The energetic costs of sub-lethal helminth parasites in mammals: a meta-analysis

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ABSTRACT

Parasites, by definition, have a negative effect on their host. However, in wild mammal health and conservation research, sub-lethal infections are commonly assumed to have negligible health effects unless parasites are present in overwhelming numbers. Here, we propose a definition for host health in mammals that includes sub-lethal effects of parasites on the host's capacity to adapt to the environment and maintain homeostasis. We synthesized the growing number of studies on helminth parasites in mammals to assess evidence for the relative magnitude of sub-lethal effects of infection across mammal taxa based on this expanded definition. Specifically, we develop and apply a framework for organizing disparate metrics of parasite effects on host health and body condition according to their impact on an animal's energetic condition, defined as the energetic burden of pathogens on host physiological and behavioural functions that relate directly to fitness. Applying this framework within a global meta-analysis of helminth parasites in wild, laboratory and domestic mammal hosts produced 142 peer-reviewed studies documenting 599 infection-condition effects. Analysing these data within a multiple working hypotheses framework allowed us to evaluate the relative weighted contribution of methodological (study design, sampling protocol, parasite quantification methods) and biological (phylogenetic relationships and host/parasite life history) moderators to variation in the magnitude of health effects. We found consistently strong negative effects of infection on host energetic condition across taxonomic groups, with unusually low heterogeneity in effect sizes when compared with other ecological meta-analyses. Observed effect size was significantly lower within cross-sectional studies (i.e. observational studies that investigated a sub-set of a population at a single point in time), the most prevalent methodology. Furthermore, opportunistic sampling led to a weaker negative effect compared to proactive sampling. In the model of host taxonomic group, the effect of infection on energetic condition in carnivores was not significant. However, when sampling method was included, it explained substantial inter-study variance; proactive sampling showing a strongly significant negative effect while opportunistic sampling detected only a weak, non-significant effect. This may partly underlie previous assumptions that sub-lethal parasites do not have significant effects on host health. We recommend future studies adopt energetic condition as the framework for assessing parasite effects on wildlife health and provide guidelines for the selection of research protocols, health proxies, and relating infection to fitness.

Key words: wildlife health, disease ecology, fitness, host–parasite, energetics, trade-offs, body condition, nutritional ecology.

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I. INTRODUCTION

(1) Helminths and mammals

Parasites are 'bad', meaning that, by definition, they must have net negative effects on their hosts, although these effects can be subtle (Poulin, 2007). In wild mammal research and conservation, emphasis has been placed on 'infectious diseases' or 'pathogens' and their relation to observed morbidity and mortality at a local scale (Han & Ostfeld, 2019). As a result, the literature has been strongly biased towards studies of microparasites such as bacteria, viruses, and protozoan parasites with clear pathogenic effects on their hosts (Geraci & St. Aubin, 1987; McCallum & Dobson, 1995; Woodroffe, 1999; Lafferty & Gerber, 2002; Altizer *et al.*, 2003; De Castro & Bolker, 2004; Smith, Sax & Lafferty, 2006; Pedersen *et al.*, 2007; Han & Ostfeld, 2019). Historically, macroparasites (helminths: nematodes, trematodes, cestodes, and acanthocephalans), were often assumed to be benign (Irvine, 2006; Pedersen *et al.*, 2007; see online Supporting Information, Appendix S1) and still receive less attention (Han & Ostfeld, 2019). Mammals were frequently reported to be unaffected by helminths due to the lack of 'observable' damage directly related to infection (Aznar *et al.*, 2001; Samuel, Pybus & Kocan, 2001; Delahay, Smith & Hutchings, 2009; Raga *et al.*, 2009), even when found in their thousands in a single host (Geraci & St. Aubin, 1987; Daily, 2005). For example, cestodes and trematodes were commonly assumed to have no 'significant' effects on wildlife populations (Samuel *et al.*, 2001; Botzier & Brown, 2014). However, helminths are ubiquitous and can have many complex effects on host behaviour, body condition, fecundity, population dynamics, systemic health, and concomitant infections (Hutchings *et al.*, 2006; Beldomenico *et al.*, 2008*a*; Degen, 2008; Bordes & Morand, 2011; Buck & Ripple, 2017; Sanchez *et al.*, 2018; Defolie, Merkling & Fichtel, 2020). Recent studies in disease ecology have emphasized the importance of these diverse effects on host health and fitness. However, measuring such effects remains a challenge and research on sub-lethal infections and their links to physiological or behavioural changes in mammalian hosts remain underrepresented (Han & Ostfeld, 2019).

Past assumptions of insignificance may thus have been due to the difficulties in identifying links between endoparasites and host health. Inherent methodological limitations associated with wild mammal research also restricts empirical assessment of these links (Irvine, 2006; Lachish & Murray, 2018). This may explain why wildlife health disciplines often focus on identified diseases or pathogens, and how they influence observable clinical signs. Such signs are easier to analyse from carcasses, but also limit our ability to assess the potential significance of endoparasite effects that are not obviously related to morbidity (Samuel *et al.*, 2001). Ethical concerns around sampling of and experimentation on wild mammals further restrict studies to opportunistic collection and *post-hoc* analysis of carcasses. Proxies for endoparasite effects are thus *de facto* biased towards direct pathology or mortality, with confounding factors on host health not always quantifiable. Conversely, field observations of live animals mostly restrict parasite identification to faecal egg counts (FECs) and non-invasive metrics of host health, behaviour, or population dynamics (Sanchez *et al.*, 2018; Shanebeck & Lagrue, 2020). Controlled, experimental infection and observation of wild mammals is rare, which limits our knowledge of sub-lethal effects like stress, reproductive behaviour/output, food intake, physiochemical disruption, or even common, non-specific clinical indicators like diarrhoea, lethargy, pain, or fever (Samuel *et al.*, 2001; Sanchez *et al.*, 2018).

(2) Shifting the relevance paradigm: fitness rather than mortality

Host health, in a broad sense, and the relevance of various parasites or pathogens are often defined by the presence or

absence of 'disease' (pathological signs and mortality) (Tompkins *et al.*, 2011; Stephen, 2014; Sanchez *et al.*, 2018), not fitness. Yet, while highly virulent parasites are often assumed to be the greatest threat for hosts, those of moderate virulence are predicted to affect host population health more strongly (Riordan, Hudson & Albon, 2007; Ryser-Degiorgis, 2013). Sub-lethal parasites tend to infect larger proportions of host populations and have a deeper and longer lasting influence on host energetics, reproductive success and population growth compared to lethal parasites that infect and kill a small percentage of the host population (Irvine, 2006; Riordan *et al.*, 2007; Tompkins *et al.*, 2011).

Individual and population fitness result from a precarious balance between fecundity and survival (maintenance, repair, growth), the currency of which is energy availability (Schoener, 1971; Araújo, Bolnick & Layman, 2011; Berta, Sumich & Kovacs, 2015; Costa-Pereira *et al.*, 2019). Mammals (along with birds), and especially marine mammals, have the highest energetic demands of modern fauna due to metabolic temperature regulation, expensive mechanisms of movement, and the high costs of pregnancy and lactation (McNab, 2012; Berta *et al.*, 2015; Thometz *et al.*, 2016; Heldstab, Van Schaik & Isler, 2017). As a result, sub-lethal trophic, environmental or health factors may significantly influence host energetics and thus individual and population fitness (Clinchy, Sheriff & Zanette, 2013; King *et al.*, 2015; May *et al.*, 2019).

