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Unveiling the significance of dog domestication in cognitive dysfunction: Are wolves protected?

Rafael Castro-Fuentes[1*] and Rosy Socas-Pérez[2]

[1]*Department of Basic Medical Sciences, School of Health Sciences, Section Medicine, University of La Laguna, San Cristóbal de La Laguna, Spain*
[2]*Rehabilitation Service, Canary Islands University Hospital Complex (CHUC), Santa Cruz de Tenerife, Spain*

ABSTRACT
Over the course of their long coexistence with humans, dogs have developed a stronger bond with humans than with any other domestic species. This close relationship has promoted notable parallels in both genetics and lifestyle, thereby facilitating the development of comparable pathological conditions, including several central nervous system disorders. Canine cognitive dysfunction (CCD) is a spontaneous model of neurodegeneration that shares clinical features, neuropathological characteristics, and risk factors with human Alzheimer's disease (AD). However, the potential role of dog domestication in increasing CCD susceptibility remains poorly explored. In this sense, the gray wolf (Canis lupus), a direct ancestor of the domestic dog (Canis lupus familiaris), represents a comparative model of great interest, as the information available on its neuropathology and behavior associated with aging is very limited. To provide a preliminary framework for assessing how domestication may have shaped vulnerability to cognitive decline in canids, this study employed a database-driven analytical approach to evaluate the degree of impact of various risk factors shared by AD and CCD—including aging, oxidative stress, inflammation, sleep disturbances, and periodontal disease—in domestic dogs and gray wolves kept in captivity or semi-captivity. Our results indicate that domestic dogs have more pronounced key risk factors for CCD than captive or semi-captive gray wolves. This finding suggests that wolves may be less vulnerable to age-related cognitive dysfunction, possibly reflecting differences in evolutionary or domestication processes. Nevertheless, given the scarcity of neuropathological and behavioral data on aged wolves, these conclusions should be interpreted with caution, and further direct investigations are warranted. Domestication may have increased susceptibility to age-related cognitive dysfunction in dogs by enhancing exposure to key risk factors, as oxidative stress, inflammation, and lifestyle-related conditions. Recognizing these domestication-linked vulnerabilities highlights the need for preventive health strategies in dogs and provides a valuable comparative framework for understanding neurodegenerative processes across species within a One Health perspective.
Keywords: Alzheimer's disease, Cognitive dysfunction, Dog, Gray wolf, Risk factors.

Introduction

Molecular, morphological, and behavioral analyses have established that domestic dogs (*Canis lupus familiaris*) are derived from gray wolves (*Canis lupus*) (Freedman and Wayne, 2017). As the earliest known domesticated species, dogs have dispersed globally alongside humans, occupying diverse habitats and ecological niches. This prolonged coexistence has fostered a uniquely close interspecies relationship compared with other domesticated animals (Freedman and Wayne, 2017). Genomic studies indicate two primary demographic bottlenecks during canine evolution: an initial domestication event involving a limited subset of regional wolf populations, followed by the selective development of modern breeds from these ancestral populations (Freedman and Wayne, 2017; Bergström *et al.*, 2022). The latter process, which has largely occurred within the last few centuries, has yielded roughly 350–400 formally recognized breeds (Parker *et al.*, 2017; Plassais *et al.*, 2019). Demographic and genomic analyses indicate that initial domestication was associated with a marked reduction in effective population size (a strong early bottleneck) and that intensive breed formation over the past ~200–300 years produced a further substantial loss of genetic diversity and increased runs of homozygosity in many modern breeds (Plassais *et al.*, 2019; Axelsson *et al.*, 2021; Meadows *et al.*, 2023).

Domestication has also induced a constellation of phenotypic modifications that distinguish domestic dogs from their wild ancestors. These include enhanced tameness, craniofacial shortening, reduced dentition, higher reproductive frequency with attenuated seasonality, diminished sexual dimorphism,

***Corresponding Author:** Rafael Castro-Fuentes. Department of Basic Medical Sciences, School of Health Sciences, Section Medicine, University of La Laguna, San Cristóbal de La Laguna, Spain. Email: *jrcastro@ull.edu.es; jrafacastro@gmail.com*

alterations in tail and ear morphology (e.g., pendulous ears), coat and skin depigmentation, hair loss, shifts in neuroendocrine parameters, neotenous behavioral traits, and reductions in overall brain volume as well as in discrete brain regions (Wilkins *et al.*, 2014; Pendleton *et al.*, 2018).

