PRION
2025, VOL. 19, NO. 1, 1–16
https://doi.org/10.1080/19336896.2025.2464753

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Chronic Wasting Disease Research in North America: A systematic review highlighting species-wise and interdisciplinary research trends

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ABSTRACT

Chronic Wasting Disease (CWD) research has experienced significant growth, spanning diverse disciplines such as genetics, immunology, modelling, and behaviour. To gain a broad understanding of the changes in CWD research focusing cervids, we analysed temporal trends in study location, species, genus investigated, infection types, and population type since the discovery of CWD in 1980s. Our findings indicate that Colorado, USA, published the highest number of articles, followed by Wisconsin, and publication numbers correlated with reported CWD cases in states/provinces. *Odocoileus* emerged as the most studied genus. Wild populations are studied more commonly than captive populations. Keyword analysis of transmission types shows the discovery of novel transmission modes in the recent past. We also used a novel approach to categorize studies into five themes: field-based, lab-based, math/analytics/modelling-based, management-based, and human dimensions. Overall, most studies captured had a lab-based component. The interdisciplinary or transdisciplinary nature of major disciplines and evolving trends in keywords, particularly the increased reliance on genetics/genomics, accentuate the beginning of using genomics to under and tackle CWD at a fundamental scale. Encapsulated in our analysis, these dynamic changes offer valuable insights for navigating CWD through scientifically informed proactive management decisions in conjunction with existing surveillance efforts not only for the commonly studied species but also for potentially susceptible species.

ARTICLE HISTORY
Received 26 July 2024
Revised 2 December 2024
Accepted 13 January 2025

KEYWORDS
Cervids; CWD research trends – interdisciplinary approach; keyword analysis; proactive management; spatiotemporal and genetic data repository

Introduction

Modern wildlife management is at the forefront of addressing the dynamic interplay between species and their environments, particularly in the face of emerging diseases. Effectively managing wildlife diseases is not just a matter of ecological balance. It is a vital strategy to mitigate the risks posed by emerging infectious diseases, which have the potential to disrupt ecosystems, shift public support for wildlife conservation, burden global economies, and pose a significant threat of zoonotic transmission [1]. Chronic Wasting Disease (CWD) in cervids stands out as an example of one such disease. An interdisciplinary perspective that integrates various fields, along with a transdisciplinary approach rooted in collaboration and communication across specialities to address complexities [2], could facilitate effective management actions as researchers delve into the challenges of wildlife disease. This systematic review explores the multifaceted research conducted over 20 years since CWD became an epidemic, especially in North America.

CWD, a transmissible spongiform encephalopathy (TSE), is a progressive, contagious, and incurable neurodegenerative disease. Other TSEs include variant Creutzfeldt-Jakob disease, which infects humans, transmissible mink encephalopathy in ranched mink, scrapie in sheep and goats, and bovine spongiform encephalopathy infecting cattle [3,4]. TSEs are caused by the misfolding of a common cell-surface protein called prion protein (PrP^C) into the infectious conformation (PrP^{CWD}), which leads to the accumulation of prions in the brain and, consequently, irreversible tissue damage and death [5]. The gene *PRNP*, which encodes for PrP^C, is conserved across mammalian phylogeny, and TSEs have emerged independently in several major mammalian groups [6]. Misfolding of PrP^C to PrP^{CWD} can occur spontaneously because of somatic or germ-line mutations in the PRNP gene, can be inherited from parents, or can be acquired from exposure to exogenous PrP^{CWD} prions directly from infected individuals or indirectly from the environment [7,8]. Clinical signs

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/19336896.2025.2464753

of infection appear months or years after exposure, in the terminal stage of CWD progression [9]. Pathological conditions include weight loss, emaciation, excessive salivation, teeth grinding, fever, anorexia, excessive consumption of water, impaired motor coordination, head tremors, ataxia, respiratory distress, hyperexcitability, isolation from the herd, and lack of awareness [10]. The prolonged period of deteriorating health also makes CWD-infected individuals highly vulnerable to other causes of death, including other illnesses and predation [11]. A long incubation period (16–24 months), presentation of clinical signs limited to the terminal stage, and similarities in clinical signs with other diseases, such as Epizootic Haemorrhagic Disease, present additional challenges to understanding and managing CWD. For example, the absence of an adaptive immune response to prions hampers the development of vaccines and therapeutic tools [12,13].

CWD naturally infects species in the genera *Odocoileus*, *Cervus*, *Alces*, and *Rangifer* [14]. Since its first detection in Colorado in 1967, CWD rapidly spread across North American cervids and is, to date, present in 36 US states and four Canadian provinces [15,16]. In 2001, the first CWD case outside North America was reported in captive elk in the Republic of Korea [17]. CWD was confirmed in Europe, as two Eurasian tundra reindeer (*R. tarandus tarandus*) were diagnosed positive in Norway in 2016 [18]. Despite extensive culling efforts in Scandinavia, CWD was diagnosed again in 2021 in 20 wild reindeer, eight moose, and two red deer (Norway), four moose (Sweden), and two moose (Finland). The prion strains affecting cervids in Europe and North America are different, suggesting independent origins [19]. Analysis of 18 CWD cases from 2016 to 2022 from Norway, Sweden and Finland by [20] concluded that the prion strain in Nordic moose is less contagious or not contagious, and was described as sporadic CWD (sCWD).

Despite independent discovery in various areas, tracking the aspects of disease trajectory and factors that promote the spread in a landscape over time has been challenging. In endemic regions, an average uniform diffusion model without accounting for long-distance dispersal estimated the geographical rate of CWD expansion near south-central Wisconsin at 1.13 kilometres per year [21]. Within species, a high prevalence (35%) of CWD has the potential to decrease white-tailed deer (WTD) population by 10.4% annually [22]. A prevalence of over 20% in the mule deer population in southeastern Wyoming resulted in an annual population decline of 21% [23]. Pathogenic prions can remain infectious in the environment for over two years [24,25], further amplifying transmission potential by remaining contagious for decades [26,27].

CWD-associated declines in cervid populations have wide-ranging impacts. Cervids are often considered keystone species because of their outsized impacts on plant community structure and composition [28,29], which in turn affects other animal species [30,31]. Cervid declines can also impact various aspects of the economy. An estimated 11.5 million people spent 135 million days pursuing big game like deer and elk in the USA in 2022, contributing to a $400 billion annual wildlife-related recreation economy in this country [32]. Cervid population declines could reduce hunting opportunities, both overall and for larger buck harvest and activities that bring revenue to stakeholders. Changes to hunting seasons, harvest rates, and regulations (e.g., bans on urine-based scent) can be confusing, and disease-related safety concerns may reduce interest in hunting [33]. Population declines, as well as the potential for contaminated venison, can threaten the food security of indigenous communities, where venison is an important component of their diet [34]. In northern Alberta, Canada, 97% of indigenous communities' cervids, such as moose, WTD, and mule deer, are important food sources [35,36]. Federal and state agencies in the United States have spent over $284 million to monitor and manage CWD since 2000 [37].

Effective management of CWD relies heavily on robust monitoring and surveillance programmes. In North America, CWD surveillance, monitoring, and management are delegated to the respective wildlife or natural resource departments at the state/province/territory level. Traditionally, key approaches have involved reporting and testing individuals showing clinical signs of CWD infection, targeted detection surveillance of harvested animals to monitor disease-free areas for emergent cases, and implementing policies that minimize transmission risk (e.g., efficient roadkill removal, prohibiting feeding and baiting, proper carcass disposal support) [38]. To further ensure disease control at a broad scale, USDA APHIS closely monitors the movement of animals across international and interstate borders. Despite their effectiveness, surveillance and testing processes are labour-intensive and often costly [37]. Improvements in our ability to manage CWD in North America depend on continued advances in our understanding of CWD across various system levels, spanning from proteins and genes to individual animals, populations, species, and the intricate interactions among hosts within their habitats and environments across spatiotemporal scales. In addition to building system-level baseline knowledge, it is necessary to understand how well these findings translate among species and populations [39], and consequently guide the development of management strategies that are both targeted and tailored. The preliminary step in this process involves conducting a systematic review to map the existing knowledge base for each endemic species, and highlight potential knowledge gaps and areas of convergence.