Mammals budget the energetic costs of survival and reproduction through a cascading system of responses, somewhat like an energy grid. Limited resources/energy induce prioritization (redirection of freely available energy), rationing (redirection from energy reserves, reduction of allocation for systemic function to minimum requirements) and rolling blackouts (redirection from essential systems or between survival and reproduction) (Beldomenico *et al.*, 2008*a*; McNab, 2012; Berta *et al.*, 2015; Collins *et al.*, 2016; Heldstab *et al.*, 2017). Energy allocation is centralized around core systemic functioning, which will tend to have a small range of tolerable change (Fig. 1). However, some resources/energy can be reallocated quickly to help mount a localized response to infection, such as increasing blood flow and creating metabolic heat (Berta *et al.*, 2015; Maceda-Veiga *et al.*, 2015; Levesque, Nowack & Stawski, 2016). Energy supply is dependent upon resource acquisition [e.g. exploration, foraging, or competition (McNab, 2012; Collins *et al.*, 2016)]. An individual's ability to acquire energy partly determines its nutritional status (growth, fat storage, muscle quality, 'body condition'), which is related to energy abundance and, especially in mammals, to absolute fitness and the individual's ability to store energy (Parker, Barboza & Gillingham, 2009; Malerba, White & Marshall, 2018; Sanchez *et al.*, 2018). Stored energy can then be allocated to defence: mounting an immune response, repairing damaged tissue, or activating hormonal stress responses (Dias *et al.*, 2017; Thompson, 2017), and ultimately absolute fitness is determined by the energy available for allocation to reproduction, both in terms of output (quantity of offspring) and

success (survival to adulthood or the 'quality' of offspring) (Tompkins *et al.*, 2011; McNab, 2012; Costa-Pereira *et al.*, 2019).

Resource rationing and allocation to specific energetic demands will depend on intra- and interspecific, as well as environmental factors. However, we suggest a general framework to predict the timing and magnitude of parasite effects on host energetic condition arranged by the five main areas of expenditure (Fig. 1B). Any energetic challenge should increase the overall burden on an animal's energetic reserves (McNab, 1989, 2012; Nagy, Girard & Brown, 1999; Berta *et al.*, 2015). This may be especially important to consider in research methodology. A failure to consider the period/severity of infection and which system is affected energetically by infection, at that time, may lead to type-II errors in our conclusions of a parasite's effects on host condition. We thus suggest that the influence of parasitic helminths on individual and population fitness, measured by energetic condition as the intersection of physiological, behavioural, and environmental influencers (Ryser-Degiorgis, 2013; Stephen, 2014), should be accounted for, not just pathological signs or mortality.

(3) Measuring energetic condition

The most common proxy used to quantify energetics, or the general health of an animal, is 'body condition', classically measured by fat stores, muscle tone or body size [also defined subjectively as 'robustness', 'vigour', 'quality', 'overall health', 'competitive ability', or 'energetic reserves' (Milner *et al.*, 2003; Beldomenico *et al.*, 2008*a*; Peig & Green, 2010; Sanchez *et al.*, 2018)]. Body condition is linked to individual fitness in the context of the animal's ability to gather excess energy and convert it into reproductive success, although this can vary as not all mammals store substantial amounts of fat in their body (Tompkins *et al.*, 2011; Stephen, 2014; Sanchez *et al.*, 2018).

The complexity of mammal physiological and behavioural responses to direct and indirect energetic (classically 'nutritional') challenges has led to some inconsistencies in the selection of response variables in studies of the effects of parasites on host energetics (Brown, Marquet & Taper, 1993; Milner *et al.*, 2003; Peig & Green, 2009; Levesque *et al.*, 2016; Sanchez *et al.*, 2018). Primary or direct effects are often easier to quantify, while secondary or downstream effects are more subtle and difficult to attribute conclusively to a parasite (see Table S1 for a glossary of terms). For example, some intestinal parasites cause ulcerative colitis or inflammation of the intestinal wall, an obvious burden on defence as they require both an inflammatory response and tissue repair. However, another intestinal parasite may simply reduce digestive efficacy, suppress appetite, or alter the gut microbiome, producing no obvious, direct pathological signs. Nevertheless, infection will lead to changes in the host's resource acquisition behaviour and the loss of fat reserves (Charlier *et al.*, 2009; Dorny *et al.*, 2011; Suzuki, 2017), or perhaps show lowered haematocrit and packed cell volume (PCV)
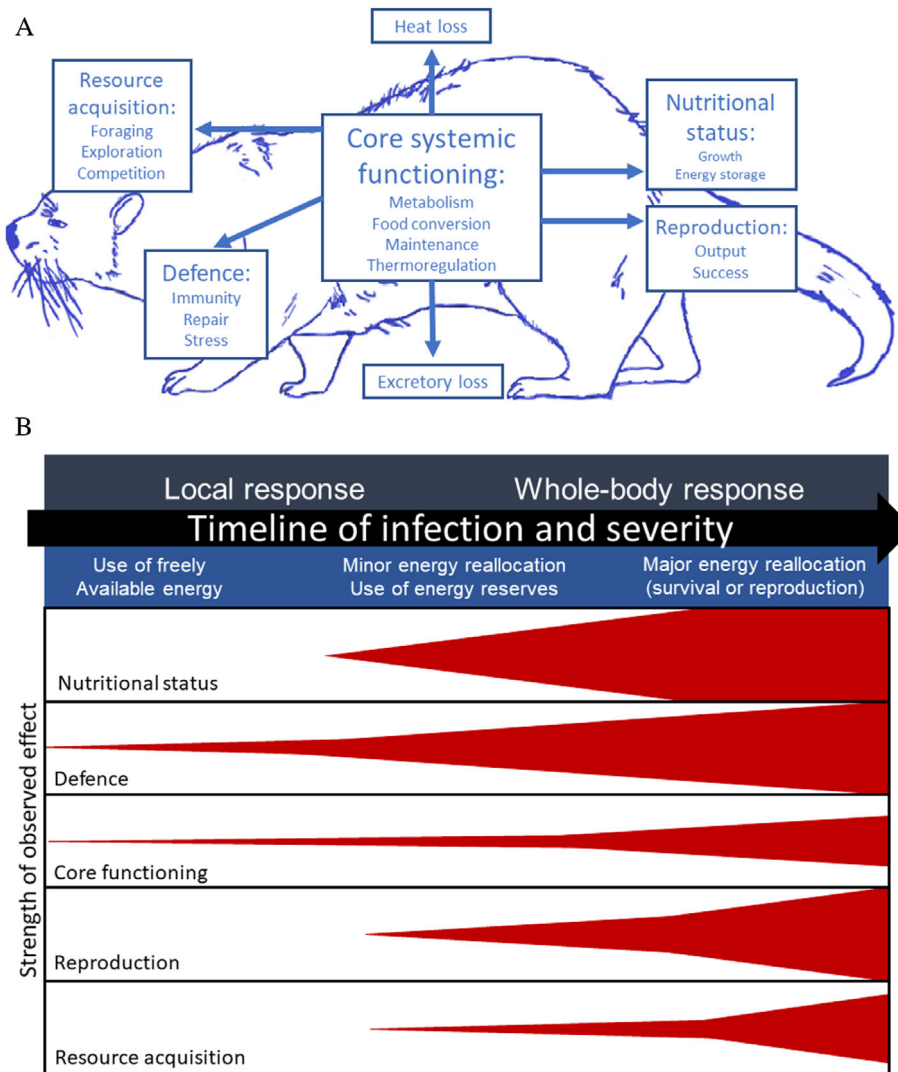
Fig. 1. Suggested framework for assessing mammal energetics by (A) pathways of energy expenditure *via* energetic functions and loss (adapted from Berta *et al.*, 2015) and (B) a hypothesized timeline for observed response by energetic function. During local responses using freely available energy, changes will be small or non-apparent, while lasting infections or those of higher severity may induce more strongly negative changes in host energetic condition.

due to nutritional deficiencies (Budischak, Jolles & Ezenwa, 2012). Another parasite may suppress the host's immune response, increasing the severity of secondary infections or causing normally neutral symbionts to become pathogenic (Shanebeck & Lagrue, 2020). This explains why many studies have tried to quantify the effect of parasites in relation to 'body condition' as a broad indicator for subtle or hard-to-measure effects on energy availability (Samuel *et al.*, 2001).

Effect sizes included in this study may reflect direct, secondary, or downstream effects of infection, and are broadly defined as the strength of disruption of host energetic condition in relation to parasitic infection (Peig & Green, 2010; Levesque *et al.*, 2016; Sanchez *et al.*, 2018). It should also be noted that causality between parasite and host body condition is not unidirectional; pre-existing energetic challenges may predispose a host to infection, but the parasite may also increase the severity of these existing energetic challenges (Beldomenico *et al.*, 2008a). Furthermore, in wildlife studies, infection duration is often unknown, data collection being limited in time, and focused on broad indices that only report downstream effects (Budischak *et al.*, 2012). All of this makes interpreting the results of studies assessing the effects of infection on energetics and animal fitness difficult as they are subject to confounding (especially temporal) variables.