Traits collectively referred to as the "domestication syndrome" are thought to emerge from selective pressures favoring reduced aggression in mammals, potentially modifying the expression of genes that govern neural crest cell development (Wilkins *et al.*, 2014). Domestic dogs are one of the most compelling examples supporting this framework (Sánchez-Villagra *et al.*, 2016; Pendleton *et al.*, 2018). Accumulating data indicate that the process of domestication in both plant and animal species results in significant genomic modifications compared with their wild ancestors (Cruz *et al.*, 2008; Freedman *et al.*, 2016). Furthermore, domesticated populations often harbor a greater load of harmful alleles than their wild relatives. Notably, the nuclear DNA of domesticated dogs contains a higher proportion of non-synonymous mutations near functionally important regions than that of gray wolves (Marsden *et al.*, 2016; Cagan and Blass, 2016; Bosse *et al.*, 2018). In fact, 25.3% of nonsynonymous mutations are predicted to be functionally harmful for dogs (Henn *et al.*, 2015). Breed dogs carry an estimated 320 additional homozygous genotypes that result in amino acid changes, which corresponds to roughly a 22% increase compared with wolves (Marsden *et al.*, 2016). These variants illustrate the genetic costs associated with domestication. In domestic populations, the occurrence of deleterious mutations is strongly positively correlated with linkage disequilibrium and negatively correlated with nucleotide diversity, highlighting the reduced effectiveness of purifying selection (Gray *et al.*, 2009; Hou *et al.*, 2020). In addition to nonsynonymous protein alterations, other forms of genetic variation have been identified in dogs (Makino *et al.*, 2018; Plassais *et al.*, 2019). The accumulation of harmful variants has also been observed in the mitochondrial genome of domestic dogs (Tkaczyk-Wlizlo *et al.*, 2022). Interestingly, positive selection acted on genes involved in neurological processes in both humans and canines. Genes involved in canine neurological processes extensively overlap with these genes in humans (Wang *et al.*, 2013). Dogs coexist with humans, inhabit the same spaces, breathe the same air, eat similar foods, and are exposed to the same environmental conditions, including air pollutants, household chemicals, pesticides, heavy metals, flame retardants, and other toxicants. This shared environment strengthens the species' translational relevance, as dogs serve as sentinels reflecting human exposure and its biological consequences (Craun *et al.*, 2020; Wise *et al.*, 2020). Chronic exposure to environmental contaminants in urban settings has been associated with oxidative stress, neuroinflammation, DNA damage, and early neuropathological changes in canine brains, resembling those seen in human neurodegenerative disorders (Calderon-Garciduenas *et al.*, 2003). Thus, the close genetic, physiological, and environmental parallels between dogs and humans make the dog an exceptional model for exploring how gene–environment interactions contribute to neurological diseases. The close interactions between humans and canines and the drastic changes in the living environments of canines may have caused some of the striking parallelism between human and canine genetic evolution (Huang *et al.*, 2020). Aggressive dog breeding practices involve high levels of inbreeding and have intensified minor morphological differences among breeds. Many purebred dogs exhibit elevated rates of breed-specific inherited disorders. Remarkably, many of these diseases and pathological conditions are also common in humans, particularly age-related disorders affecting organs such as the brain, kidneys, and cardiovascular system. The clinical manifestations observed in dogs often mirror those in humans, making dogs a valuable translational model for studying complex and age-associated diseases. Comparative genomic analyses further demonstrate that dogs and humans share a highly similar gene repertoire, with many orthologous genes implicated in analogous diseases (Hytönen and Lohi, 2016; Marsden *et al.*, 2016; Hoffman *et al.*, 2018; Plassais *et al.*, 2019; Axelsson *et al.*, 2021; Ruple *et al.*, 2022; Donner *et al.*, 2018). When wolves began their transformation into the first dogs, artificial selection acted strongly on genes expressed in the brain, promoting the evolution of behavior patterns characteristic of domestic dogs (Li *et al.*, 2013). To gain broader insight into how domestication drives behavioral changes, researchers analyzed genomic and transcriptomic data from chickens and six other domesticated mammals, including dogs (Hou *et al.*, 2020). These studies revealed overlaps between the molecular foundations of animal behavior and human mental health conditions (Shpigler *et al.*, 2017; Vaz *et al.*, 2018). The results further showed that many of the genes recurrently shaped by selection were deeply conserved across species and shared links with human neuropsychiatric disorders, highlighting a compromise: adaptation to human environments was achieved at the expense of neural alterations that may reduce fitness in natural habitats (Hou *et al.*, 2020). Genetic studies suggest that during domestication, neurobiological processes have been targeted by selection (O'Rourke and Boeckx, 2020; Benítez-Burraco *et al.*, 2023). This selection has involved genes related to neurological processes, behavior, and synapse activity. Using brain samples, several differentially metilated regions have been found in genes (epigenetic factors) related to neurotransmission between domestic dogs and their ancestors, providing further evidence that domestication has targeted neurological functions (Sundman *et al.*, 2020). Natural selection does not always efficiently

eliminate harmful variants; therefore, pleiotropic genes can remain in the genome, increasing the likelihood of disease. A classic example is the strong association between coat color and sensorineural deafness, which has been reported in many dog breeds (Webb and Cullen, 2010). Brachycephaly, characterized by shortened facial features, is another widespread condition that appears in various breeds (Dupré and Heidenreich, 2016). Beyond external traits, humans and dogs share a predisposition to nearly 360 illnesses, including compulsive behaviors, epilepsy, and Alzheimer's-like syndromes, many of which involve the nervous system (Shearin and Ostrander, 2010; De Risio *et al.*, 2015; Ostrander *et al.*, 2017; Dewey *et al.*, 2019). The shared social and environmental contexts of both species may account for these parallels (Zhang *et al.*, 2020).

Alzheimer's disease is a progressive disorder of the nervous system that results in global cognitive deterioration and gradual memory loss. It is the principal cause of dementia and is increasingly recognized as one of the most lethal and economically demanding illnesses of this century (Scheltens *et al.*, 2021). Although many studies have aimed to identify treatments for AD, therapies that effectively modify disease progression are still lacking, partly because the disease's underlying biology remains incompletely understood (Klein *et al.*, 2016). Age-related cognitive deterioration is also observed in dogs as part of the normal aging process. However, similar to humans, a proportion of elderly dogs develop a specific dementia-like syndrome known as CCD or canine dementia (Dewey *et al.*, 2019). CCD exhibits many of the same signs seen in human AD dementia (Youssef *et al.*, 2016; Mihevc and Majdič, 2019; Kim *et al.*, 2024). Affected dogs may experience confusion, anxiety, memory impairments, difficulty learning, altered social behaviors, disrupted sleep-wake cycles, and changes in activity, along with structural alterations such as brain atrophy. Neuropathologically, CCD involves intracellular Aβ oligomers, extracellular amyloid plaques, and amyloid accumulation around blood vessels, particularly in the frontal lobes and hippocampus. Neuron loss projecting to the hippocampus, microbleeds, microgliosis, and intraneuronal hyperphosphorylated tau (pTau) have also been observed (Schmidt *et al.*, 2015; Habiba *et al.*, 2021). Some studies have reported that pTau can form neurofibrillary tangles in aged dogs, typically over 10 years of age, although this may vary according to breed, size, and study design (Schmidt *et al.*, 2015; Smolek *et al.*, 2016). Similar to humans, tau pathology in dogs spreads through the entorhinal cortex, hippocampus, and neocortex (Smolek *et al.*, 2016; Davidson *et al.*, 2018; Abey *et al.*, 2021; Yushkevich *et al.*, 2021), contributing to CCD's cognitive and behavioral impairments (Mihevc and Majdič, 2019). Notably, CCD develops spontaneously in dogs across diverse genetic backgrounds, with all animals carrying the AD risk allele APOE4 in homozygous form (Bunyaluk *et al.*, 2022). This combination of features has fostered growing interest in using CCD as a large-animal model for AD, as it presents a dementia-like condition that mirrors key aspects of human AD (Schütt *et al.*, 2016; Mihevc and Majdič, 2019; Ruple *et al.*, 2022).

