Who let the cats out: a global meta-analysis on risk of parasitic infection in indoor versus outdoor domestic cats (*Felis catus*)

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Abstract

Parasitic infection risks in domestic animals may increase as a result of outdoor activities, often leading to transmission events to and from owners, other domestic animals, and wildlife. Furthermore, outdoor access has not been quantified in domestic animals as a risk factor with respect to latitude or parasite transmission pathway. Cats are an ideal model to test parasitic infection risk in outdoor animals because there have been a considerable number of studies analyzing this risk factor in this species; and unlike other domestic pet animals, there is a useful dichotomy in cat ownership between indoor-only cats and those with outdoor access. Thus, we used meta-analysis to determine whether outdoor access is a significant risk factor for parasitic infection in domestic pet cats across 19 different pathogens including many relevant to human, domestic animal and wildlife health such as *Toxoplasma gondii*, *Toxocara cati*, and *Giardia lamblia*. Cats with outdoor access were 2.77 times more likely to be infected with parasites than indoor-only cats. Furthermore, absolute latitude trended towards significance such that each degree increase in absolute latitude increased likelihood of infection by 4%. Thus, restricting outdoor access can reduce risk of parasitic infection in cats therefore also reducing risk of zoonotic parasite transmission, spillover to sympatric wildlife, and negative impacts on feline health.

Keywords: felid, latitude, pathogen, pet, transmission, zoonotic

Background

Domestic animals, including pets, are responsible for spreading pathogens to humans and sympatric wildlife (1-3). Notable examples include dogs in transmitting rabies to humans (CITE) or cattle transmitting *Cryptosporidium parvum* to humans and sympatric wild ruminants (5,6). However, relatively few domestic animals have such stark dichotomies regarding outdoor access, where environmental contact can therefore be evaluated as a means of exposure. Understanding how outdoor access affects infection, and infection by which pathogens are most affected by this risk factor, can have important implications when mitigating parasite transmission among domestic animals, humans and wildlife.

A model organism that is widespread and lives in close proximity to humans is the domestic cat (*Felis catus*), which has coexisted with humans globally for millennia (ca. 9500 years; 7,8,9). In fact, pet cats often sit on their owner's lap and sleep in their beds (10). Furthermore, cats are common as pets around the world, with an estimated 89-90 million in the United States alone (10). Given that cats are widespread and associated with humans, risk factors for parasitic infections in pet cats are important for zoonotic parasite transmission and have implications for cat health as well as spillover of parasites to sympatric wildlife (11,12).

Domestic pet cats allowed outdoors can also pose health risks to cat owners (13-19). For instance, *Toxoplasma gondii* (the causative agent of toxoplasmosis; 15) and *Bartonella henslae* (which causes cat-scratch disease; CITE) both infect people worldwide. In addition, there are a number of infectious diseases that have health consequences for cats themselves, including feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), and feline coronavirus (FCoV), all associated with morbidity. For example, FIV causes immunosuppression which may in turn increase susceptibility to other infections (CITE). Finally, interactions with sympatric wildlife may result in spillover of parasites from domestic cats. For example, domestic cats have been responsible for the spread of FIV to mountain lions (*Puma concolor*) and feline panleukopenia to the Florida panther (*Puma concolor coryi*) (11,12).

Many parasites known to infect cats have life cycles involving transmission from soil, prey, or other cats (15, 21-23). Here, we hypothesize that cats with outdoor access (meaning free-roaming) will be more likely to be infected with parasites than indoor-only cats. To test our hypothesis we conducted a meta-analysis of outdoor access as a risk factor for infection across 19 pathogens and 16 countries. Because differences in risk of infection may exist due to changes in pathogen diversity (i.e. richness and abundance) across transmission type and space (24-26), we considered transmission type and latitude as moderators.

Results

Overall Effects

Our synthesis incorporated 21 studies with 31 sets of infection prevalence between indoor-only cats and those with outdoor access due to multiple pathogens in some studies. Among the 21 studies, 19 parasites were analyzed (see Supplementary Figure 1 for odds ratios by parasite and study). According to the overall model, cats with outdoor access are 2.77 (2.10-3.67 95% Confidence Limit (CL); $p < 0.0001$) times as likely to be infected with parasites as indoor-only cats (Figure 1). Heterogeneity, or differences in outcomes between studies (Higgins 2002), in the overall model was high ($I^2 = 84.02\%$). The publication bias analysis estimated 6 missing studies on the left side of the funnel plot (Figures 2a, 2b), and incorporation of these randomly created studies using the trim and fill technique still resulted in infection status as a signifticant risk factor (2.39 OR; p < 0.0001).

Moderators

Transmission type was not a significant moderator (p = 0.62; Figure 1), but infection risk in indoor-only pet cats versus those with outdoor access trended towards significance with latitude as a moderator (Figure 2). Specifically, for every degree increase in absolute latitude, cats with outdoor access were 4% more likely to be infected with parasites (1.0%-7.0% 95% C.L.; p = 0.081; Figure 2a). Heterogeneity decreased considerably with the inclusion of this moderator to $I^2 = 55.7\%$ (from 84.0%), suggesting that differences in latitude may account for a significant portion of the variation among studies.