Motivated by a need to comprehensively track the evolution of CWD research in Cervidae, our overarching goal was to shed light on the dynamic landscape of this field. Recognizing the disparities in available literature and knowledge among the natural host species in North America, we initiated a systematic review focused on North American cervids from 1980 to July 2022. We aimed to categorize major research themes and areas of connection among disciplines, emphasizing a multidisciplinary approach in the study of CWD. Our objectives included analysing temporal trends in study location, species and genus investigated, and types of CWD infection and transmission. We classified studies into five themes – field-based, lab-based, math/analytics/modelling-based, management-based, and human dimensions – to discern patterns and identify areas prime for growth. Utilizing these data, we quantified research activity in these themes, comparing across species and in wild versus captive populations. We delved into the evolution of keywords, focusing on terms related to infection and transmission types. Additionally, we conducted a nuanced analysis of trends in the five themes over the years, highlighting the interdisciplinary nature of CWD research.

Results

Trends in data

Geographic origin

Among all 606 records from the peer-reviewed literature that were evaluated, 12.9% were reviews and 87.1% were research articles (Figure S1). A higher proportion of research articles reported studies carried out in North America (86.3%) and Europe (11.4%) compared to Asia (1.8%), Oceania (0.2%), and South America (0.4%; Figure S1). Studies undertaken in Norway accounted for 31.9% of all publications outside North America (Figure S1). Of all the studies carried out in North America ($n = 378$), 328 (86.8%) were from the USA, 49 (12.9%) were from Canada, and 1 (0.2%) were from Mexico. Most studies carried out in the USA were undertaken in Colorado (30.2% of 328) and Wisconsin (17.4% of 328; Figure 2). Most Canadian studies were done in Alberta and Saskatchewan (each with 34.7% of 49).

In North America, the number of publications related to CWD in all cervid species dramatically increased from 1997 to 2005, then levelling off at about 20 publications per year with considerable variation from year to year (Figure 3). The increase in publications follows the sharp increase in the number of states and provinces reporting their first CWD cases over time (Figure 3).

Study species

Most publications (88.5%) were focused on natural cervid host species (i.e., *Odocoileus*, *Cervus*, *Alces*, and *Rangifer*) than on any other species (Figure S2). Common study models in CWD research were also represented in publications, albeit infrequently, including rodents (3.5%), caprines (1.6%), livestock (1.4%), and mustelids (1.4%) (Figure S1). When comparing the number of publications between genera of natural cervid hosts, clear differences were observed between *Odocoileus*, *Cervus*, *Alces*, and *Rangifer* (Figure 4). While more studies were published in all four genera over time, a clear bias towards *Odocoileus* spp. was found overall (48% of all studies; Figure 4).

Keyword trends show that more recent research has been carried out in *Odocoileus virginianus, Cervus canadensis*, *Cervus nippon*, and *Rangifer tarandus* (Figure S3a-g). The representation of *Cervus elaphus* not being used after 2015 indicated a shift to the use of accurate nomenclature to represent elk as *Cervus canadensis* in North America (Figure S3 (c) &; (d)). Many early studies, especially developing immunoassays using monoclonal antibodies for detecting CWD, were carried out in *Odocoileus hemionus*. Among the endemic species, the fewest studies have been carried out in *Alces alces* (4%), followed by *Rangifer tarandus* (6%) (Figure 4). About 4% of the studies did not include a study species; these included studies with a broader focus on human dimensions or strategizing management plans.

Population type

41% of the published articles studied wild or free-ranging cervids (Figure 5). About 37% of the studies did not describe using a captive or a free-ranging population. This can be attributed to aspects like testing method development, human dimension, or simulation studies.

Infection types

In total, 27 articles focused on the captive population, and 8 on the free-ranging population studied transmission types. Among these publications, 21 articles in captive populations were published between 2000 and 2014. Keyword trend map (Figure 6) showed that terms such as ‘spontaneously affected,’ ‘naturally affected,’ and ‘interspecific lateral’ were investigated more around the year 2000. There is a shift in the use of keywords, especially in the wild populations. In more recent studies, 'mother-to-offspring' and 'parasite-borne/bloodborne' transmission have been studied. Overall, the most studied infection types are oral, intracerebral, and environmental.

Trends in literature and keyword analysis of study disciplines

Of the 378 studies, 242 (64.02%) were non-interdisciplinary, and 136 were interdisciplinary (35.97%). Overall, lab-based studies predominate (Figure 7a) with 220 publications having a lab component in their study (Figure 7b). Of these, 25.45% were interdisciplinary (Figure 7c). Interdisciplinary research in lab-based studies was linked mostly to field-based studies, followed by analytics/maths-based and management efforts (Figure 7c). In contrast to lab-based studies, management-based studies were more transdisciplinary in nature, involving the stakeholders, such as landowners, managers, and/or hunters. Similarly, analytics/maths-based studies were predominantly inter/trans-disciplinary linking to management-based and field-based research (Figure 7c). All disciplines have at least one interdisciplinary component.

Author keyword analysis (Figure 8) shows that in the earlier days, most published articles were linked to words such as 'immunocytochemistry, 'amyloid', 'CNS', and 'rocky mountain elk.' In comparison, the more recent trend includes words such as 'SNP', 'CWD response', 'non-model species', retrospective and a large suite of words pointing towards the use of genomics. A bulk of links from the keyword CWD are to WTD followed by elk.

Field-based studies have moved from using more spatial data (keywords: geographic information system, spatial model) in the early 2000s to using more genetics (keywords: radseq, snp, synonymous polymorphism, prion protein gene) (Figure S4a). Links between SNPs and management in the recent field-based studies suggest the application of these tools in CWD management in the field. In field-based studies, we observed a shift in terms associated with direct transmission (e.g., contact rate, animal movement) towards a broader array of potential vectors of prion transmission such as ticks (Figure S4a).

In lab-based studies, a shift is seen from monoclonal antibodies to immunoassays to RT-QuIC, indicating evolving diagnostic tools (Figure S4b). Keywords such as 'wildlife disease', 'hunter harvest', 'cwd response', and 'culling' in more recent times indicate a focus on lab-based studies in CWD management and translational research being useful. In contrast to field-based studies, where the keyword 'culling' appeared around 2010, lab-based studies have incorporated this term more recently, suggesting a shift in decision-making processes and an increased focus on management applications of lab-based CWD research.

Modelling studies have moved from being epidemiological to more focused agent-based models in recent times (Figure S4c). With more than four decades of CWD history in North America, the analytics-based study appears to draw from experience. Though there is no direct link present in the keyword map for analytics-based CWD research (Figure S4c), the term 'retrospective' in both Figure S4c & S4d suggests history-informed CWD management. Diagnostic tools in management-based studies have moved from immunoassays around 2005 to rt-quic around 2020 (Figure S4d). Hot keywords in the human dimension (Figure S4e) are 'vCJD,' 'bse,' 'protease resistant papers', and 'prion,' indicative of the natural connection between human dimensions research and human health, for example, concerns about potential for humans to acquire variant Creutzfeldt–Jakob disease from venison consumption.

Discussion

A multidisciplinary perspective in understanding and managing CWD

Chronic Wasting Disease (CWD) poses a significant risk to wildlife populations, and it is imperative that we take immediate action to address this issue [40]. To achieve this, we must prioritize comprehensive and interdisciplinary research to gain a deeper understanding of CWD and develop effective management strategies [41]. A thorough analysis of CWD research trends has revealed differences in the knowledge of host species and the interdisciplinary nature of CWD research.