In this context, we propose the following hypothesis: if the domestication of the dog contributed to the development of CCD, then its wild conspecifics, the gray wolves, should be more protected from the signs of such pathology. To provide a preliminary framework for assessing how domestication may have shaped vulnerability to cognitive decline in canids and given the scarce availability in the scientific literature (both of cerebral neuropathological studies and of behaviors related to the CCD) about wolves, this study employed the approach of evaluating the degree of impact of several key risk factors (shared by AD and CCD) in domestic dogs and gray wolves kept in captivity or semi-captivity.

Methodology

This narrative review adopted an analytical and comparative approach to examine the potential link between dog domestication and increased susceptibility to CCD compared with the gray wolf. A literature search was performed in PubMed, Scopus, and Google Scholar covering 2015–2025, using combinations of terms related to domestication, species, key risk factors (aging, oxidative stress, inflammation, sleep disturbances, and periodontal disease), and cognitive decline. Because comparative neuropathological and behavioral data on gray wolves are scarce, several seminal studies published before 2015 were also included to provide relevant foundational evidence on key mechanisms. Eligible studies addressed at least one of the selected risk factors and reported neurological or behavioral findings in domestic dogs and captive or semi-captive gray wolves. Data were thematically synthesized and qualitatively compared to identify similarities and differences in the expression and impact of risk factors between species.

Aging

Age is widely recognized as a significant risk factor for Alzheimer's disease in humans and for CCD in dogs (Azkona *et al*., 2009; Mihevc and Majdič, 2019; Yarborough *et al.*, 2022; Liu *et al.*, 2024). Interestingly, research suggests that the process of domestication has a stronger impact on brain regions involved in homeostatic regulation—thereby influencing senescence and aging—while exerting comparatively less influence on neural circuits associated with emotions and behaviors typical of ancestral canids (Mazzatenta *et al.*, 2017). CCD is considered one of the leading contributors to morbidity in geriatric dogs. Despite its high prevalence, the syndrome remains markedly underdiagnosed, resulting in a substantial proportion of older adult dogs being affected without recognizing the condition (Mihevc and Majdič, 2019). Similar to the situation in humans with AD, the prevalence of CCD

increases exponentially as dogs age (Yarborough *et al.*, 2022). CCD is present in approximately 28% of dogs aged 11–12 years, with a prevalence that increases to up to 68% in dogs aged 15–16 years (Chapagain *et al.*, 2018; MacQuiddy *et al.*, 2022). Recent large-scale studies, such as those from the Dog Aging Project, have confirmed that the prevalence of CCD rises markedly with age, showing a strong age-related effect independent of breed or sex (Urfer *et al.*, 2021; Yarborough *et al.*, 2022; Bray *et al.*, 2023) and that there are no breed-specific differences in the clinical signs or pathology of CCD (Mihevc and Majdič, 2019). Because large-breed dogs generally exhibit shorter lifespans than their smaller counterparts (Turcsán and Kubinyi, 2024), the clinical manifestations of CCD are more frequently identified in small-sized breeds (Schmidt *et al.*, 2015) as well as in purebred populations (Turcsán and Kubinyi, 2024). Purebred dogs appear to have a higher susceptibility to CCD than crossbred animals. One possible explanation is that mixed-breed dogs typically enjoy greater longevity across all body size categories, which has been linked to reduced levels of inbreeding and, consequently, a lower probability of homozygosity for deleterious alleles (Donner *et al.*, 2018; Yordy *et al.*, 2020). This helps mixed-breed dogs maintain their cognitive health for longer periods (Donner *et al.*, 2018). Current evidence linking the domestication of dogs with aging processes remains limited. Nevertheless, Holecková and Chvapil demonstrated that domestication can negatively influence both physiological development and aging in laboratory rats. In comparison to domestic rats (*Rattus norvegicus*), wild Norway rats displayed several distinct traits: shorter latency of tissue explants, reduced structural stability of collagen fibers, heightened excitability of the central nervous system, prolonged reproductive capacity, improved tolerance to cold exposure, and a lower prevalence of spontaneous tumor formation (Holečková and Chvapil, 1965). In wild canids, such as wolves, senescence is also observed, but some age-related traits may enhance survival and fitness, thus persisting under natural selection (MacNulty *et al.*, 2009; Charruau *et al.*, 2016; Schwarz *et al.*, 2016). In contrast, the manifestation of these ancestral aging patterns within highly modified environments may become maladaptive in domestic dogs and contribute to disease susceptibility (Charruau *et al.*, 2016). Likewise, gene expression patterns that evolved under a hunter-gatherer lifestyle in humans may lead to health problems for individuals with a Western lifestyle and diet (Kopp 2019; Johnson *et al.*, 2021). Consequently, such legacy effects may result in disease in aging individuals for both modern humans and their domestic companions (Charruau *et al.*, 2016). Several ecological studies have indicated that it is unusual for wild gray wolves to reach or surpass 10 years of age (Lawler *et al.*, 2016; Barber-Meyer *et al.*, 2021). However, age-associated pathologies, which are often observed in domestic or protected settings, are rare in natural environments. Factors such as frailty, nutritional stress, and predation dominate mortality patterns, resulting in a considerably shorter average lifespan in free-ranging populations (Tidière *et al.*, 2016). These survival data align with the view that late-life stages are infrequently attained in wild wolves. This is particularly relevant given that the onset of increased risk for CCD and the escalation in symptom severity have been reported to occur from approximately 10 years of age onward (Bray *et al.*, 2023; Turcsán and Kubinyi, 2024). There is considerable evidence that the processes leading to this clinical state begin earlier in life (Dewey *et al.*, 2019). Accordingly, it would be difficult to find signs of CCD in free-roaming wolves because they would not have enough time to develop such a pathology. However, the older wolves expressed a capacity for longevity that exceeded those of similar-sized domestic dogs and breeds (Lawler *et al.*, 2016). In contrast to free-ranging populations, evidence from captive or sanctuary settings indicates that gray wolves can achieve considerably longer lifespans, ranging from approximately 9–16 years (Mech, 1988). For instance, an investigation that assessed scapular glenoids and proximal humeral joints from wolves housed in a sanctuary environment reported mortality at ages ranging from 5 to 19 years (Lawler *et al.*, 2016). The presence of individuals surviving to such advanced ages clearly supports the genetic potential of this species to reach extended longevity. Indeed, gray wolves appear capable of living as long as domestic dogs when not exposed to the challenges of a free-roaming existence. Additionally, aged gray wolves demonstrated a lifespan potential that, in some instances, surpassed that observed in domestic dog breeds of comparable body size (Lawler *et al.*, 2016). Therefore, gray wolves kept in captivity or semi-captivity can be studied from the point of view of the onset and development of canine cognitive dysfunction, in comparison with domestic dogs, according to their longevity, and that certain age-related traits might improve survival and reproductive success (remaining present through natural selection).