To determine the true effect of latitude (since odds ratio is only a relative comparison of the indoor-only and outdoor cats), we also conducted a meta-regression using a raw proportion of the total number of infected cats compared to the total number sampled, with absolute latitude as a moderator. In this model, the overall proportion of infected cats significantly increased 0.7% (0.17%-1.3% or 1.01-1.07 OR1 95% C.L.; p = 0.010) for each degree latitude increase (see Figure 2b), indicating that increasing risk of infection in cats with outdoor access with increasing latitude is an important interaction in the overall model.

Discussion

Outdoor access is a significant risk factor for parasitic infection in pet cats, where cats with outdoor access were 2.77 times more likely to be infected with parasites than indoor-only cats, demonstrating support for our hypothesis. Furthermore, latitude had a marginally significant effect on the likelihood of infection. Of the 21 studies included in our meta-analysis, only three suggested non-significantly higher risk of infection in indoor-only cats. While there was publication bias indicating positive results for outdoor access as a risk factor, following the trim and fill method, the effects were similar and still significant, suggesting that publication bias did not influence the significance of the meta-analysis results.

The parasites we analyzed have relevance to zoonotic parasite transmission, feline health, and wildlife conservation. Given the association between humans and domestic cats (9), habitat and lifestyle risk factors ought to be investigated with respect to zoonotic parasite infection. Furthermore, despite the ubiquity of domestic cats, cat-human transmission is likely under-reported (29).

Not only are parasitic infections impactful to feline health, they are also relevant to neighboring wildlife. Parasites of domestic cats have already been reported in sympatric wild congeners, such as FIV in cougars (*Felis concolor*) and Florida panthers (*Felis concolor coryi*) and *Candidatus Mycoplasma haemominutum* in wild felids deriving from domestic cats (11,12, 30). Positive associations between FHV-1 and *Bartonella* in cougars and urban land-use have also been reported, suggesting interactions with free-roaming domestic cats (31). However, further investigation into infection prevalence in wild populations and risk factors for transmission between domestic cats and these species is warranted (12).

Among the transmission types analyzed (direct, vector-borne, and environmental), none differed significantly from each other with respect to effect of outdoor access on parasitic infection. One explanation is the small sample size between groups or within studies, and high variability across studies. Additionally, a Bayesian approach using a Markov Chain Monte Carlo method may have better accounted for this uncertainty (Higgins et al. 2009). Directly transmitted parasites (i.e., cat to cat transmission) such as FIV, was not significantly different from other transmission types with respect to outdoor access, which suggests that these parasites may be more frequently encountered through contact with feral populations or other pet cats allowed outdoor access rather than other cats in shelters or the household.

Latitude as a moderator on infection risk in cats with outdoor access trended towards a significant positive effect. The trend identified ran contrary to what has been demonstrated for parasite richness and diversity, which typically decreases with increasing latitude (24-26). Although one might assume that higher parasite diversity results in higher risk of infection in hosts, there have been multiple findings demonstrating the opposite—that infection rates decrease with higher parasite diversity (32, 33) —which is consistent with our findings that cats with outdoor access in northern regions are at greater risk of infection. Interestingly, these results were also consistent with global patterns of zoonoses in rodents, a common prey of domestic cats, where higher latitudes saw greater numbers of species carrying zoonoses (34). Higher latitudes also predicted greater risk of helminth parasites from wildlife found in domestic animals (CITE Wells).

Organizations, including American Bird Conservancy, People for the Ethical Treatment of Animals, and the American Veterinary Medical Association (AVMA), have created campaigns that raise awareness about the detrimental impacts of cats with outdoor access in relation to feline health and impacts on wildlife (35, 36, CITE), though allowing pet cats outdoors is still common occurrence (37,38). Increased awareness of the risks involved in outdoor access is one facet, but legislation restricting outdoor access in cats (similar to rules imposed on dog owners) would be an ideal outcome (39). Despite the hurdles in changing public perception and enacting new legislation, this issue has a relatively simple solution—keep cats indoors.

Domestic cats are widespread and act as potent reservoirs for parasites transmissible to wildlife and humans (40-43), and are a unique model for understanding pathogen transmission dynamics given their global ubiquity and their contact with humans, other animals and the environment. Our analysis is the first to summarize across a broad range of parasites and geographic localities that outdoor access increases odds of parasitic infection in pet cats as a model for domestic animals. Future research might investigate this risk factor across other domestic species and across factors such as land use and presence of sympatric congeners to parasitic infection risk. While we do not necessarily advocate that all domestic animals be restricted indoors, determining routes and risk factors of transmission with respect to environmental contact may be useful in mitigating parasitic infection in domestic animals.

Methods

Literature Search

A literature search using Web of Science was conducted on 11 January 2018, following PRISMA (44) guidelines with the following keywords: “feral cat” OR “feral dog*” AND “infect*” OR “parasit*” OR “disease*” OR “virus*”, excluding reviews. This search returned 500 research articles, which were manually sorted for relevance. Final output was based on the following exclusion criteria: review articles; case studies;

sample size <20 cats sampled; lack of comparison between indoor-only versus outdoor access pet domestic cats; or outdoor access group included feral or stray cats.