Previous reviews have sought to address key biological questions, such as the genetic factors driving CWD progression in affected species [42], CWD aetiology and management strategies [41,43–45], and epidemiological models to understand the baseline scenarios of CWD [40,46]. These reviews, however, have primarily focused on specialized aspects of CWD research, often emphasizing individual species or specific contexts. A more nuanced understanding of species-specific differences in CWD research remains essential. This systematic review compares and describes trends in published research on CWD over time based on the geographic origin, species, population type, infection type, and research discipline intervention since the first peer-reviewed article on CWD was published in 1980. By comparing the types of studies conducted among species, we can assess whether findings from one species apply to other species or are generalizable across different population types and ecosystems.

A large proportion of studies are from the epicentre of CWD emergence in Colorado, United States, and focused on the species in which CWD was first described (*Odocoileus hemionus*). Data originating from natural or wild populations is more frequently documented in peer-reviewed literature than information derived from captive populations. The implication is that although captive populations undergo monitoring and research, the findings may not always be reported in peer-reviewed articles. Of the 378 publications analysed, most were focused on a single major discipline. Lab-based research was the most common approach, followed by field-based studies. Although lab-based studies were the most prevalent, they were less often interdisciplinary than other disciplines. About a third of studies were interdisciplinary, and most field-based, management-based, math/analytical, and human dimensions studies were interdisciplinary. When laboratory-based studies were interdisciplinary, they were most often linked to field-based studies. It will be interesting to see how laboratory-based studies connect more directly with management, indicating translation of lab-based knowledge for management purposes, incorporating analytical approaches, and considering aspects of human dimensions going forward. For example, in a study by [47] a model-based approach was used to estimate the risk of prions entering the human food chain and environment from a single CWD positive deer, through abattoirs and field slaughters. The authors of the study faced difficulties in estimating many input parameters, such as the relative infectivity in different tissues due to differences in bioassays or tests used to detect infective prions. They also emphasized the need for lab-based studies to estimate such titre values to improve their modelling approach in risk assessment. Looking at temporal trends, CWD research evolved from initial laboratory-based investigations, focusing on basic epidemiological knowledge and diagnostic tools, to include more ecological and management-oriented research. The shift is reflected in a notable increase in field-based studies and a broader exploration of population genetics over time. Keywords in research similarly evolved, focusing on diagnostic tools and modelling disease spread in the early 2000s towards using a more individual-based approach today. These findings provide a comprehensive picture of the dynamic landscape of CWD research since its inception.

In the context of any epidemiological investigation, an initial focus of CWD research was on establishing a fundamental understanding of prions as pathogens [48], developing diagnostic tools [49], and spatial modelling to understand prevalence [50]. Significant advances have been made in the field of CWD epidemiology through the development of various research methodologies. For instance, studies characterizing both native and pathogenic forms of the prion protein [51] have provided further insights into the pathogenesis of CWD. Additionally, understanding the accumulation of pathogenic prions in various organs [52,53] has provided a basis for targeting specific organs in the diagnosis of CWD. Furthermore, experimental transmission across species [54] has facilitated the identification of genotypes that influence individual susceptibility, as demonstrated in studies by [55]. These studies have played a critical role in advancing our understanding of CWD and have paved the way for further research in this field. Due to the transmissible nature of CWD, epidemiological and spatial modelling approaches were key to comprehending its spatial spread [56,57]. Subsequently, these approaches were utilized in formulating management strategies based on the severity of the disease and available expertise and resources. Presently, advanced detection tools, simulation methods, and genomics [58] have paved the way for precision in targeting management actions at the population level. High-sensitivity prion detection tools, such as the RT-QuIC technique, enable the identification of PrP^{CWD} in diverse environmental substrates [59]. Agent-based models incorporate individual-level stochasticity to understand epidemiological processes better, which can facilitate the development of effective control strategies [60]. The conserved nature of the prion gene in the mammalian genome, differential expression of proteins in challenged animals, and the association of numerous genes with disease susceptibility have triggered a recent shift towards genomics. This shift aims to better comprehend factors influencing prion expression and understand variation in individual host susceptibility. For wild populations, these approaches hold promise for applying genomics and population variables to understand risk of disease and incorporate genetics/genomics into existing predictive models to help guide management activities [61], to get accurate and real-time prevalence estimates, and to identify host population attributes and environmental conditions that mitigate disease spread. Integrating landscape genomics into existing predictive models holds great potential for enhancing our understanding of CWD transmission dynamics and identifying effective management strategies to mitigate its spread. This will require continued collaboration and research across different disciplines to develop a comprehensive and multidisciplinary approach to tackling this complex issue.

Susceptible species and management implications

Since the discovery of CWD, many studies have been carried out on *Odocoileus* spp. when compared to the other genera that are known to be susceptible to CWD in the wild (i.e., *Cervus*, *Alces*, or *Rangifer*), which is most likely linked to the chronology of CWD discovery and the abundance and distribution of *Odocoileus* spp. (Figure S5). CWD was first discovered in 1960s in captive mule deer in Colorado, USA [16]. With over 30 million WTD and 4 million mule deer in the USA [62,63], these large populations of cervids drive the composition of local ecosystems, and CWD-associated population declines can have cascading effects on the community ecology. As we continue to learn more about CWD management in native deer, the knowledge gained can be applied to other non-native cervid species. This is especially crucial as CWD is spreading globally, and it will become increasingly important to incorporate more cervid species in CWD research activity. It is also noteworthy that many non-native cervid species are found in North America, and studying their susceptibility and response to CWD can provide valuable insights into the disease's epidemiology and potential control measures.

Besides being commonly available, major game and exotic species are economically important and these cervids have conserved prion protein gene, which can be leveraged for management activities. The presence of these cervids in various landscapes is underscored by their economic contributions, as evidenced by the collective expenditure of approximately 20 billion per year by federal government agencies and the U.S. Department of Agriculture's Animal and Plant Health Inspection Service between 2000 and 2021 for CWD-related work [37]. Additionally, the North American Deer Farmers Association reported that breeding and hunting components of the cervid industry contributes $7.9 billion annually to the US economy [64]. Exotic species, such as *Axis axis* (Chital), *Dama dama* (fallow deer), and *Rusa unicolor* (Sambar deer), are not only maintained in captivity within private ranches [65] but are also living as free-ranging populations in Texas [66], Delaware [67], and Kentucky [68]. These exotic species contribute to the economic importance of cervids in North America, but also complicate our understanding of CWD spread given the conservation of the PRNP gene within cervids [69]. This emphasizes the importance of tracking not only native species but also exotic species coexisting in the same landscape. A study by Texas Tech University recently identified *Axis axis* as potentially susceptible to CWD based on PRNP gene sequence similarity to *Cervus canadensis*, though further research is needed to determine whether *Axis axis* is naturally susceptible [70]. In contrast, *Dama dama* was is not susceptible to CWD when exposed to a prion-contaminated environment from *O. hemionus* [71]. Because different species with potential CWD susceptibility occupy the same spaces, regulatory agencies have implemented various measures to mitigate the risk of CWD in both wild and captive populations [44]. USDA APHIS supports state agencies in monitoring international and interstate movements of animals [72]. Surveillance in farmed cervids began in 1997 [73]. USDA has developed a national herd-certification program (HCP) to control and prevent the spread of CWD in farmed cervids. Culling has been one of the most effective ways to manage CWD in captivity. Depopulation is recommended only in extreme cases to encourage monitoring, reporting, and minimizing economic loss for the herd owners [72].