Oxidative stress

An imbalance between free radical overproduction and the antioxidant defenses of the brain defines oxidative stress. This disturbance is widely recognized as a contributor to the aging process (Iakovou and Kourti, 2022; Maldonado *et al.*, 2023). The brain is especially prone to oxidative injury because it demands about one-fifth of the body's oxygen supply, is enriched in polyunsaturated fatty acids, and exhibits relatively weak endogenous antioxidant protection when compared to other tissues (Lushchak *et al.*, 2021; Sienes Bailo *et al.*, 2022). Small-breed dogs may generate reactive oxygen species at elevated levels owing to their higher metabolic intensity and rapid developmental pace (Jimenez, 2016). Circulating lipid peroxidation is reported to be more pronounced in small breeds than

in large breeds (Middleton *et al.*, 2017; Jimenez and Downs, 2020). By contrast, large-breed dogs remain in a growth phase for a more extended period (Jimenez, 2021). Interestingly, while no measurable elevation of circulating antioxidants has been observed in small breeds (Jimenez and Downs, 2020), they tend to outlive large breeds and display a lower incidence of cancer (Jimenez, 2016; Middleton *et al.*, 2017). Nevertheless, smaller-sized dogs have a higher CCD risk prevalence than larger dogs (Turcsán and Kubinyi, 2024). Naked mole-rats (NMRs, *Heterocephalus glaber*) are the longest-lived rodents with a maximum life span exceeding 37 years (Oka *et al.*, 2023). As shown in dogs, antioxidant enzyme activities in NMRs do not change with age, unlike mice of similar size, in which some antioxidant enzymes decline with age (Jimenez and Downs, 2020; Buffenstein Amoroso *et al.*, 2022). However, similar to small-breed dogs, NMRs also exhibit higher levels of lipid peroxidation (Jacobs *et al.*, 2023). NMRs exhibit a delayed aging phenotype and resistance to age-related functional decline or diseases (Oka *et al.*, 2023). The artificial selection of domestic dogs seems to have favored traits unrelated to the conservation of antioxidant defenses. Other authors have found that the levels of total antioxidants, such as bilirubin and glutathione metabolites, are significantly lower in small-breed domestic dogs than in large breeds (Jiménez, 2024).