(4) Meta-analysis goals and hypotheses

Through a meta-analysis of the literature, we asked: (*i*) do sub-lethal (or 'sub-clinical') infections by helminth parasites reduce mammal energetic condition, and therefore influence

fitness? (*ii*) If so, how do observed effects change according to biological and methodological factors? Historically, helminth parasites were assumed to have limited effects on host energetics (Appendix S1). However, a cursory survey of the literature suggests otherwise. A wealth of research from the agricultural sphere, which has long been concerned with the exact energetic (and therefore financial) burden helminths have on their mammalian hosts, seems to indicate that negative effects on host energetic condition are common (Crompton, 1986; Vlassoff, Leathwick & Heath, 2001; Nieuwhof & Bishop, 2005; Charlier *et al.*, 2009). Evidence from wildlife research is more variable and sometimes conflicting; species, environmental factors, methodological constraints, and other unknown factors may be influencing the ultimate observed magnitude of the effects of infection on wild mammal fitness (Coulson *et al.*, 2018; Han & Ostfeld, 2019).

A previous review of the literature on the effects of antiparasitic medications on wild vertebrate fitness reported that only 62% of studies showed a significant positive effect of antiparasitic treatment (Pedersen & Fenton, 2015). A review and meta-analysis by Sanchez *et al.* (2018) noted an overall negative effect of infection by helminths on body condition in wild vertebrates. Specific to mammals, a recent meta-analysis by Defolie *et al.* (2020) showed a strong association between parasitic infection and stress hormone response (glucocorticoids) in mammal hosts. How these effects are quantified and qualified, then reported in the literature, vary by context, host, and discipline (Schulte-Hostedde, Millar & Hickling, 2001; Peig & Green, 2010; Labocha, Schutz & Hayes, 2014; Sanchez *et al.*, 2018). Consequently, results and conclusions on the magnitude and significance of these effects may largely depend upon study designs. What is increasingly clear from parasitological research is that helminths have complex, significant effects on both hosts and ecosystems. Yet, they have been largely neglected in evaluations of ecological functioning beyond disease and mortality (Irvine, 2006; Lafferty *et al.*, 2008; Buck & Ripple, 2017).

To build upon these previous reviews, excluding microparasites which are well reported to cause mortality or disease (pathological signs and symptoms), and to try to explain the observed variations in the strength of effects, we focused on studies investigating sub-lethal infections by helmith parasites in mammals (both domestic and wild). We tested the common assumption that mammals are less likely to be affected energetically by sub-lethal parasitic infection. Domesticated animals were included to examine the wealth of experimental reports on the specific energetic consequences of helminth infections, as the agricultural industry is concerned with the exact financial costs of reduced nutrition, growth and reproductive success on meat and dairy mammals (Charlier *et al.*, 2009). To address the heterogeneity in wildlife studies and conflicting reports of helminth effects on mammalian hosts, we emphasized careful analysis of various moderators like project design, sampling procedures, energetic condition proxies, identification and quantification of parasite infection, and phylogenetic variation. We hypothesized that, overall, helminths would have significant

negative effects on host energetic condition, moderated by both methodological and biological factors which may induce variance and heterogeneity in the literature (Table 1).

II. METHODS

(1) Literature search

For this analysis, we ran a systematic literature search, according to the standards outlined in the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA; Moher *et al.*, 2015). The initial search was performed on February 13th, 2020, based on titles, abstracts, and key words from the *Web of Science* and *Scopus* databases. We ran the following search parameters: (Helminth* Or Cestod* OR Trematod* OR digenea* OR Acanthoceph* OR Nematod* OR ascari* OR worm* OR fluke* OR flatworm OR tapeworm OR roundworm* OR hookworm* OR 'intestinal parasite' OR 'gastrointestinal parasite*') AND (fitness OR 'reproductive success' OR 'milk production' OR 'lactation' OR reproduction OR longevity OR fecundity OR sub-lethal OR sublethal OR 'cumulative effect*' OR stress* OR 'reduce tolerance' OR 'antagonistic interaction*' OR 'negative interaction*' OR 'host health' OR 'host behavior*' OR 'host behaviour*' OR 'body condition*' OR Pathology OR 'host physiology' OR performance OR 'body mass index' OR 'host susceptibility') AND (mammal* OR cetacea* OR primate* OR rodent* OR marsupial* OR carnivor* OR livestock OR cattle OR bovid* OR sheep OR swine OR ruminant* OR buffalo OR ungulat* OR pinniped* OR seal OR mustelid*) AND (host*) AND NOT (tick* OR elegans OR schistosom* OR treatment OR antihelminth* OR bird* OR vaccine*). Adding the specific exclusion categories after initial searches avoided these unrelated categories overwhelming the search results.

After combining the search results between *Scopus* and *Web of Science* and deleting duplicates, the search yielded 1115 potential articles. These articles were screened independently through blind review of abstracts by one of the authors (K.M.S.) and an independent reader, mediated by another author (C.L.), using Rayyan, an online software for meta-analysis (Ouzzani *et al.*, 2016). When it was unclear from the abstract if the study was relevant, it was included by default for full-text review. A total of 265 articles were identified for full-text assessment. Review papers were included during this blind screening and used to conduct a backward search of the literature, assessing their cited references for inclusion. This identified an additional 78 papers for full-text assessment. Full-text reviews were conducted to confirm relevance according to inclusion/exclusion criteria and to determine whether usable data were provided. If articles did not report sufficient information, the corresponding author was contacted to request the relevant data. After full-text review, 85 of the original and 58 of the additional

Table 1. Hypothesized effects of included moderators on the effects of helminth infection on energetic condition in mammals, according to methodological and biological categories.

	Moderator	Predicted relationship	Suggested reasoning	References
Methodology	**Experimental design** *Cross-sectional* *Experimental* *Field experiment*	Cross-sectional designs will generally lead to lower resolution (weaker effect, greater variance).	Time of infection is an important factor in disruption of energetic condition; cross-sectional studies have difficulties controlling this factor.	Beldomenico *et al.* (2008*a*); Sanchez *et al.* (2018)
	Host sampling origin *Wild live sampled* *Wild opportunistic* *Domestic bred* *Laboratory bred*	Live sampling of wild animals will increase effect strength and reduce variance compared to opportunistic sampling. Sampling of domestic or laboratory-bred animals will increase the strength of the interaction.	Opportunistic sampling is species and system specific, and especially for mammals can be limited. Animals found dead in the wild are more likely already to be in poor health/condition and sample quality may be reduced by decomposition. Human-raised animals can be controlled for both infection and general health, allowing an equal baseline for comparison of infected/uninfected groups.	Budischak *et al.* (2012); Ryser-Degiorgis (2013); Kołodziej-Sobocińska (2019); Shanebeck & Lagrue (2020)
	Infection confirmation *Visual confirmation* *Faecal egg count* *Infection assumed*	Faecal egg count will produce weaker effect sizes with more variance compared to visual observation. Assumed infections will produce non-significant effects due to high variance.	Faecal egg count can result in false negatives and limit resolution of infection intensity. Lack of confirmation may lead to inclusion of false positives, adding variance.	Nielsen *et al.* (2010); Byrne *et al.* (2018)
	Parasite quantification *Intensity* *Presence/absence* *Treated/untreated* *Infection over time* *Species richness*	Correlation between parasite intensity and host energetic condition will show stronger effects with less variance compared to presence/absence. Infection over time and species richness will also show strong effects on energetic condition.	Presence/absence measurements reduce resolution *via* variance due to inclusion of low-intensity infections which may have limited host effects. Including infection timeline in analysis is essential, although many wild studies cannot measure this. Intensity may be a good substitute as parasites tend to accumulate over time. Concomitant infections of parasites can have compounding effects on host health.	Bush *et al.* (1997); Fenton *et al.* (2014); Sanchez *et al.* (2018); Defolie *et al.* (2020)
Biology	**Host taxonomic group** *Ungulates* *Rodents* *Primates* *Marsupials* *Lagomorphs* *Cingulates* *Carnivores*	Effects will generally be consistent across groups, with significant variance, although ungulates will be associated with the strongest effect.	Variation will be more due to species- or system-specific factors, as all mammals have high metabolic requirements, and will have unique physiological and behavioural adaptations to energetic stressors. However, ungulates are the best studied, and may be easier to monitor for changes due to their size, accessibility, and propensity to store fat.	Parker *et al.* (2009); McNab (2012); Berta *et al.* (2015); Flores-Saavedra *et al.* (2018)
	Energetic proxy *Systemic function* *Nutrition* *Defence/stress* *Reproduction*	Mammal condition will similarly be strongly affected across all moderators. Systemic functioning will show slightly stronger effect.	Due to strong differences in study design, variations are more likely to be explained by methodology than by features of the response system.	Table S2; Brock *et al.* (2013); Maceda-Veiga *et al.* (2015)