An additional search was performed in Web of Science on 31 May 2018, using the following keywords: "domestic cat*" OR "pet cat*" OR "Felis catus" AND "outdoor access" AND TOPIC: ("infection*" OR "parasit*" OR "disease*" OR "pathogen*" OR "virus*" OR "sick*" OR "illness*") which returned 213 additional articles. One search was conducted in Google Scholar using the keywords as follows: domestic OR pet cat OR Felis catus, outdoor access, infection* OR parasite*. This Google Scholar search returned 1,190 results. We manually sorted through the first 100 studies using the exclusion criteria described above. After manually sorting the original output of 813 studies, 21 studies fit the inclusion criteria and were used in the meta-analysis (see https://figshare.com/s/3eebaf42e161c0e7e1ef to access data-set).

Treatment of moderators

Parasite transmission type was split into direct, vector-borne, and environmental pathways (see Supplementary Figure S2 for list of citations for each parasite). Latitude of each study was determined using Google Earth by selecting the middle of the smallest geographic area provided (such as country, state/province or city). Studies that included large geographic areas (multiple countries) were removed from analysis of this moderator

Statistical Analysis

All analyses were completed in R version 1.1.453 using the metafor package for random effects models tto account for between study heterogeneity using the odds ratio effect size (for R code used, see figshare.com/s/a334c7815b128cb63b98) (45), where an odds ratio (OR) is the probability of an outcome as related to an exposure (46). Here, the outcome is likelihood of infection as related to outdoor access as the exposure mechanism. OR = 1 means outdoor access does not affect the likelihood of infection; OR < 1 means outdoor access is associated with lower odds of infection; and OR > 1 means outdoor access is associated with greater odds of infection. We considered $p < 0.05$ to indicate significance of effect size. Two moderators, transmission type and latitude, were evaluated using mixed effects models.

To estimate heterogeneity across studies, we used I^2, where a value of 0% indicates no heterogeneity; 25% indicates low heterogeneity; 50%, moderate; and 75% is considered high heterogeneity (47, 48). To test for publication bias, we used a trim and fill method to estimate the number of missing studies (45, 49).

Competing Interests

The authors declare no competing interests.

Author contributions

KC designed the study, conducted literature review and statistical analyses, and wrote the manuscript; AW participated in statistical analyses, study design, and manuscript writing; CL participated in statistical analyses and manuscript writing; SZ participated in statistical analyses and manuscript writing.

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Figure Legends

Figure 1- Overall effect size and effect sizes across transmission type moderators for infection prevalence in cats with outdoor access versus indoor-only cats. Cats with outdoor access are 2.77 (2.10-3.67 95% CL; $p < 0.0001$) times as likely to be infected with parasites as indoor-only cats. Transmission types include environmental (soil-borne and intermediate prey hosts), vector-borne, and direct transmission. Transmission type was not a significant moderator ($p=0.62$) for outdoor access on infection prevalence in domestic pet cats.

Figure 2 a) Plot demonstrating the relationship between odds ratio for each study/parasite in domestic pet cats across a range of latitudes. For every degree increase in latitude, cats with outdoor access were 1.04 times as likely to be infected with parasites (1.01-1.07 95% C.L.). This relationship, treating latitude as a moderator to indoor/outdoor infection risk, was trending towards significance ($p=0.08$).

b) Total proportions of infected cats for each study/parasite across a range of latitudes where overall proportion of infected cats significantly increased 0.7% (0.17%-1.3% 95% C.L.; $p=0.01$) for each degree latitude increase.

Table 2. Pathogen prevalence in domestic cats (*Felis catus*) from each study by country

Pathogen	Country	Prevalence	Citations
Aelurostrongylus abstrusus	Cyprus	0.02	(77)
Cystoisospora revolta	Cyprus	0.12	(77)
Cytauxzoon spp.	Spain	0.01	(78)
Dipylidium caninum	Cyprus	0.01	(77)
Feline coronavirus	Australia	0.41	(79)
FIV	Australia	0.10	(80)
		0.31	(81)
	Canada	0.63	(82)
Giardia lamblia	Cyprus	0.07	(77)
Hemoplasma spp.	Chile	0.15	(83)
Mycoplasma spp.	Spain	0.07	(78)
	Germany	0.10	(84)
	Switzerland	0.09	(86)
Neospora caninum	Brazil	0.03	(87)
Taenia spp.	Cyprus	0.01	(77)
Toxocara spp.	Cyprus	0.12	(77)
	Netherlands	0.05	(88)
Toxoplasma gondii	Estonia	0.62	(89)
	Pakistan	0.26	(90)
	Latvia	0.53	(91)
	Romania	0.48	(92)
Trichuris spp.	St. Kitts	0.22	(93)
Troglostrongylus spp.	Cyprus	0.05	(77)
	Netherlands	0.20	(94)