Oxidative stress has been strongly linked to brain aging and a higher susceptibility to AD in humans (Ionescu-Tucker and Cotman, 2021; Tchekalarova and Tzoneva, 2023). Patients with AD undergo pronounced oxidative insults during disease progression, accompanied by a marked decline in endogenous antioxidant defenses compared with individuals of similar age without AD (Isik *et al.*, 2023; Jain *et al.*, 2024). Comparable patterns are seen in CCD, where oxidative lesions are strongly linked to impaired cognition (Romanucci and Della Salda, 2015; Pérez-Montero *et al.*, 2024). The accumulation of oxidative by-products parallels the severity of behavioral impairments in elderly companion dogs (Pan, 2021; Pérez-Montero *et al.*, 2024). Furthermore, reductions in brain and plasma antioxidant reserves are correlated with the progression of cognitive deficits (Mongillo *et al.*, 2015). Therapeutic strategies that include antioxidant diets and behavioral enrichment can result in significant improvements (Mazzatenta *et al.*, 2017; Blanchard *et al.*, 2025). It is important to note that oxidative stress patterns in the blood of wild canids are different from those found in domestic dogs. Recent investigations have shown that lipid peroxidation markers increase with advancing age in domestic dogs, whereas this pattern is not observed in wild canids housed in zoological facilities or under veterinary care. In contrast, wild canids demonstrate an age-related increase in total antioxidant capacity (TAC) and glutathione peroxidase (GPx) activity scales with age and maximum lifespan (Jimenez and Downs, 2020). Such physiological adaptations may contribute to the greater longevity potential of wolves. In addition, larger-bodied wild canids exhibited significantly higher TAC and GPx activity, a trend not evident in domestic dogs, suggesting that selective breeding may have diminished antioxidant defenses in the latter (Jimenez and Downs, 2020). A broader comparative study assessing oxidative stress across 48 mammalian species similarly reported that older individuals often accumulate lipid damage (Jimenez *et al.*, 2019). This outcome parallels findings in small domestic dogs but contrasts with the resilience observed in wild canids (Jimenez and Downs, 2020). The capacity of large wild species, such as the gray wolf, to enhance antioxidant defenses with age could partly explain their extended lifespan relative to domestic breeds of comparable size, representing a distinctive physiological feature not commonly seen in other mammals (Jimenez *et al.*, 2019; Jimenez and Downs, 2020). Comparable results have been noted in NMRs, which maintain stable antioxidant levels throughout aging and exhibit lifespans that far exceed those of rodents of similar body size (Jacobs *et al.*, 2023). The preservation of antioxidant defenses in NMRs is consistent with delayed senescence, as these animals display negligible age-related mortality, rarely develop cancer, and show resistance to Alzheimer's-like pathologies (Oka *et al.*, 2023). Other aging model organisms typically demonstrate that longer lifespans are associated with higher levels of antioxidants and reduced oxidative damage to most molecules (Jimenez, 2016; Domínguez de Barros *et al.*, 2023; Domínguez-De-Barros *et al.*, 2025). It is important to note that the degree of oxidative stress is also lower in healthy human centenarians than in aged subjects (Belenguer-Varea *et al.*, 2020). Healthy centenarians have a particular profile in which high levels of antioxidants seem to be important for their extreme longevity (Martínez de Toda *et al.*, 2020). The remarkable longevity of human centenarians is linked to enhanced resistance and resilience to Alzheimer's disease (Andersen, 2020). In contrast, NMRs inhabit subterranean colonies in East Africa, where oxygen availability is limited, and they have evolved a notable tolerance to hypoxic conditions (Park and Reznick, 2022; Oka *et al.*, 2023). In this context, recent comparative work has also highlighted pronounced differences in aerobic performance, hypoxia tolerance, and immune function when gray wolves are compared with domestic dogs (Yang *et al.*, 2018). Aerobic capacity, response to hypoxia endurance training, and immune function were all significantly higher in gray wolves than in domestic dogs (Yang *et al.*, 2018). All of the abovementioned characteristics, which are related to oxidative stress, may confer greater protection against CCD to the gray wolf compared to the domestic dog.

Inflammation

Inflammation is a constant biological process that occurs throughout the lifespan and is essential for defending

the body against infectious agents. Nevertheless, the same response can harm cells, tissues, and organs and has been identified as a major contributor to the aging process (Li *et al.*, 2023). This association has led to the concept of "inflammaging" which describes a persistent, low-grade inflammatory state that tends to increase with age (Calder *et al.*, 2017; Franceschi *et al.*, 2018; Saavedra *et al.*, 2023). Accumulating evidence indicates that the interplay between aging and inflammation is highly context-dependent and may differ across species and physiological conditions. Thus, a recent study compared exhaustive data on inflammatory molecules from two industrialized populations (Singapore Longitudinal Aging Study-SLAS and Italian-InCHIANTI) and two non-industrialized indigenous populations (Bolivian Amazon's Tsimane and Peninsular Malaysia's Orang Asli) and observed clear links between inflammatory aging and chronic diseases in industrialized populations, unlike populations with high infection rates (no industrialized) in which inflammation seems to reflect more infectious diseases than aging itself (Franck *et al.*, 2025). The evidence indicates that inflammatory processes are not uniform but can manifest through diverse mechanisms, showing variable associations with aging depending on the environmental exposures characteristic of a given population. Moreover, current data support the idea of an evolutionary imbalance between the immune system and modern ecological conditions (Franck *et al.*, 2025). Thus, age-related inflammation may represent less of a natural outcome of senescence and more of an adaptive response to industrialized lifestyles and environments. Numerous evidence suggest that the domestic dog has evolved toward high dependence and sensitivity against industrialized human environments due to its history of domestication and adaptation to living with humans. This has led to the dog becoming more vulnerable to stress, diseases, and social changes compared with gray wolves in semi-captivity, which retain more resilient and adaptive behaviors outside human control (Marshall-Pescini *et al.*, 2016; Wynne, 2021; Range and Marshall-Pescini, 2022; Tancredi and Cardinali, 2023). Day (2010) described that in domestic dogs, aging entails the elevation of low-degree systemic inflammation, a decrease in immune function, and greater susceptibility to chronic diseases (Day, 2010). Domestic dogs show increased spontaneous chronic inflammation with age (inflammaging) (Jiménez, 2023; Schmid *et al.*, 2024). In this sense, domestic dogs experience an increase in the expression of chronic inflammation markers, for example, IL-6, TNF -α (Schmid *et al.*, 2024), and IgM, oxidative damage, and C-reactive protein (CRP) (Alexander *et al.*, 2018).