Table 1. *(Cont.)*

Moderator	Predicted relationship	Suggested reasoning	References
		Systemic function response metrics often have quick response times, i.e. are more likely to show changes rapidly, reducing variation due to timeline of infection.	
Energetic scale *Physiological* *Morphological* *Observational*	Effect will depend on interaction with proxy, although physiological and observational measurements will tend to show stronger effects.	Physiological proxies tend to show changes rapidly, although with less range of difference. Similarly, observational proxies like behaviour can be easily measured and change rapidly, although differences in measurement can increase variance.	Brock *et al.* (2013); Maceda-Veiga *et al.* (2015); Collins *et al.* (2016); Levesque *et al.* (2016)
Parasite group *Cestode* *Trematode* *Nematode* *Mixed*	Mixed infections with multiple groups will have the strongest effects; all other groups will show similar strength of effects.	Co-infections are reported to increase host susceptibility due to parasite's ability to suppress host immune responses, as well as the compounding effects of infection in multiple tissues/systems.	Bordes & Morand (2011); Budischak *et al.* (2012); Serrano & Millán (2014)
Sex and age *Female/male* *Juvenile/adult*	Female and juvenile condition will be more strongly affected by helminth infection.	Female energetic burdens are greater due to the high cost of reproduction and lactation. Juvenile energetic burdens are greater due to the cost of growth.	Degen (2008); McNab (2012); Heldstab *et al.* (2017)

backward search references were used for data extraction. Inclusion and exclusion decisions followed a predetermined criterion (Appendix S2).

(2) Data extraction

From the 143 studies included, we recorded the host species, taxonomic reference number from the Open Tree of Life (McTavish *et al.*, 2015), sex, standardized age, parasite group (cestode, nematode, trematode, mixed), species (if available), location in the host body, how infection severity was quantified, how infection was confirmed, and study design. In addition, for each effect size calculation, we recorded the energetic condition proxy measured and what general function it related to. The scale of the proxy used (physiological, morphological, observational; Table S2), proxy data type (direct numerical, scaled numerical, proportional, ordinal), sample size, test statistics, how the effect size was calculated, and the direction of the effect (positive or negative relationship between infection and condition) were also recorded.

We used Cohen's d as our metric of effect size between parasite infection and host condition (Cohen, 1988). Cohen's d was calculated using open-source effect size calculators from the Campbell Collaboration (Lipsey & Wilson, 2001; Wilson, 2001) and Psychometrica (Lenhard & Lenhard, 2016). We converted reported effect sizes, test statistics, data, graphical data, etc. into Cohen's d following a predetermined hierarchy of conversion methods (Fig. S1), recording how the effect size was calculated in the metadata. We determined the direction of effect based upon the correlation between infection and host energetic condition. When changes in an energetic proxy were related to a reduction or challenge to energetic condition, the effect was considered negative. If both increasing and decreasing values in a specific condition proxy are known to be associated with reduced host health (for example liver mass, where both increases and decreases are related to poor health) (Penzo-Méndez & Stanger, 2015), any effect was considered negative. When experimental studies included repeated measures over time, we compared the means of the change over time between control and experimental groups when possible. However, if data were not available, we extracted the mean and standard deviation from the last measurement of the experiment. From the 143 studies, we calculated a total of 602 effect sizes. However, after investigation for negative bias, three strongly negative outliers were excluded ($d = -11.86$, -8.30, -7.96). All were from laboratory experiments on rodents. One of these was the only effect size calculated from a particular article, bringing our total number of included studies down to 142 and included effect sizes to 599.

(3) Defining moderators: methodology and energetic condition

Metrics of 'body condition' can vary strongly across ecological studies. They may include qualitative and quantitative (proportional, direct numerical, adjusted numerical) measurements. Methodology also differs widely in terms of sampling period, sampling source, parasite identification methods, etc. (Brown *et al.*, 1993; Beldomenico *et al.*, 2008*a*; Peig & Green, 2010; Sanchez *et al.*, 2018). As these differences may influence assessment of host condition–parasite correlations (Sanchez *et al.*, 2018), we grouped moderators as described below.

Energetic condition assembled response metrics by the specific response system or effect they indicate changes in (Table S2). These included metrics related to (*i*) reproduction, (*ii*) core systemic functioning (excretory, digestive, cardio-pulmonary systems and metabolism), (*iii*) nutritional status (fat storage, growth, muscle tone, body size, mass, and other qualitative assessments) and (*iv*) defence (physiological and behavioural stress responses, immunity). Very few studies investigated resource acquisition as a response metric; two measured time spent foraging and some recorded host activity ($k = 9$) such as time spent travelling. To reduce the bias of zero-inflation, these effects were nested within stress/defence as changes in these behaviours are also often linked to systemic stress response.

Energetic scale grouped response metrics by physiological, morphological, and observational scales (Table S2). Physiological metrics were defined as small-scale, physiochemical proxies linked to specific systemic processes such as hormone concentrations, waste products, proteins in blood or tissue, blood parameters (such as haematocrit or haemoglobin), concentrations of specific nutrients and others (Table S2). Physiochemical processes may vary strongly over time and be directly or indirectly affected by parasite infection (Beldomenico *et al.*, 2008*b*; Defolie *et al.*, 2020). For example, infection by intestinal helminths may be related directly to reduced haemoglobin levels *via* blood loss (Seguel *et al.*, 2018). However, haemoglobin level also is affected by nutrition and therefore could be indirectly related to helminth infection due to reduction in digestive efficacy (Beldomenico *et al.*, 2008*b*; Budischak *et al.*, 2012). Reduced haemoglobin also has implications for cardio-pulmonary and metabolic health and can lead to fatigue, behavioural changes, and reproductive effects (Budischak *et al.*, 2012). Similarly, cortisol is used as a proxy for systemic stress response and may be related directly to immune challenge by parasitic infection (Seguel *et al.*, 2019). However, systemic stress may also be a cumulative response to compounding factors indirectly linked to nutritional challenge due to infection (Pawluski *et al.*, 2017; Defolie *et al.*, 2020).

Morphological metrics were defined as proxies that can be easily observed, measured, and calculated, such as organ mass, body mass, body/scaled mass indices, muscle depth, fat levels, milk production, and others (Table S2). For example, splenic mass is linked to immune response and increases in animals with significant immune challenges (Corbin *et al.*, 2008). Liver mass tends to be regulated strictly in the bodies of mammals and restricted to a specific percentage of total body mass. Changes in size are often related to disease or nutritional challenge (Penzo-Méndez & Stanger, 2015).

'Observational metrics were defined as any proxies that did not directly measure physical changes in the host's body, but instead recorded external changes directly linked to energetic condition, such as behaviour, reproductive success (e.g. number of offspring produced or mass of offspring post weaning), physical endurance, elective food intake, and others (Table S2). This category of metrics is closely related to trade-off theory where responses to energetic challenges induce adjustment in energy allocation and behaviour in mammals (Hutchings *et al.*, 2006; Brock *et al.*, 2013; Berta *et al.*, 2015). For example, milk production or offspring body mass gain in controlled settings are good indicators of the mother's nutritional condition and ability to allocate resources to milk production and quality, which may be challenged by parasitic infection (Landete-Castillejos *et al.*, 2005; Moore & Hopkins, 2009).

