as some softwares are siloed within enterprise applications. Thus, they are prima facie unable to resolve the interoperability dilemma that ontologies are supposed to resolve [6]. Most of the terminologies used to represent causation and causal relations are varies based on the purpose of the ontology at hand and its domain. For example, the relation indicated by the verb "infect" may be useful in the medical domain but will have little or no use in the computer domain [74], except perhaps in the context of a computer virus "infecting" a machine. The term "causes" itself is often replaced with causal words, such as "produces" [61], "induces" [72], "influences" [31], "bring about" [75], "is a result of" [37], "is responsible for" [60]. Causality is also expressed in the forms of sentence connectives (e.g., because, since), prepositions (e.g., due to, because of), and lexical causatives (e.g., drug-associated with Adverse Effect (AE)) [54] that jointly encode both cause and effect.

Remarkably, many studies used the terms "causality," "causation," and "cause and effect" as synonyms. However, those who use them may have different meanings and concepts in mind. Many studies appear to define these terms inconsistently or ignore their definition entirely. Sometimes, a definition of "cause" provides no more information about the nature of cause than does the term "cause" itself. For example, in [38], "cause" is defined as "the reason why some event happens."

Another example is that the "etiology of lipoprotein dysregulation" is defined as "a possible cause of lipoprotein dysregulation" [27]. Such definitions are similar to the notion that a cause is something that produces or creates an effect [76], without additional explanation of what "produce" and "create" actually mean. We suspect that in most cases, investigators refer to "causal production," where a cause brings about its effect in the sense of being responsible for it. Causes simply defined as "A causes B if A precedes B in time" would allow for the inference that the rooster's crowing makes the sun rise.

Discussions of the meaning of causality often include the concepts of necessitation and sufficiency. For example, some authors of the papers we reviewed seem to claim that the effect cannot happen without a certain cause [38,77]. This proposition is that of a cause being necessary for the effect to occur. A sufficient cause, on the other hand, does not need to be necessary for the effect to occur (other causes might do the same) but it does not need any other ingredient to be causal. Rothman [78] has proposed a model of causation for health research that distinguishes between necessary and sufficient causes. He proposes that sufficient causes are almost always constellations of multiple factors that are causal when acting in concert, but only some of which might be necessary to make such constellations sufficient.

Most causal information in the medical domain is represented in uncertain or vague statements, the truth value of which cannot be established or inferred in all cases. With the current semantic structures of the ontology languages (e.g., Web Ontology Language (OWL)), any statement must be either true or false. This statement should hold for all individuals/instances of that class. Thus, it is difficult, and perhaps even impossible, to represent probabilistic causal relations. Although, causal relationship between exposure to radiation and breast cancer is firmly established, not every person with breast cancer has been exposed to radiation. Therefore, building an ontology-based application, such as a clinical decision support system (CDSS) based on this expression, might exclude the diagnosis of breast cancer if the patient hadn't been exposed to radiation. A mismatch between the intended meaning and the formal model would lead to an unreliable automated reasoner.

Although, several approaches in the reviewed literature aim to overcome this rigidity of the semantic structure of current ontologies, they are however, inconsistent with their representation in a given area, and researchers tend to generate their own model. The authors of [79] for example uses both existential restrictions, such as, "A causes some B" (e.g., radiation causes breast cancer in some cases) and universal restrictions, such as "A causes only B" (e.g., radiation causes only breast cancer). The authors of [30,33,53] minimize the deterministic assumptions in favor of probabilism, where the verbs indicating causality such as "cause" and "effect" are replaced by "may-cause" [53], "can-cause" [30], and "may_affect" [33]. Causality does not always require that A must be present if B is present, and it also does not require that B is present if A is present. Probabilistic verbs still indicate a statistical association between cause and effect. In essence, a causal ontology should allow for the representation of relationships that denote possibility, not necessity. Theoretical underpinnings of such representation could come from disposition accounts of causation [6,80]. On such accounts, radiation and breast cancer are not cause and effect, respectively, but represent a unit of causal change. When placed in the situation of being exposed to radiation, the breast tissue tends to develop cancer.

REVIEW LIMITATIONS

Due to the fact that the recommendations for reporting of ontology development [24] came after the development of most of the included ontologies, it is possible that some aspects of development were not reported and hence missing from our review. Moreover, the quality assessment of whether the identified ontologies were evaluated or not was restricted only to the information written in the given paper without searching for any subsequent ontology evaluation papers the authors of this paper would have been done, thus it might be not captured in our review.

CONCLUSION

In this systematic review, we synthesized data from 50 articles on the existing biomedical ontologies that include concepts of causality and causation. In summary, we found that causal relationships are represented in ontologies in very heterogeneous ways, and very little attention is being paid to the need to define the causal terminology and concepts employed. Although there are many published medical ontologies that include entities related to causality and causation, we are far from having established an explicit common conceptualization of the causality domain. The diversity and inconsistency in causality representation pose a challenge for the integration and reuse of these existed ontologies. Therefore, and in future work, we aim to stand up our approach and bridge the gaps of current works by forming definitions and classifying this heterogeneous information to avoid idiosyncrasies to improve domain knowledge interoperability and provide consistency in data description. We will concentrate on developing an ontology that domain experts and researchers can be used to assist in the detection of the cause of diseases. The potential practical implications and future recommendations based on this review are summarized in Table 4.

Table 4. Implication and Future Recommendation of the Study

Suggestion	Implications
Developing a robust ontological framework for representing causality and causation	Causality representation using ontology as a representational tool can serve as a definitive and comprehensive source of causality-related knowledge. It can be utilized in healthcare decision-making, intervention development, detection risk factors, capturing current and future findings from different applications and publications, etc.

Gold standard for Ontology evaluation	It would be valuable to further evaluate the Ontologies to form a more coherent picture of their effectiveness in representing causality and causation. A gold standard for Ontology evaluation is needed to draw a clear conclusion on these ontologies' efficacy and determine the best ways to guarantee reusing or designing a new interoperable framework for causality and causation. The literature also needs to focus more on reporting accurate information about ontology evaluation to assessing the effectiveness of these frameworks and facilitating their successful adaptation, and implementation (e.g., designing applications)
Future Review	Due to the lack of information regarding ontologies development and documentation in most studies, especially for those published before issuing the Minimum Information for Reporting an Ontology (MIRO) guidance [24], some important information was missed. Therefore, we recommend doing another review when there are more studies available in the future. In the future, we can increase the quality of the review by including only the open access ontologies.
Methods to Build Ontologies	It would be valuable to examine how different methods and approaches for ontology engineering could affect causality representations reported in the study. A comparison between different methods could be helpful to draw a clear conclusion.
Interoperability	Ontology reusability and integration are the fundamental principles of interoperability between diverse systems and groups of people. Therefore, national and international collaborations between developers are highly recommended. A study that accesses the association between interconnectivity and ontology reusability is suggested.

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