Cerebral inflammation plays a crucial and multifactorial role in AD pathogenesis (Si *et al.*, 2023; Thakur *et al.*, 2023; Almutary *et al.*, 2025). Far from being just a consequence of neurodegeneration, today it is recognized as an active process that contributes to the disease's onset and progression (Twarowski and Herbert, 2023). Neuroinflammation arises from the activity of multiple cellular and molecular components, including astrocytes, microglial populations, and signaling proteins such as chemokines and cytokines. This inflammatory cascade disrupts the neuronal microenvironment, resulting in neuronal injury, oxidative stress, and, in some cases, the programed cell death, processes that have been strongly associated with AD onset (Fakhoury, 2020; Zhang *et al.*, 2024). Chronic neuroinflammation is increasingly recognized as a central feature of age-related cognitive decline in dogs in veterinary medicine. Microglia, the innate immune cells of the brain, exhibit sustained activation in response to neuropathological alterations that occur with aging. Their persistent release of inflammatory mediators promotes neurodegenerative changes, which are closely associated with the clinical presentation of CCD (Pan *et al.*, 2018; Prpar-Mihevc *et al.*, 2020; Hines *et al.*, 2023). Although classical systemic inflammatory markers (e.g., IL-6 or tumor necrosis factor a in plasma) have not been consistently found to be significantly elevated, multiple studies have found that central neuroinflammation (e.g., glial activation and accumulation of Aβ and phosphorylated tau) and increased neurofilament light chain (NfL) levels in the blood are robustly associated with cognitive decline in older dogs. These changes may reflect inflammatory processes in the brain that accompany or precede CCD, similar to that observed in AD (Pan *et al.*, 2018; Vikartovska *et al.*, 2021; Phochantachinda *et al.*, 2021; Hines *et al.*, 2023; Wu *et al.*, 2023; Kim *et al.*, 2024). No comparative studies have directly measured the levels of proinflammatory markers (IL-6, TNF-α, and CRP) in older domestic dogs and semi-captive gray wolves. However, some studies have described how domestic dogs develop greater chronic inflammation compared with captive gray wolves, suggesting that domestication may have influenced differential immunological responses (Marsden *et al.*, 2016; Yang *et al.*, 2018; Barragán-Sánchez *et al.*, 2025). The lower levels of chronic inflammation observed in wolves, relative to domestic dogs, may indicate a lower susceptibility to age-related cognitive decline. However, given the limited data available on cognitive aging in wolves, such an interpretation should be regarded as preliminary. Further comparative studies are needed to determine whether reduced systemic inflammation indeed translates into lower CCD incidence or severity.

Sleep disturbances

Sleep is a vital physiological function in mammals, including domestic dogs. It contributes to the restoration of energy reserves, supports the stabilization and reorganization of memory processes, counteracts performance deficits resulting from wakefulness, and facilitates the clearance of potentially harmful metabolites that accumulate in the brain during periods

Fig. 1. The process of dog domestication approximately 15,000 years ago: population bottleneck since wolves, human artificial selection, and modern dog breeds diversity.

of activity (Krueger *et al.*, 2016; Kis *et al.*, 2017; Frank and Craig Heller, 2019; Iotchev *et al.*, 2020; Ji and Yun, 2025). Sleep is essential for preserving cognitive stability, and its relevance increases with aging, as the clearance of Aβ-closely associated with AD pathogenesis and occurs predominantly during sleep (Mondino *et al.*, 2023). In mammals, the sleep-wake cycle is typically divided into three distinct phases: wakefulness (W), non-rapid eye movement sleep (NREM, also referred to as slow-wave sleep), and rapid eye movement sleep, REM (Mondino *et al*., 2021). Accumulating evidence shows that sleep disturbance contributes to cognitive decline and increases the risk of AD dementia by increasing the brain's Aβ burden (Cedernaes *et al.*, 2017; Shi *et al.*, 2018; Ungvari *et al.*, 2025). According to meta-analyses, both decreased NREM and REM were significantly associated with the severity of cognitive impairment in patients with AD (Zhang *et al.*, 2022). Similar to humans and other mammals, dogs experience age-related changes in their sleep-wakefulness cycle (Woods *et al.*, 2020; Mondino *et al.*, 2023). CCD has been associated with significant alterations in sleep behavior in dogs (Dewey *et al.*, 2019). Evidence from a longitudinal study indicated that sleep-wake rhythm disruptions were the most frequently observed clinical feature of the disorder (Fast *et al.*, 2013). Consistent with findings in AD, dogs with higher dementia scores and poorer problem-solving performance spent less time in NREM and REM sleep. Recently, a non-invasive polysomnography protocol was applied to record the sleep of captive, extensively socialized young and adult wolves. The control population of companion dogs included both juvenile and geriatric individuals matched to the age categories of the corresponding wolf groups. The analysis indicated that while young dogs and wolves exhibited a comparable distribution of sleep stages, dogs spent a shorter duration in REM sleep. This difference was even more evident in senior animals (Reicher *et al.*, 2022). REM sleep, the stage during which memory consolidation occurs (Mondino *et al.*, 2023), is essential for maintaining neuronal homeostasis in the brain. Disturbances in REM sleep can impair neurogenesis and synaptic pruning, and prolonged reductions or loss of this sleep phase have been associated with the development of neurodegenerative changes (Chauhan and Mallick, 2019; Zhang *et al.*, 2022). Increased REM sleep may contribute to the decreased vulnerability of gray wolves to CCD. However, the relationship between REM sleep duration and CCD remains correlative.