Research methodologies were grouped according to sampling and parasite identification methods. *Research method* identified if the study was (*i*) cross-sectional (observational studies that investigated a sub-set of a population), (*ii*) experimental (studies that investigated effects in a controlled setting), or (*iii*) field experimental (semi-controlled studies conducted in the field). *Host origin* recorded the sampling source of the host. Sources were (*i*) laboratory bred (animals reared in a laboratory setting for experimentation), (*ii*) domestic (domesticated animals, raised for human industry), (*iii*) live-caught wild animals (hosts sampled directly for the study following set sampling protocols; may have been killed but were sampled live) and (*iv*) opportunistically collected wild animals (carcasses collected opportunistically from roadkill, hunters, stranding, etc.). *Parasite identification* recorded how parasite infection was confirmed. Identification could be *via* (*i*) direct observation (visual confirmation of parasites in the host), (*ii*) faecal egg count (FEC, confirmation of eggs in the host's faeces), (*iii*) assumed infection (study included a group treated with anti-helminthic and untreated groups assumed to be infected). *Parasite quantification* relates to how parasite infection severity was accounted for in study analyses. Infection classically could be reported as (*i*) intensity/abundance (number of parasites per individual host), (*ii*) presence/absence (including studies that measured by prevalence) or (*iii*) richness (diversity of parasite species). Alternatively, some studies reported infection as (*iv*) treated/untreated hosts (i.e. compared animals treated with anti-helminthics *versus* untreated hosts) or (*v*) infection over time (quantified infection severity by period of infection, artificially infecting animals with an equal number of parasites).

(4) Statistical analysis

(a) Addressing non-independence

The effects of phylogenetic and methodological non-independence are important considerations to include in

the synthesis of meta-analytical data (Noble *et al.*, 2017). To control for non-independence, we included phylogenetic relationships using the packages *rotl* (Michonneau, Brown & Winter, 2016) and *ape* (Paradis & Schliep, 2019) to extract a phylogeny from the Open Tree of Life (Rees & Cranston, 2017), construct a phylogenetic tree, randomized to deal with polytomies, and create a correlation matrix (Sanchez *et al.*, 2018; Sánchez-Tójar *et al.*, 2020).

For laboratory or other controlled studies that included multiple groups with a shared control, non-independence of experimental groups is a possible source of type-I error in the analysis due to artificial inflation of sample size (Noble *et al.*, 2017; Fernández-Castilla *et al.*, 2020). To avoid this, we included the sub-group variance in the pooled SD or used multigroup effect size calculations to provide a single effect (Lipsey & Wilson, 2001).

Non-independence can also affect analysis of overall effect size when studies provide multiple measurements for the same group. Our final data set had an average of four effect sizes per study. Studies may have reported multiple condition proxies from the same population, effects on different age groups or sexes, differences between parasite groups from the same sampled population, or included multiple independent experimental designs. For example, conducting an experiment for males and females or food-supplemented *versus* non-supplemented, each with their own control group, would yield multiple effect sizes. During data extraction, to monitor this, effect size metadata included not only the study the measurement was taken from, but also a unique observation group number to identify effect sizes measured from the same experimental group. For example, Arias-Hernández *et al.* (2019) investigated the effect of parasite infection on rabbit energetics and included two different experimental protocols. In one, rabbits were fed a normal commercial diet and in the other, rabbits were fed to obesity. This produced effect sizes for each metric of energetic condition, which were identified by a group ID number between the normal and obese rabbit experiments. Both observation ID and study were included as random effects to structure inter- and intra-study variance in the model.

(b) Meta-regression modelling

Effect size analysis and graphical representation were carried out in RStudio (RStudio Team, 2020), with the package *metafor* (Viechtbauer, 2010). Within our multiple working hypothesis framework, we used a random effect multivariate regression model ('rma.mv' function, *metafor* package), fitted with a restricted maximum likelihood (REML) estimator to reduce underestimation of heterogeneity (Viechtbauer, 2005). We then calculated heterogeneity as I^2, a better measure of true variance (Nakagawa & Santos, 2012). We used a crossed design explicitly to model residual variance, including the random effects: observation group (intra-study variance), study, and host species (phylogenetic correlation). We investigated the effects of our various moderators *via* multimodel inference, through variance explained (R^2),

heterogeneity (I^2 and Q), and the Akaike Information Criterion (AIC) to summarize the relative importance of our various predictors hypothesized *a priori* to be of concern (Elliott & Brook, 2007). To address publication bias, we analysed meta-regression models *via* contour-enhanced funnel plots (Peters *et al.*, 2008).

(c) Graphical representation

Visual representation was conducted in RStudio (RStudio Team, 2020) with the new package *orchaRd*, which expands the classic forest plot including trunk (point estimate) and branches (confidence intervals) only to an 'orchard plot', adding 'twigs' (prediction interval) and 'fruit' (individual effect sizes scaled by the inverse of their standard error in semi-random clustering (Nakagawa *et al.*, 2021). Point estimates (PIs) give a perspective of the range of possible or 'plausible' effect sizes for hypothetical new studies and give a perspective of the heterogeneity of the meta-regression. Heterogeneity is to be expected in meta-analysis of ecological research and is therefore important to represent (Senior *et al.*, 2016; Nakagawa *et al.*, 2021).

III. RESULTS AND DISCUSSION

Our final data set (see Datafile S1) included 599 effect sizes from 142 studies, across 78 species of mammals grouped into seven clades: cingulates ($k = 3$), marsupials ($k = 12$), primates ($k = 35$), lagomorphs ($k = 49$), carnivores ($k = 81$), rodents ($k = 165$), and ungulates ($k = 254$) (Fig. S2). Recorded effect sizes came from domesticated species (21.5%), laboratory-bred species (10.4%), live-sampled wild species (46.2%), and opportunistically sampled carcasses of wild species (21.9%). Effect sizes by energetic condition proxy skewed toward nutritional status (50.1%), then core systemic functioning (20.0%), defence/stress (17.4%), and reproduction (12.5%). Most effect sizes were measured on the morphological (60.4%), then split between the physiological (22.0%) and observational/external (17.5%) measurement scales (see Section II(3)). Effect sizes also came from studies across many years and systems, using various methods (Appendix S3, Fig. S3). Average effect size (Cohen's *d*) for the intercept-only multivariate meta-analytic model of the correlation between helminth infection and mammal energetic condition was strongly negative ($d = -0.59$ [95% CI = −0.78 to −0.39], SE = 0.10, $P < 0.0001$, $k = 599$), with moderate heterogeneity ($I^2 = 56.89\%$) (Fig. 2), supporting our hypothesis that sub-lethal helminth infections are important influencers of mammal energetic condition.

(1) Effects of methodological factors

Methodological differences among studies strongly influenced effect size. As predicted, cross-sectional studies showed weaker negative effects of infection on host energetics

($d = -0.47$ [95% CI $= -0.71$ to -0.24], SE $= 0.12$, $P < 0.001$, $k = 320$) when compared to experimental studies ($d = -0.82$ [95% CI $= -1.09$ to -0.55], $P < 0.001$, $k = 227$), although not significantly so as their confidence intervals overlapped (Fig. 3A). They also made up the largest proportion of included effect sizes. Semi-controlled field experiments yielded intermediate effect sizes and showed the most variance (Fig. 3A). This may be because infection period (i.e. time since infection) is an essential variable
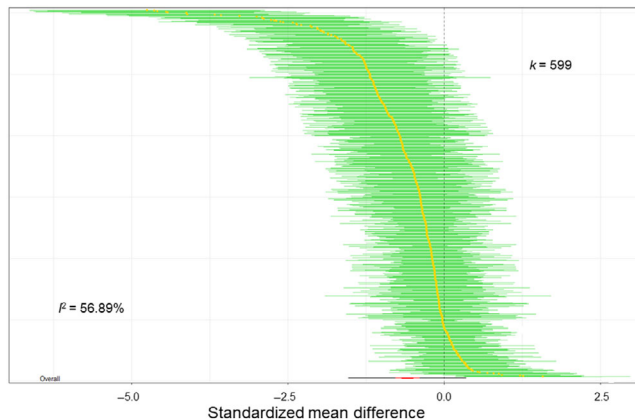

Fig. 2. Mean effect sizes (yellow dots), 95% confidence intervals (dark green lines), and precision interval (pale green lines) across effects from all studies ($k = 599$), including the heterogeneity (I^2), average effect (red box) with 95% confidence interval (red line) and precision interval (black line) of the intercept-only model.