Need for a data repository

Establishing and maintaining a unified repository of samples and data is crucial to effectively managing and comprehensively understanding CWD across diverse regions. Researchers across diverse disciplines have diligently collaborated to unravel the intricacies of CWD. Consolidating this collective knowledge on a larger scale holds immense potential, benefiting regions currently unaffected by CWD and those where it is endemic. A centralized repository encompassing demographic, genomic and epidemiological data becomes invaluable for identifying spatial and temporal patterns in affected areas. An effort to compile surveillance data in *O. virginianus* was exemplified by [74]. This data repository has aided in predicting CWD incidence by county and holds potential for surveillance planning [75]. The National Wildlife Health Center in Madison, Wisconsin, consistently releases data on CWD-positive counties and states in the USA [76]. In addition to this, every state should contribute to maintaining a comprehensive repository, annually documenting the population of each cervid species by county or management unit, CWD prevalence, and scrutinizing the population's genetic composition, with a specific focus on CWD-associated genes. Such collaborative efforts foster a holistic understanding of CWD dynamics, enhancing informed management strategies nationwide.

Materials and methods

Literature search

To ensure the data extraction was reliable and reproducible, the following protocol was developed a priori, based on the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) flowchart [77]. We used the PRISMA checklist and flowchart for the data collection process only since our analysis focused primarily on quantitative publication metrics. We recognize that such an approach may still contain subjectivity in screening and selection because the decision to include/exclude publications was made without evaluating methodological quality (e.g., heterogeneity, context, or potential conflicts of interest in included studies). There may also be bias introduced by publication selection, for instance, by excluding the grey literature or non-English studies. Yet, by providing detailed justifications for inclusion/exclusion criteria, we aim for transparency of our rationale behind critical decisions and reproducibility of our findings. The electronic databases Scopus (https://www.scopus.com), Web of Science (https://www.webofknowledge.com), and PubMed (https://pubmed.ncbi.nlm.nih.gov/) were used. The literature search was performed in July 2022 and included articles from 1980 to 2022. Peer-reviewed literature was selected using the following combination of keywords: (Odocoileus OR Cervus OR Alces OR Rangifer) AND (chronic wasting disease OR CWD OR prion).

A total of 606 records (i.e., Scopus: 372; Web of Science: 532; PubMed: 216) were returned from the initial literature search. These publications were subsequently screened by their title and abstract based on the following inclusion and exclusion criteria (Figure 1). Only studies written in English were retained (stage 1). To ensure avoiding repetitions in the selection of publications, reviews were removed from the final list of selected articles (stage 2). Only studies carried out in North America (i.e., USA, Canada, and Mexico) were included (stage 3). Out of the 606 records, we excluded 1 article written in Italian, 78 reviews, and 71 carried out outside of North America, leading to a total of 459 selected articles. To be included in the final synthesis, studies had to investigate the impacts of CWD on species

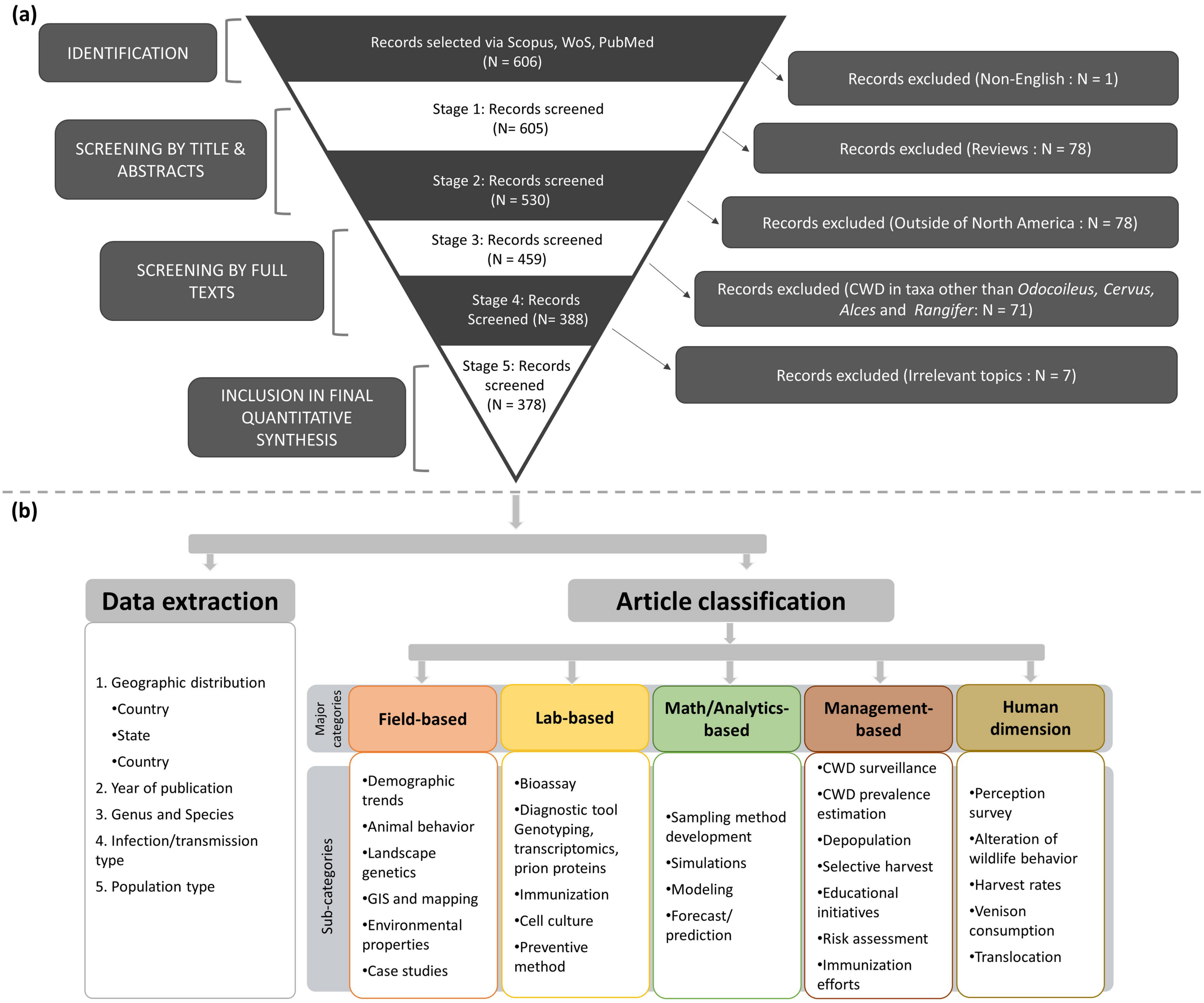

Figure 1. Workflow (a) for the prisma-guided literature search. (b) Data extraction and article classification.