Periodontal disease

Periodontal disease (PD) is one of the most common oral disorders affecting both dogs and humans. It involves a progressive inflammatory reaction triggered by subgingival colonization with diverse pathogenic microorganisms that damages the connective tissues supporting the teeth, ultimately leading to tooth loss (Kinane *et al.*, 2017; Cunha *et al.*, 2022). The likelihood and severity of PD increase with advancing age (Wallis *et al.*, 2018; Wallis *et al.*, 2019; Wallis and Holcombe, 2020). Interestingly, the progression and age-related aggravation of this condition occur at an even faster rate in dogs than in humans, despite sharing similar underlying causes (Struillou *et al.*, 2010). Despite dietary improvements that have positively influenced the overall health of companion dogs, PD remains a major oral health concern (Cunha *et al.*, 2022). It is considered the most prevalent dental disorder among adult dogs, with reported rates ranging from 44% to nearly 100% (Stella *et al.*, 2018; Wallis *et al.*, 2019; Wallis and Holcombe, 2020). The condition is largely associated with insufficient dental hygiene practices in household animals (Garanayak *et al.*, 2019; Wallis *et al.*, 2019). Although all breeds are susceptible (Di Bello *et al.*, 2014), smaller dogs (under 15 kg), and brachycephalic types tend to be more frequently and severely affected than larger breeds (Wallis *et al.*, 2021). As previously mentioned, are precisely small breeds that have a higher prevalence of CCD (Turcsán and Kubinyi, 2024). Moreover, since PD is more prevalent and more severe in small and brachycephalic breeds, gray wolves, which are larger in size (generally > 25 Kg), would have lesser CCD risk prevalence. Over the last decade, a large body of evidence has demonstrated that PD and its characteristic oral microbial dysbiosis play an important role in the initiation and progression of AD (Dominy *et al.*, 2019; Wan and Fan, 2023; Chaple-Gil *et al.*, 2025), with PD being recognized as a risk factor for the development of AD (Dominy *et al.*, 2019; Hu *et al.*, 2021; Chaple-Gil *et al.*, 2025). Recent experimental research in animal models has provided stronger support for a possible causal association between periodontitis and AD, describing biologically plausible and clinically consistent pathways through which periodontal inflammation might contribute to the onset or progression of AD (Dominy *et al.*, 2019; Hajishengallis and Chavakis, 2021; Kong *et al.*, 2025). To explore the links between PD and CCD, a scoring system was applied to evaluate PD severity in dogs diagnosed with presumptive CCD and in control dogs without any reported signs of cognitive decline. Results showed a significant association between periodontal and cognitive scores, with dogs with more severe PD having higher cognitive impairment scores and vice versa (Dewey and Rishniw, 2021; Templeton *et al.*, 2023). PD is less common in wild carnivores than in domestic dogs (Kapoor *et al.*, 2016; Döring *et al.*, 2018). Several domestication-related elements—including stress, increased longevity, dietary composition, and texture, along with genetic predisposition—may help explain why dogs exhibit a higher frequency of PD than their wild relatives (Pires *et al.*, 2020). Evidence indicates

that the physical and nutritional characteristics of food are key determinants of oral health in domestic dogs. Certain types of diet promote inflammation in the gums and teeth. Diets with soft, wet, or paste-like textures (e.g., canned or home-cooked foods) offer less mechanical abrasion, promoting bacterial plaque accumulation at the gingival margin and on tooth surfaces, which in turn provokes gingivitis and facilitates enamel demineralization (Oba *et al.*, 2022; Wallis *et al.*, 2025). Diets rich in fermentable carbohydrates similarly feed acid-producing bacteria, lowering oral pH and promoting gum and dental tissue inflammation (Hiney *et al.*, 2021). Harder, dry, or extruded foods, dental chews, or well-formulated raw meat/bone diets tend to reduce plaque and calculus, maintain a higher salivary pH, and are associated with fewer signs of gingival and dental inflammation, thereby maintaining a healthier oral microbiota (Cunha *et al.*, 2022; Hiney *et al.*, 2024). Additionally, the absence of mechanical cleaning and the presence of dietary sugars and acids can alter plaque composition, increasing the proportion of Gram-negative anaerobes and predisposing to periodontal dysbiosis (Borsa *et al.*, 2021; Cunha *et al.*, 2022). Consequently, feeding practices that incorporate natural chewing activity—such as bones retaining muscle or connective tissues—have been consistently associated with lower prevalence of gingivitis and periodontal disorders compared with predominantly soft-textured diets (Marx *et al.*, 2016; Pinto *et al.*, 2020; Casarin *et al.*, 2023). Research on the trophic behavior of the Iberian wolf in Europe shows that medium-sized ungulates are their principal prey, yet domestic species also make up a notable share of their consumption (Barja *et al.*, 2023). The occasional intake of fish has also been documented (Pires *et al.*, 2020). Where wild prey is scarce due to human disturbance, these predators shift toward anthropogenic sources, relying on livestock and human-related materials, such as waste and carcasses (Newsome *et al.*, 2016). Dental pathologies were examined in predominantly adult Iberian wolf specimens from a Portuguese museum collection. A total of 65 deceased individuals—comprising 61 complete crania and 4 isolated mandibles—collected in Portugal between 1977 and 1995 were assessed. Oral pathology was assessed by combining visual inspection with radiographic techniques, documenting wear, breakage, gum disease, and additional dental problems. The survey revealed that nearly 90% of the teeth exhibited some degree of PD between stages 2–4. However, most findings were classified as stage 2, with a prevalence of 73.9% in the upper jaw and 68% in the lower jaw. Severe manifestations (stage 4) are rare (Pires *et al.*, 2020). The link between nutrition and periodontal changes during aging is still under debate. A possible explanation is that older animals exert less chewing pressure on hard dry feed, which reduces stimulation of the periodontal tissues and diminishes saliva flow, which could accelerate oral disease (Inui 2015). In contrast, according to a 2005 review of biting mammals, the gray wolf has the strongest bite of any canine, at 593 Newtons (Wroe *et al.*, 2005), which may contribute to their developing less severe PD than dogs. Considering the established association between PD and CCD in domestic dogs, this finding suggests a potential protective effect in wolves. However, direct comparative studies assessing cognitive outcomes are required to confirm this.

The results of this study indicate that key risk factors for CCD are more pronounced in domestic dogs than in

Table 1. Main differences in CCD risk factors between domestic dogs and gray wolves kept in captivity or semi-captivity. Refer to the references in the manuscript.