(Sanchez *et al.*, 2018), which cross-sectional studies can rarely include in their analysis. However, such trends may also be influenced by a variety of environmental or physiological variables. This could similarly explain the increased variance observed in semi-controlled field experiments, as study design and duration were highly variable. In studies where wild animals were treated against parasites, it could not always be confirmed that animals were not re-infected after treatment, or that the 'control' animals were infected (Newey & Thirgood, 2004; Pederson & Greives, 2008; Gobush, Baker & Gulland, 2011; Ezenwa & Snider, 2016). Furthermore, anthelminthics can have a range of efficacy in the per cent reduction of parasite abundance and among parasite species (Murray, Keith & Cary, 1998; Pedersen & Fenton, 2015), all of which may increase variance. Infection period may also explain the stronger negative effects seen in mammals sourced from domestic or laboratory-bred animals, as they almost always were used in controlled experiments and artificially infected, allowing for exact measurement of infection period and inclusion of this factor into the model (Fig. 3B). Wild hosts were most often used in cross-sectional studies, which may explain the generally weaker effect size detected. The effect size was, as predicted, weakest for opportunistic sampling. This may be because mammals found deceased in the wild are more likely to be in poor condition already due to disease processes or physical harm (Shanebeck & Lagrue, 2020). Cross-sectional studies often cannot quantify infection period, limiting them to snapshot comparisons between infected and uninfected hosts. Observed effects of parasitic infection may thus be weakened

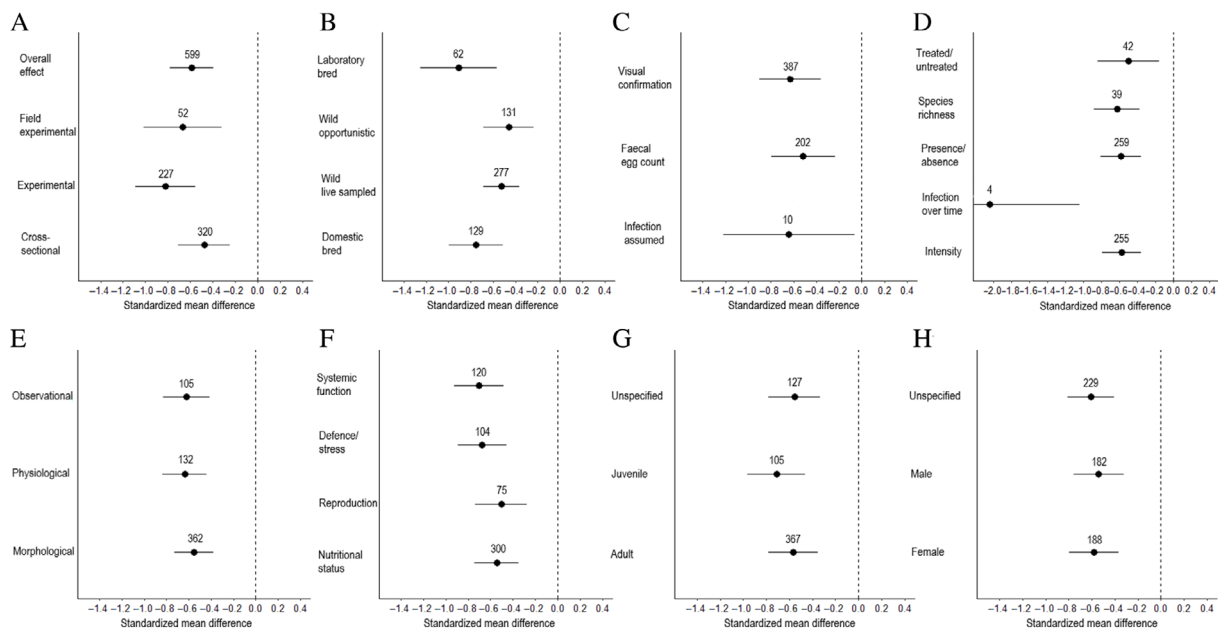**Fig. 3.** Average effect sizes of the hypothesized moderators, number of included effect sizes and 95% confidence intervals according to methodological factors. (A) Overall effect across all effect sizes and by project design, (B) host sampling origin, (C) method of infection confirmation, (D) parasite quantification as well as the biological factors, (E) energetic proxy scale, (F) energetic proxy, (G) age, and (H) sex.

by confounding factors influencing host condition such as unrelated diseases, injuries, or anthropogenic effects.

Methods used to identify and quantify parasitic infection did not have a strong effect on the average effect size. Our prediction that visual confirmation should show a stronger negative effect compared to FEC was not confirmed (Fig. 3C). This suggests that, while FEC has its limitations when trying to quantify infection intensity, these did not significantly obscure the effects of infection. Again, infection period may be more important in determining the strength of effect (Nielsen *et al.*, 2010; Byrne *et al.*, 2018). The few studies that used infection over time as their metric produced a very strong negative effect, albeit with strong variance, likely due to low sample size of effects (Fig. 3D). Studies that assumed infection without confirmation predictably showed high variance, suggesting that infection status of hosts should always be confirmed, rather than assumed (Fig. 3C). Similarly, defining individual host infection status as 'treated' or 'untreated' increased variance and weakened the strength of the negative effect, likely because these studies did not always guarantee that all 'treated' individuals received treatment or were parasite free (Fig. 3D). Contrary to our prediction, there was little difference in effect size among studies where parasite infections were quantified by intensity, presence/absence or species richness.

(2) Effect of biological factors

Biological factors were also significant determinants of the strength of the negative effect of infection on host energetic condition. As predicted (Table 1), this effect was similar across energetic proxy and proxy scale but slightly stronger for proxies and scales more likely to respond quickly to infection (physiological and observational scales, and systemic function and defence/stress), although this difference was not significant (Fig. 3E,F). Age and sex did not lead to strong variation in effect sizes among groups; juveniles and females showed slightly stronger negative effects of infection on host energetic condition (Fig. 3G,H), although this was not significant. This variance may have come from a variety of sources, and many studies did not differentiate between ages or sexes, which may have influenced these results.

The increased energetic requirements for growth in juveniles and pregnancy and lactation in females can be extreme in some groups like mustelids (Thometz *et al.*, 2016; Heldstab *et al.*, 2017; Felska-Blaszczyk & Seremak, 2020). Furthermore, some energetic burdens such as pregnancy and lactation are time specific, and cross-sectional studies may not have observed females during periods of higher energetic burden. Additionally, very few studies differentiated adults to include aged adults or adults past their reproductive prime or considered to be of advanced age (Milner *et al.*, 2003). This is an important consideration when analysing energetic condition as this group is also likely to be in poorer condition, regardless of parasitic infection, due to the increased rates of age-related health problems that may affect their body condition and ability to acquire sufficient resources (Milner

et al., 2003; Beldomenico *et al.*, 2008*a*; McNab, 2012). Many studies did not report or differentiate the age or sex of the host animals, which reduced the overall sample size to quantify this difference. Future studies would benefit from collecting and explicitly modelling the effect of such information when investigating energetic effects related to helminth infections. Species-specific host life-history traits such as age and sex can affect energetic requirements as well as average base energetic condition (McNab, 2012).

Interestingly, there was little difference among parasite taxonomic groups but, contrary to previous assumptions that cestodes are generally of little significance for mammals (Appendix S1), cestodes showed a strong negative effect ($d = -0.61$ [95% CI = -0.91 to -0.30], SE = 0.15, $P < 0.0001$, $k = 49$) (Fig. S4). When location of the parasite was considered, all were significantly negative moderate or strong effects except for those located in muscle tissue, likely due to low sample size ($k = 2$) (Fig. S5). Our survey of the literature found no study investigating the effects of sub-lethal acanthocephalan infections on energetic condition, although acanthocephalans are ubiquitous parasites of marine mammals (Shanebeck & Lagrue, 2020). Most effect sizes came from gastrointestinal infections ($k = 485$). It should be noted that for both parasite tissue location and parasite clade, mixed infections where more than one parasite group infect the same host or infections were in multiple tissues (which was most often also mixed-clade infections) showed the strongest negative effects on the host. This matches our prediction (Table 1), and the available literature showing that concomitant infections and the compounding effects of multiple nutritional, immune, and systemic burdens have stronger effects on overall host condition (Bordes & Morand, 2011; Budischak *et al.*, 2012; Serrano & Millán, 2014).