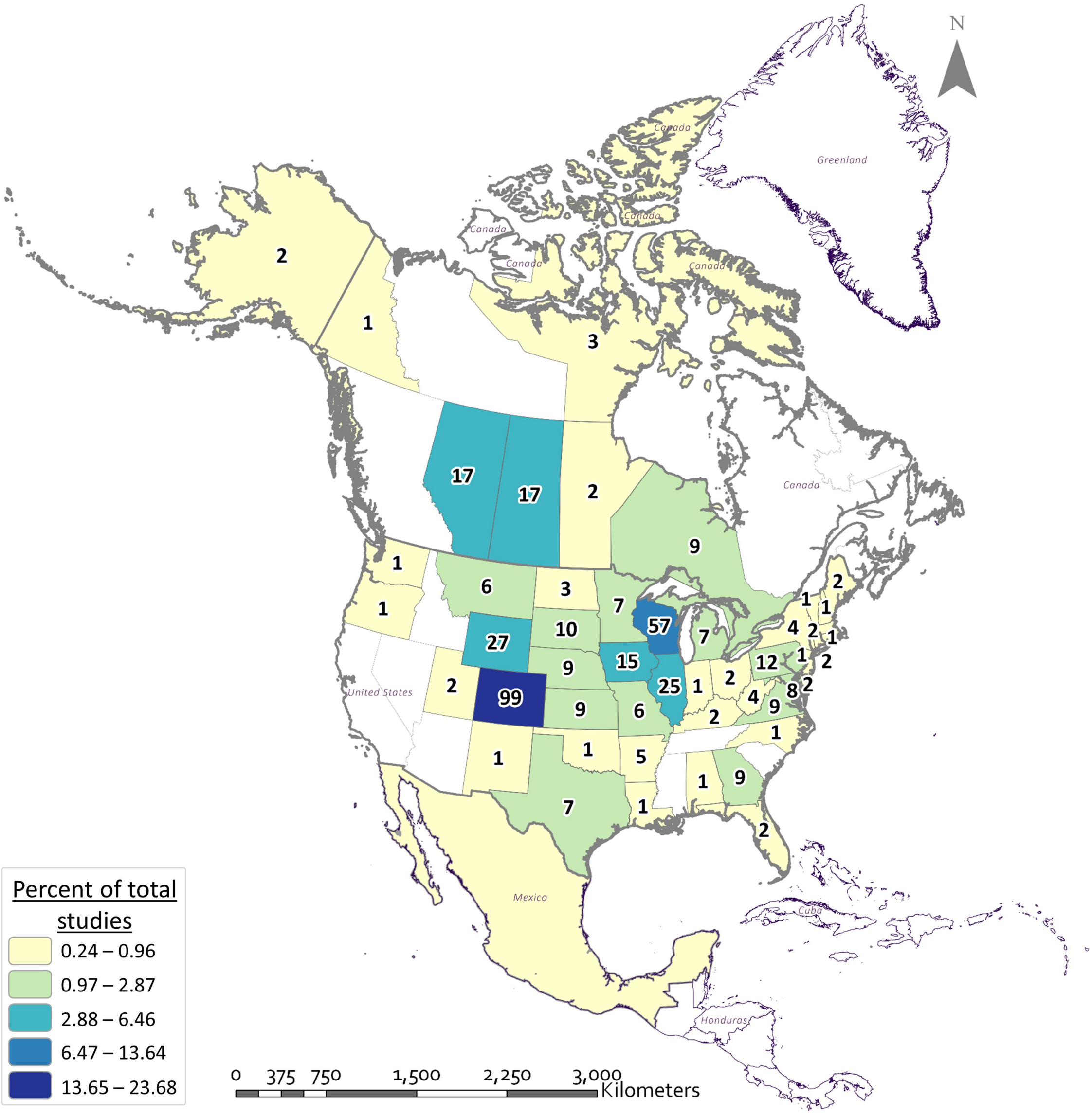

Figure 2. Geographic distribution of selected publications.

that are described as natural CWD hosts, including the genera Odocoileus, Cervus, Alces and Rangifer (stage 4). Their full text was assessed for eligibility. A total of

(1) additional publications were removed from the final list as their full text could not be found anywhere (stage 5). A total of 378 publications fulfilled all inclusion criteria and were kept in the final synthesis. Workflow of the literature search, exclusion criteria, data extraction and classification are depicted in Figure 1. The repository of retained articles is available in Table S1.

(2) Data extraction

For each retained article, the following data were extracted and added as separate column in Table S1: (1) year of publication, (2) geographic area (more precisely, state and country) where the study was conducted, (3) Genus and species studied, (4) Population type and (5) transmission/infection types. Except for the year of publication, all other data, i.e., (2) to (5) were acquired from the title or abstract of the article.

Article classification and Scoring

We used the abstract and methods section of each article to classify the article. Given the implicit comprehension within the CWD research domain, we developed five overarching major categories of broad discipline to classify the articles: field-based, lab-based, math/analytics, management-based, and human dimensions. The category ‘other’ included studies that developed hardware or carried out general disease monitoring, which may or may not have specifically focused on CWD.

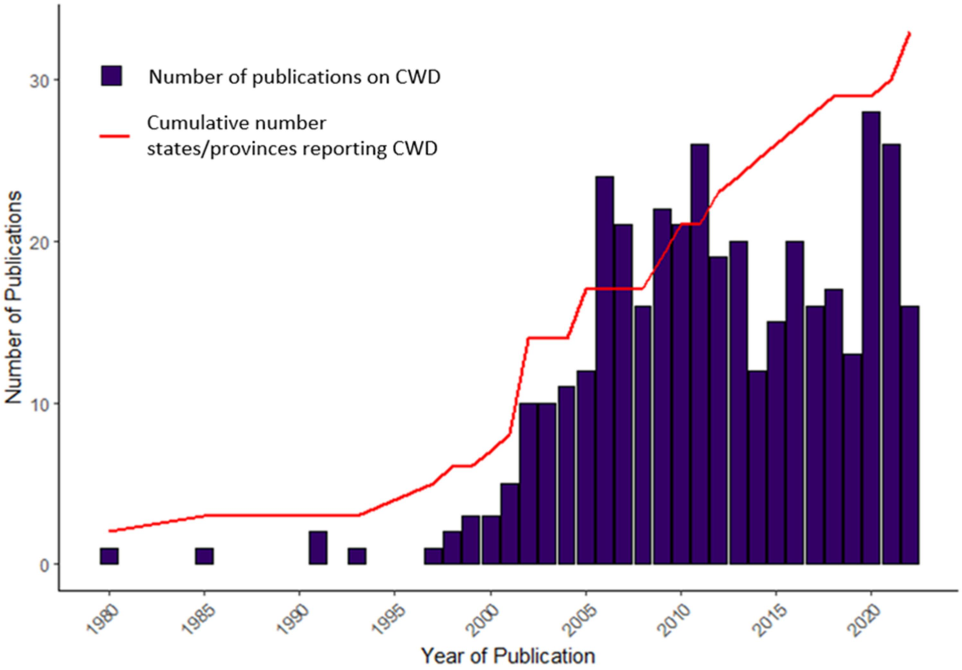

Figure 3. Number of publications per year was shown in correlation to the number of North American states/provinces reporting CWD cases.