CCD-Risk factors	Dog	Wolf
Aging	-Small potential life span -Maladaptive ancestral patterns may cause disease	-Long potential life span -May maintain fitness
Oxidative stress	-High lipid levels peroxidation -Decline or no increase antioxidant capacity -Low aerobic capacity, hypoxia endurance and immune function	-No increase in lipid damage -Increased total antioxidant capacity/ antioxidant enzymes -Higher aerobic capacity, hypoxia endurance and immune function
Inflammation	-High levels of chronic inflammation -More vulnerable to stress, diseases and social changes	-Lower chronic inflammation -More Resilient and Adaptive behaviors
Sleep disorders	-Low time in the REM	-Higher REM time
Periodontal disease	-High (diet, genetics, domestication, stress)	-Lower

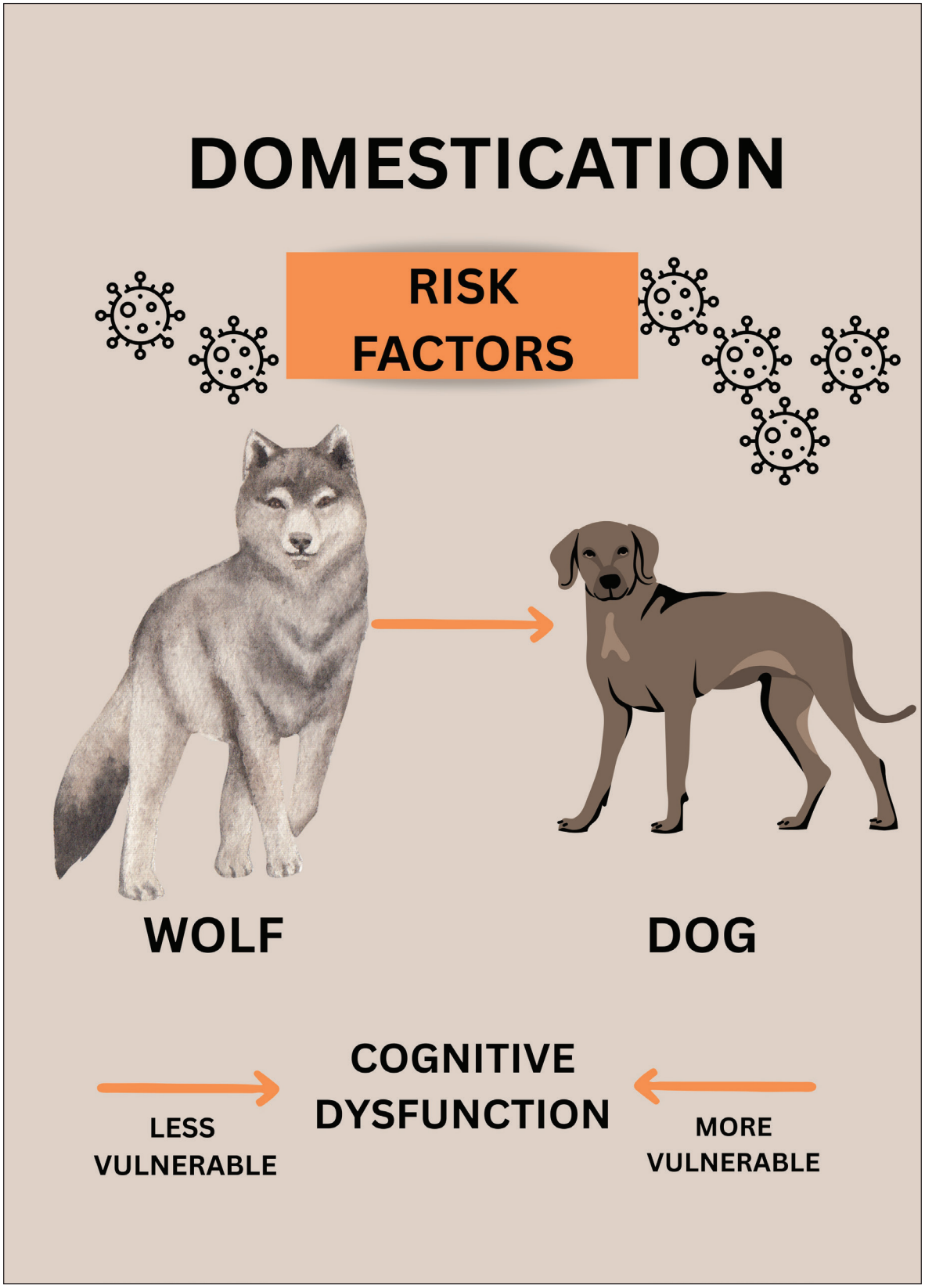

Fig. 2. Domestication may increase the incidence of canine cognitive dysfunction (CCD)-risk factors in dogs compared with gray wolves kept in captivity or semi-captivity; hence, wolves may be less vulnerable to CCD than dogs.

gray wolves maintained in captivity or semi-captivity (Table 1; Fig. 2).

Conclusion

The results of this literature review suggest that dog domestication may have increased their vulnerability to canine cognitive dysfunction compared with the gray wolf. The risk factors analyzed are more pronounced in domestic dogs than in gray wolves kept in captivity or semi-captivity. This finding suggests that gray wolves may exhibit lower susceptibility to age-associated cognitive decline. However, given the scarcity of neuropathological and behavioral data on aged wolves, these conclusions should be interpreted with caution. Taken together, the results reinforce the need to expand comparative research between dogs and wolves, both at the molecular and behavioral levels, to clarify the role of domestication in brain health and aging. Furthermore, the findings highlight the importance of implementing preventive strategies aimed at mitigating the identified risk factors in domestic dogs, which could help reduce the incidence and progression of CCD. Within the One Health perspective, examining naturally occurring cognitive decline associated with aging in domestic dogs in comparison to wolves can provide valuable knowledge, offering opportunities to deepen our understanding of neurodegenerative diseases across species, including humans.

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Conflict of interest

The authors have no competing interests to declare.

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Authors' contributions

RCF: conceptual design, data acquisition, methodology, figures, and original draft preparation. RSP: table, review, and editing. Both authors have approved the final version.

Data availability

All relevant data are included within the manuscript.

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