There were strong variations among host taxonomic group (Carnivora, Ungulata, Rodenta, etc.), although interpretation of differences may not be fully due to taxonomic differences (Fig. 4A). For example, of the five clades with the largest number of reported effect sizes, primates showed the strongest effect. However, studies of primates were focused predominantly on defence (stress response), *via* analysis of cortisol levels in faeces or behavioural responses. Effects based on metrics that can change rapidly, like physiological measurements of defence/stress proxies (e.g. cortisol), are likely to produce stronger negative effects when time period is not included, compared to proxies like nutritional condition that may take more time to show significant changes (Stevenson & Woods, 2006; St. Juliana *et al.*, 2014; Sanchez *et al.*, 2018). Contrary to our prediction (Table 1), there was no significant difference between members of Ungulata (the clade with the largest average body size), and Rodenta or Lagomorpha (the clades with the smallest average sizes). Of the five clades with the most recorded effect sizes, when considered alone, only Carnivora did not show a significantly negative effect (Fig. 4A). While this seemed to confirm an assumption that carnivores (like pinnipeds) are less likely to be affected by sub-lethal infections like gastrointestinal helminths; all these studies were cross-sectional,
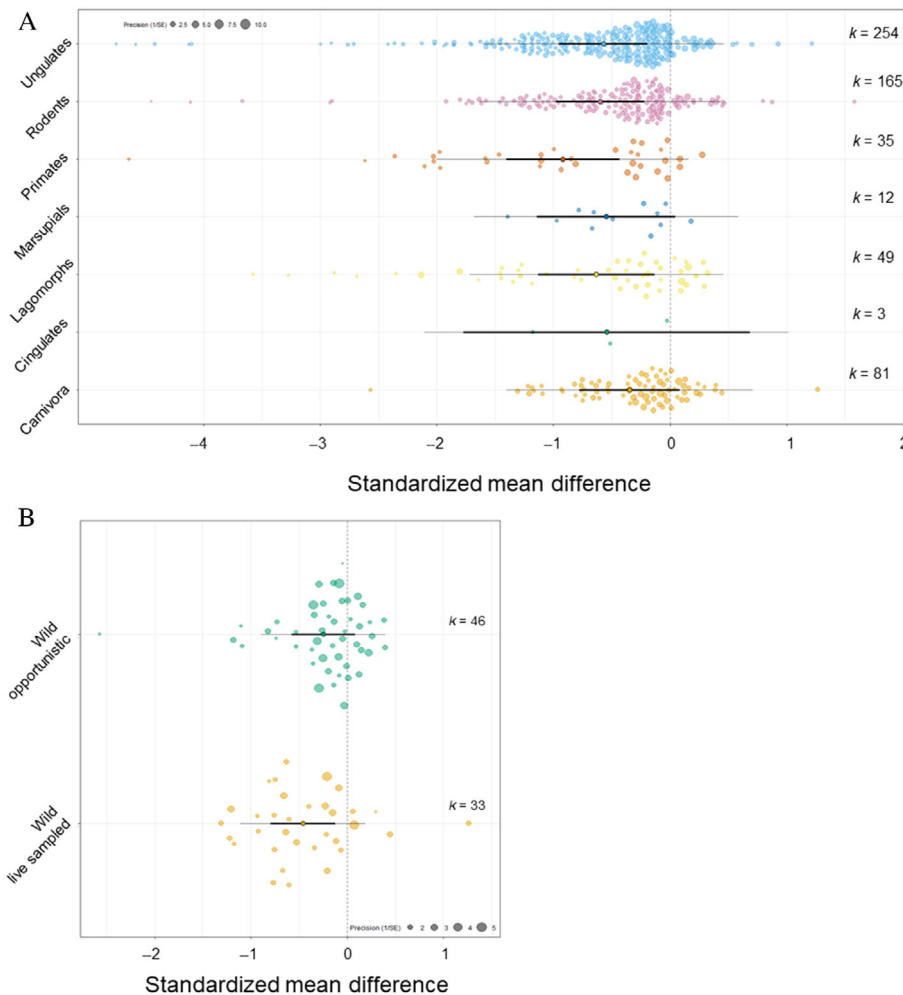
Fig. 4. (A) Orchard plot showing average effect sizes (point, 'trunk') including 95% confidence intervals (bold line, 'branch') and precision intervals (small line, 'twig'), individual effect sizes scaled by precision ('fruit') spread on the *y*-axis based on quasi-random noise (Nakagawa *et al.*, 2021), and number of included effect sizes (*k*) according to taxonomic group. (B) Effect sizes for carnivores only according to sampling origin of the host: opportunistically collected as carcasses or sampled live according to specific experimental protocols (included studies were predominantly cross-sectional in design).

and variance may be explained by methodological bias. When the interaction of host sampling origin and taxonomic group was modelled (Fig. 4B), carnivores sampled live in the wild *via* proactive experimental protocols showed a significant negative effect of infection on energetic condition ($d = -0.48$ [95% CI $= -0.80$ to -0.17], SE $= 0.16$, $P = 0.003$, $k = 33$). Contrastingly, limitations inherent to opportunistic sampling led to a weaker, non-significant effect ($d = -0.24$ [95% CI $= -0.54$ to 0.05], SE $= 0.15$, $P = 0.106$, $k = 46$).

(3) Best fit models: two-factor interactions

Host sampling origin largely explained variations in the data and was a contributing factor in the two best models based on AIC, heterogeneity and variance explained (Table 2). This underscores the importance of explicitly modelling the effect

of methodology in meta-analysis of complex, difficult-to-measure effects. When separated by host sampling origin and energetic proxy, differences in methodology revealed some interesting trends. Studies investigating wild mammals showed the same trend but slightly stronger effects in live-sampled hosts compared to opportunistically sampled hosts. There was however little variation among energetic proxies (Fig. 5).

For laboratory-bred and domestic hosts (which are most often tested in controlled experiments), a few strong differences were apparent. For laboratory animals, the effects of infection on stress/defence were much larger than for any other group, which may be an artefact of selective breeding making laboratory rodents more tolerant of large changes to systemic function. This may artificially induce larger differences between normal and highly stressed systemic functioning or indicate that stress/defence responses require

Table 2. Intercept-only model compared against the top five moderator models. The top five models are shown based on the lowest Akaike Information Criterion score (AIC). Heterogeneity (I^2) is also shown, Cochran's Q [residual heterogeneity (Q_E), and the heterogeneity explained by moderators (Q_M)], the per cent variance explained by the model, [R^2 conditional (R_c^2)], and the variance explained by moderators [R^2 marginal (R_M^2)].

| Model	I^2	Q_E	Q_M	R_c^2	R_M^2	AIC
Intercept only	56.89	1174	—	89.64	—	1134
Host sampling: energetic proxy	53.96	1062	226	99.99	25.36	1090
Host taxa: energetic proxy	55.88	1052	75	87.76	21.08	1098
Parasite quantification: energetic proxy	56.06	1101	73	89.11	21.21	1108
Host taxa: host sampling	51.51	1061	206	100.00	27.04	1109
Experimental design: parasite quantification	56.38	1031	46	77.84	18.75	1112
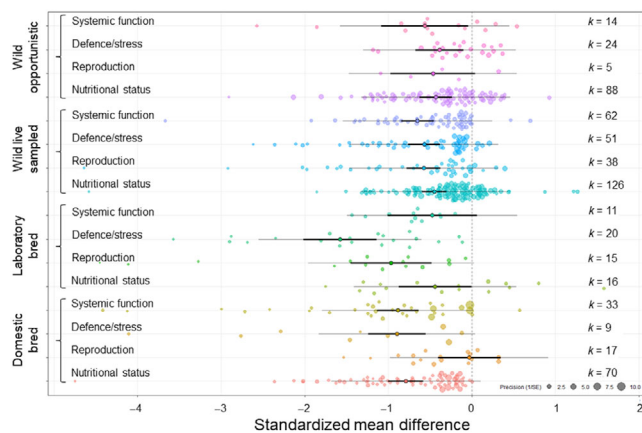
Fig. 5. Orchard plot showing average effect size (point) of energetic proxy by host sampling origin and energetic category (core systemic function, defence/stress response, reproduction and nutritional status), with 95% confidence interval (bold line), precision interval (thin line), and individual effect sizes scaled by precision and clustered quasi-randomly. Domestic and laboratory-bred species tend to have a higher starting energetic condition due to food supplementation and being bred to put on muscle and fat easily. Wild species in comparison will have a lower average starting condition due to differences in resource availability, environmental stressors, or other negative influences of condition. The 'Wild live sampled' group sampled by an experimental protocol tends to represent a more accurate cross section of the population, although is still limited by the researcher's ability to sample truly randomly. 'Wild opportunistic' sampling tends toward lower average body condition, as animals found deceased in the wild are more likely to be in poor condition due to disease, injury, or other processes that led to their death.