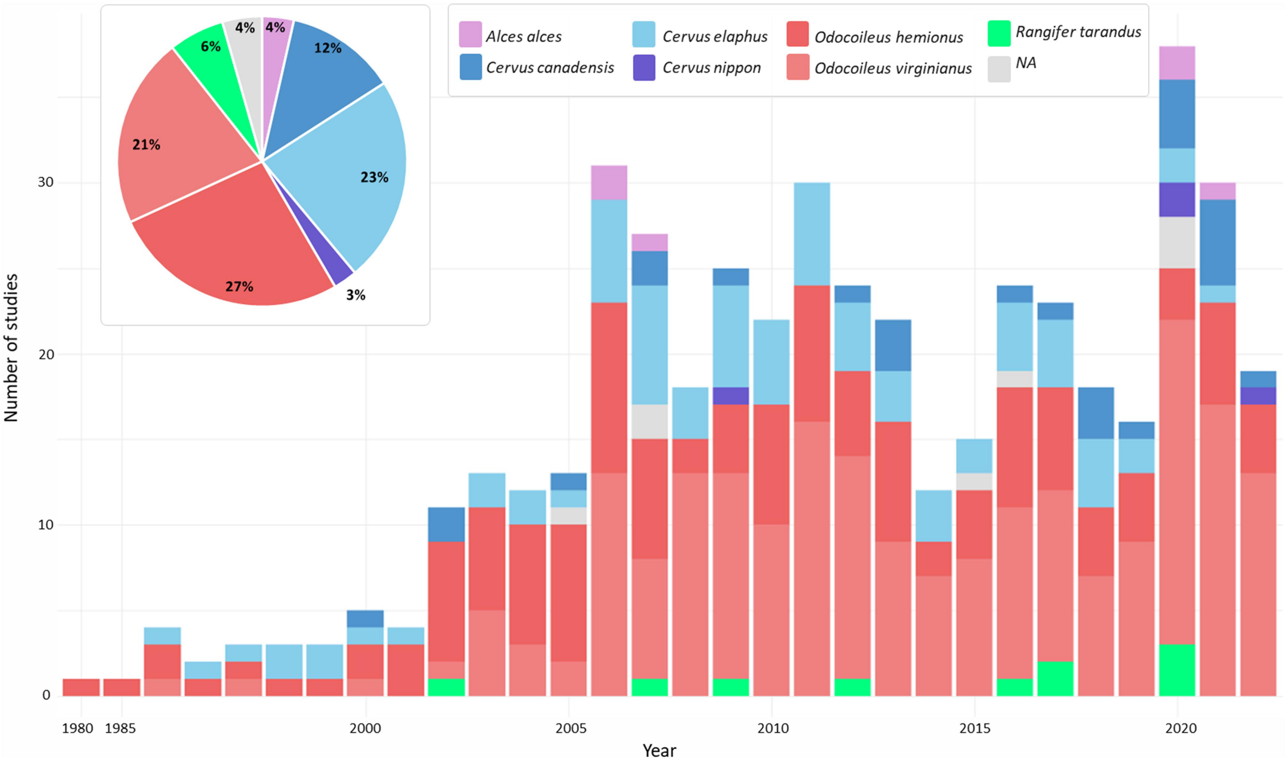

Figure 4. Number of published articles for each species in a year. The inset pie chart represents the species-wise percentage of published articles from 1980 to 2022.

The five major discipline categories were subdivided into specific research themes (Table S1) to categorize recurring topics precisely. Field-based study research themes included demographic trends, animal behaviour, landscape genetics, GIS and mapping, environmental properties, and case studies. Lab-based research themes included bioassays,

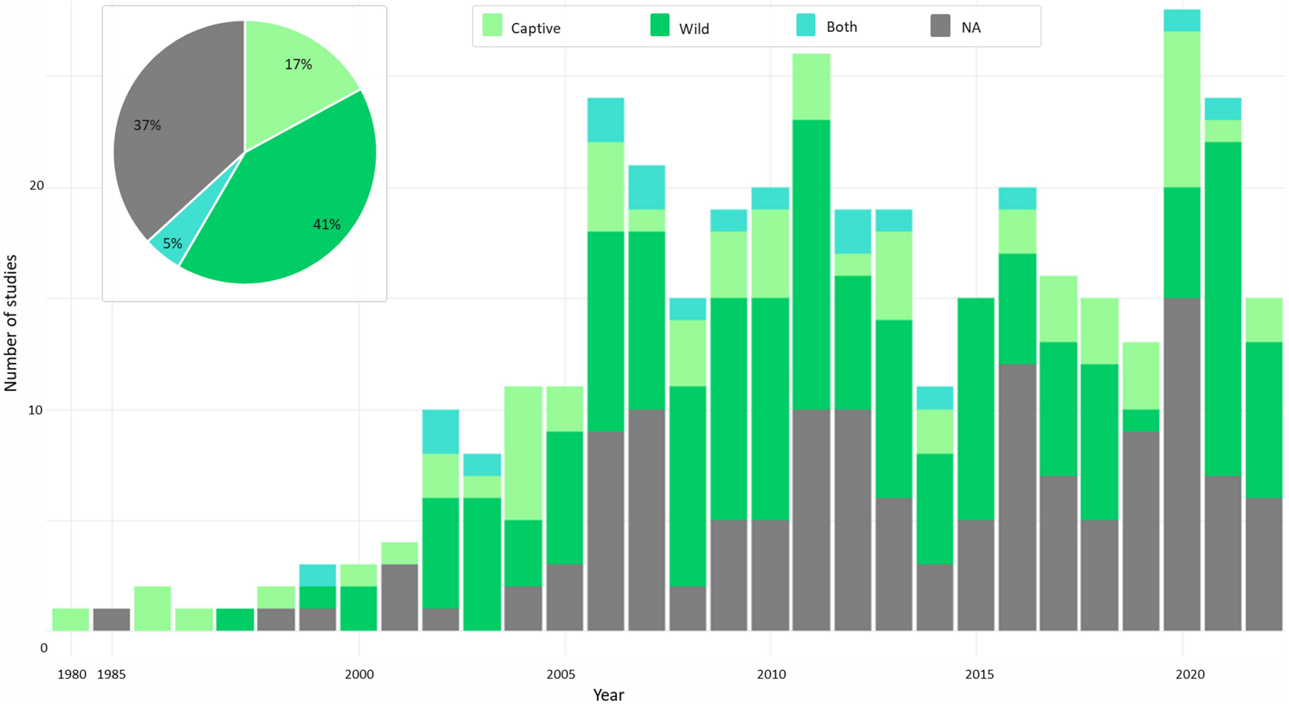

Figure 5. The bar graph represents the number of articles studying a defined population type over the years. The inset pie charts show the overall proportion of articles segregated by population type.

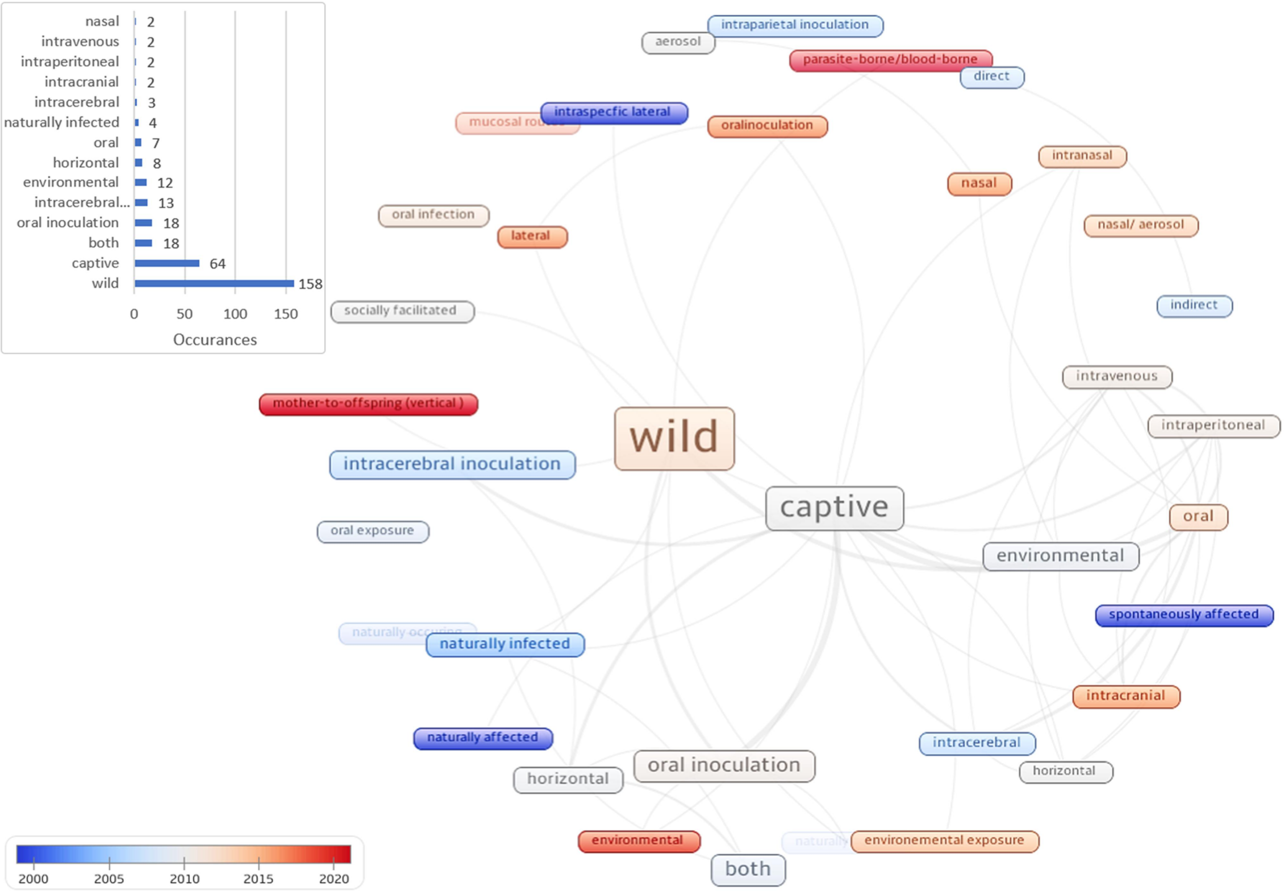

Figure 6. Trends in words relating to Transmission/infection types. The box size changes proportionally to the number of occurrences of the word. The number of occurrences of words that appear two or more times is shown in the inset bar graph; all other words occurred only once. The line connects the co-occurring words. The thickness of the line indicates the number of times each word co-occurs.

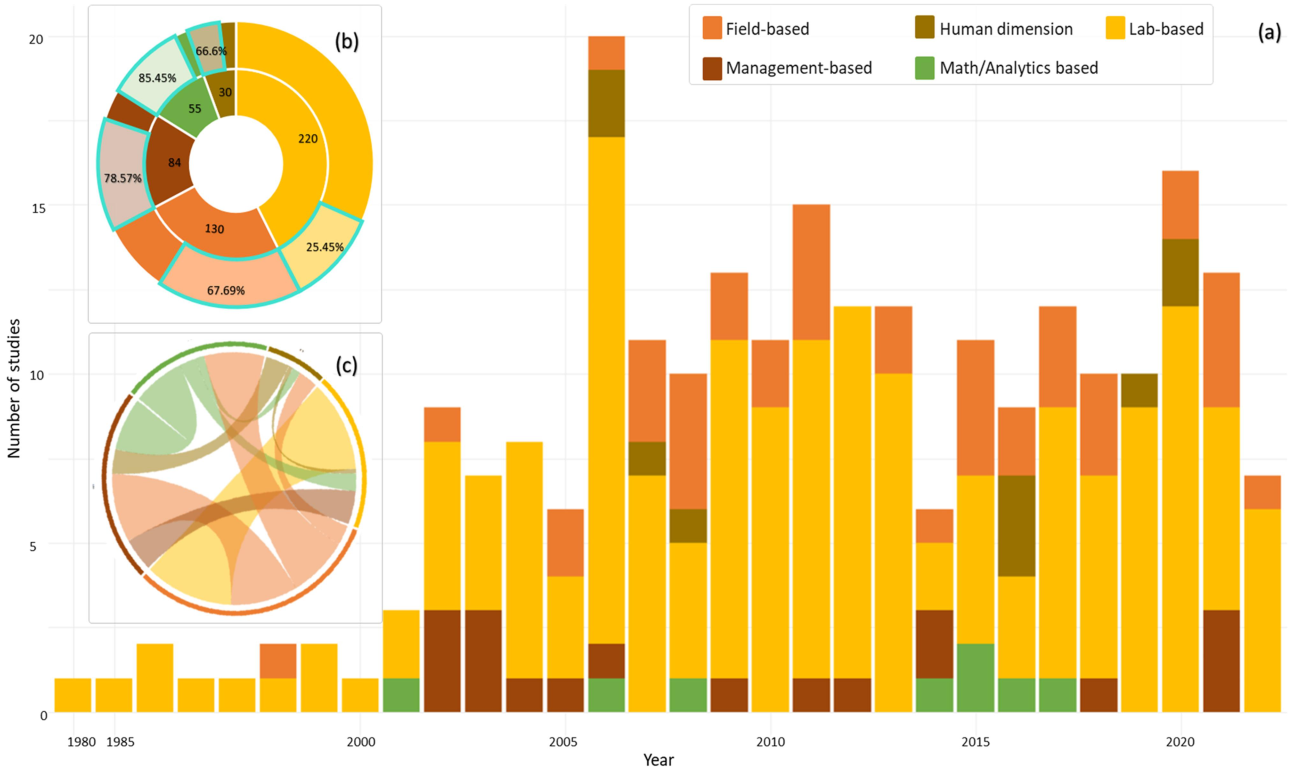

Figure 7. (a) Trends in study disciplines over time (b) Inner circle shows the proportion of studies in each major category (F: field-based, L: lab-based, A: analytical-based, M: management-based, H: human dimension) across all years. Number indicates the total count in that category. The outer circle serves as a visual representation of the percentage of studies categorized in one (colours as in inner circle) or multiple (lighter shades) categories. (c) Links between studies that have a multi-disciplinary approach.

diagnostic tool development/validation, genotyping, transcriptomics, prion proteins, immunization, cell culture, and preventive method demonstration. Math/Analytics were subdivided into sampling method development, simulations, modelling, and forecast/prediction studies. Management-based studies were sorted under CWD monitoring/surveillance, CWD estimation/prevalence estimates, depopulation, selective removal/harvest, educational initiative, risk assessment, and immunization efforts. Finally, human dimensions studies were subcategorized under perception survey, alterations of wildlife behaviour, harvest rates, venison consumption, and translocation. Each major discipline category also had an ‘other’ research theme if the study fell within a major discipline but did not fall clearly under the abovementioned sub-themes.

The table of the final article list (Table S1) was expanded to include a column for each sub-theme. The articles were classified based on these sub-criteria by assigning a score of 1 if the text, particularly the abstract or methods section, indicated a specific sub-category. All articles were eligible for classification under multiple sub-themes.

A major category was assigned a score of 1 when the cumulative score of all the sub-categories under a major category per article, calculated by summing the scores across relevant sub-categories within that major category, exceeded 0. This step was repeated for all articles. The score was consolidated across all articles to identify the number of articles under each of the five major criteria.

Trends in data

a. *Geographic origin*: We tabulated the frequency of occurrence for each state and country using all the articles. Subsequently, we subset and represented the aggregated number of articles corresponding to each state on a North American continent map using ArcGIS Pro. Color code was based on Natural Breaks (Jenks), i.e., unequal class width because of the non-uniform distribution of data across various states. Since the categorization of geographic origin and species investigated was based on information provided by the authors in the articles ($n = 316$; Table S1), some publications lacked such data and were not kept for the analyses. The number of

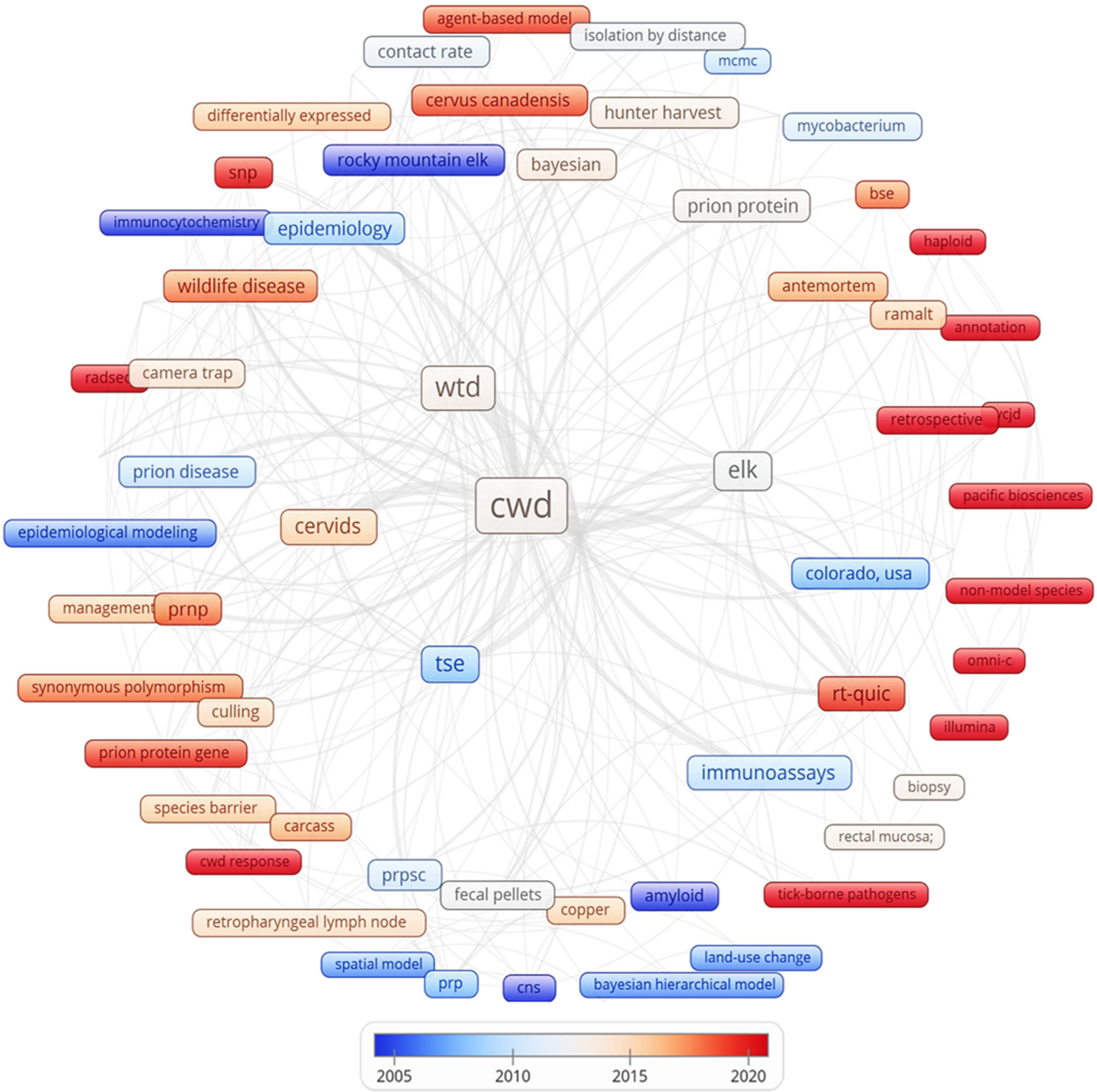

Figure 8. Evolution of keywords. The colour indicates the average publication year of the term – Blue shades indicate words associated with early studies, and darker red indicates words associated with more recent studies. The box size changes proportionally to the number of occurrences of the word. Lines connect co-occurring words. The thickness of the line indicates the number of times each word co-occurs.

publications per year was plotted in correlation to the number of North American states/provinces reporting CWD cases. For each state, the first CWD case detection year was reported using their respective Department of Natural Resources (DNR) or equivalent websites. We also described the geographic distribution of the 71 articles from outside North America (those omitted in Stage 3).

b. *Study species*: We assessed the proportion of publications on CWD across study species. Of the 378 articles retained, 300 mentioned one species, 67 mentioned more than one species, and 11 did not mention a particular species. Among cervids, we captured the following species - *Alces alces, Cervus canadensis, Cervus elaphus, Cervus nippon, Odocoileus hemionus, Odocoileus virginianus* and *Rangifer tarandus*. Note that *Cervus elaphus* taxonomically represents red deer found especially in Eurasia [78]. However, researchers have used both *Cervus elaphus* and *Cervus canadensis* to represent North American elk [79]. For the purposes of this review, we considered both binomial names to represent North American elk when the study was geographically located in North America, but kept names separate to evaluate trends in nomenclature.

We compared the year-wise trends and keyword trends across species. We created a keyword map using bibliometric data using VOSviewer 1.6.19. To visualise changes in keywords over time (overlay visualization) for different species, we imported the title (TI), authors (AU), abstract (AB), publication year (PY) and author keywords (DE). We also surveyed the taxa that were omitted in stage 4.

c. *Population type*: We quantified the proportion of publications that studied wild or captive populations each year and the total proportion of each population type in all studies ($n = 240$). Population type was extracted when an article specified the population type.

d. *Infection types*: We identified a comprehensive list of transmission/inoculation types terms. 75 articles had one of these terms – environmentally acquired, naturally affected, spontaneously affected, Intraspecific lateral transmission, oral inoculation, intracerebral inoculation, Horizontal transmission, Intraparietal inoculation, horizontal, aerosol, nasal transmission, socially facilitated transmission, intravenous, mucosal routes, intracranial, Mother-to-offspring (vertical transmission), and parasite-borne/blood borne. We created a keyword map using bibliometric data using VOSviewer 1.6.19. To visualise changes in keywords over time (overlay visualization), we imported the title (TI), authors (AU), abstract (AB), and publication year (PY). We modified the keywords (DE) column to include infection types and population types to evaluate the co-occurrence of words.

Trends in study discipline

To gauge the trends in major categories over time, we summed the number of studies under each major category. We also assessed the proportion of interdisciplinary studies under each major category and the links between each discipline when listed as interdisciplinary. Since the count data does not explain the changes in the keywords, we used bibliometric analysis to understand the evolution of keywords over time.

We created a keyword map using bibliometric data using VOSviewer 1.6.19. Title (TI), authors (AU), abstract (AB), publication year (PY) and author keywords (DE) were imported in VOSviewer in Web of Science format to visualize keyword clustering and changes in the use of keywords over time. Initially, we conducted a co-occurrence analysis of author keywords by counting 715 from all 378 articles. 129 articles lacking author-generated keywords were excluded from this analysis. Due to the presence of singular or semantically related terms, variations in grammatical form, or abbreviations, we enhanced the quality of the map by creating a thesaurus that involved relabelling such terms (as detailed in Table S2). The final map had 59 keywords of which 52 occurred at least twice. We rebuilt a word map of the keywords to show the clustering of words and changes over time. We separately visualized the keywords in each major category and each species by segregating the list of articles.

Conclusion

(1) CWD gained attention as an emerging infectious wildlife disease known to humankind. Naturally, research to understand the dynamics of this disease mostly focused on the predominant natural hosts - *Odocoileus virginianus* and *Odocoileus hemionus*. Most studies originated from Colorado, a state that identified and reported the first case of CWD in the 1960s.

(2) Both captive and free-ranging populations of cervids are affected by CWD. Since CWD is transmissible when infected individuals reside in close proximity, it is expected to be a serious concern in captive populations. Despite this issue, the peer-reviewed literature was strongly biased towards CWD research in free-ranging populations.

(3) A rapidly evolving paradigm is indicated in the keyword analysis. Infection types being reported shifted from generalized terms (e.g., naturally infected) to recognition of more specific transmission types (e.g., parasite-borne). Overall, the author's keywords also evolved from indicating foundational research such as studying amyloid plaques and developing diagnostic tools to applying knowledge and tools in the field. Recent studies also indicate the use of genomics, indicating the need to understand the fundamental cause of CWD. Additionally, stakeholders are recognizing the importance of spatially targeted surveillance along with individual-based modelling. These advances will be helpful in predicting disease risk and spread on the landscape to improve monitoring and management.

(4) Data-driven management actions can be achieved when academic, research, private, and government stakeholders collaborate to create and maintain a unified open-access data repository.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research did not receive specific funding.

Author contribution

AT, CRG, and EKL conceptualized and designed the work. AT collected the data, and CRG and AT performed data analysis and interpretation. CRG and AT drafted the article. EKL made critical revisions to the article, and all the authors approved publishing the final version.

Data availability statement

Table S1 and Table S2, used to support the findings of this study, are in the Havard Dataverse repository. Please use https://doi.org/10.7910/DVN/A5YFQG to access these tables.

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