strictly controlled settings when investigating the breadth of change. The weakest average effects of infection were seen in domestic host reproduction. However, this does not necessarily mean that parasites do not have significant effects on reproduction. First, most research on farm animals investigating the effects of helminth infections offered consistent *ad libitum* feed for all individuals, potentially allowing hosts to compensate for some of the sub-lethal effects of parasites *via* higher food intake. Second, these experiments often use controlled

infections over short periods (weeks/months not years). As reproduction should be most strongly affected by long-term infections and additional energetic burdens (secondary effects like lethargy, behavioural stress response, and reduced ability to secure food resources), short-term infections and subsidized energy intake may have masked long-term, cumulative effects of parasite-induced nutritional deficiency on reproduction. Laboratory-bred hosts did not show a similar weak effect on reproduction, but this may be because those studies often used observational proxies like reproductive behaviour (e.g. number of mounting attempts) which can be rapidly altered but may not be the best proxy for reproductive success. This may explain why the next best model (host taxa: energetic proxy; Table 2) showed similar patterns, again likely due to methodological trends nested within the various groups, like primate studies which are often limited to observational metrics and commonly focus on stress response.

Another model where variance was well explained (parasite quantification: energetic proxy), showed consistent results. Categories with the strongest or weakest results were those with the lowest sample effect size (Fig. S6). However, as seen in the parasite-quantification only model (Fig. 3D), for the categories with the largest sample sizes, defence: presence/absence ($k = 42$), defence: intensity ($k = 46$), nutrition: presence/absence ($k = 104$), nutrition: intensity ($k = 155$), there was no strong difference between intensity or presence/absence. Similarly, in the last model (study design: parasite quantification), effect sizes were consistent between intensity and presence/absence (Fig. S7), with similar differences based on experimental, field experimental, or cross-sectional studies as seen in the study-design only model (Fig. 3A). This contradicted our hypothesis that measuring parasite infection by intensity would detect stronger effects than simply presence/absence, suggesting that even low-intensity infections can have a significant influence on host energetic condition. If studies are limited in their ability to measure intensity, presence/absence is still a valuable metric.

(4) Effect of gastrointestinal parasites on standard body condition metrics

When the data set was reduced to effect sizes calculated only from infections by gastrointestinal helminths using classic

metrics of 'body condition' (nutritional status; Table S2), the effect was still significant and moderately strong ($d = -0.43$ [95% CI $= -0.62$ to -0.24], SE $= 0.1$, $P = <0.0001$, $k = 239$; Table S3; $I^2 = 52.06\%$, $R_c^2 = 88.90$). The meta-regression model by specific groupings of condition proxies ($I^2 = 47.93\%$, $R_c^2 = 85.71$, $R_M^2 = 16.27$) showed strong differences in effect according to how nutrition was measured (Table S3); again indicating that methodological considerations are essential when reviewing experimental findings. Observations based on a subjective body condition score (often a categorical qualitative assessment) and body size/length (which is too unspecific) showed the weakest effects; body size/length leading to a non-significant effect (Fig. 6, Table S3). This is consistent with previous reports that caution the use of these indices because of the loss of resolution inherent to qualitative scores, and overly general metrics like length that vary strongly by species, age, sex, and mitigating circumstances (Stevenson & Woods, 2006; Peig & Green, 2010; Sanchez *et al.*, 2018). Growth rate, which inherently accounts for time of infection, showed the strongest negative effect. The most consistent and significant metrics, all with an effect size around -0.4, were body mass index, body mass, and measurements of fat (kidney fat index, fat mass, fat depth), which are better indicators of the availability of energy in the animal for storage in fat or for growth (Brown *et al.*, 1993; Peig & Green, 2010). While historically gastrointestinal parasites have been seldom considered influencers of mammal health (Appendix S1), it is clear that sub-lethal infections of gastrointestinal helminths are negatively affecting mammal energetic condition and should clearly be included into the analysis of both mammal health and population dynamics.

(5) Heterogeneity and bias

Heterogeneity is expected to be high in ecological meta-analysis, generally $I^2 = 83$–92% (Senior *et al.*, 2016). This is due likely to limitations in ecological sampling which create diverse methodological practices. Surprisingly, even though most of our included effect sizes came from studies of wildlife ($k = 408$), overall heterogeneity was moderate ($I^2 = 56.89\%$), and closer to what would be expected in meta-analyses of human medicine and controlled experiments (Senior *et al.*, 2016). Analysis of publication bias showed a left skew in the funnel plot of the intercept-only model. However, when repeated for the best-fit meta-regression model, this was reduced (Fig. S8). Some level of skewed distribution should be expected due to the nature of the effect size measurement, a comparison of means, most often between infected and uninfected animals. This means that we are less likely to get strongly positive effect sizes as that would require infected animals independent of the control group to increase their energetic condition drastically. It is more likely they would have similar averages, leading to a weakly positive or weakly negative effect.

Publication bias tends to lead to type-1 errors as studies producing significant results are more likely to be published.
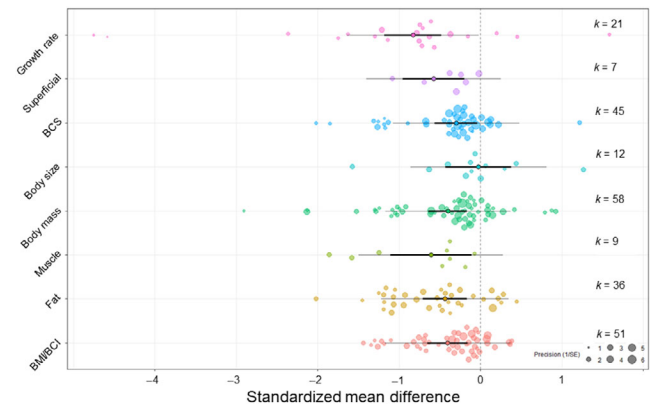

Fig. 6. Orchard plot showing average effect size (point) of gastrointestinal parasite infection on 'Body condition' (morphological energetic proxy measures), with 95% confidence interval (bold line), precision interval (thin line), and individual effect sizes scaled by precision and clustered quasi-randomly. Sub-sets of included effect sizes of studies that investigated gastrointestinal helminths and measured energetic condition by nutritional status, i.e. classic metrics of body condition. These include growth rate, superficial features (like antler size or fur quality), body condition score (BCS), body size, body mass, muscle (often muscle depth at specific locations), fat (such as fat mass or kidney fat index), and body mass index (BMI) or body condition index (BCI).

This is why ecological cross-sectional studies generally have higher heterogeneity and stronger effect sizes than controlled experimental studies which tend to reduce negative bias and moderate the observed effect (Peters *et al.*, 2008). However, heterogeneity may not always be due to publication bias. Any factor that can influence effect size may increase heterogeneity, such as sampling bias and poor study design (Peters *et al.*, 2008). Our results showed the opposite trend; methodological limitations of cross-sectional studies reduced the strength of the negative effect, while experimental, controlled studies increased the strength of the negative effect (Fig. 3A). This suggests that methodological bias, not publication bias, may be increasing heterogeneity, feeding the incorrect assumption that large wildlife, like marine mammals, may be unaffected by helminth parasites.

Similar trends are obvious within cross-sectional studies. In the meta-regression where only host taxonomic group was considered, the negative effect of infection was not significant for carnivores (Fig. 4A). If sampling methodology had not been considered in our analysis, this distinction would have been missed. In addition to publication bias, we encourage the consideration of methodological bias in meta-analyses, especially in ecological research, as it might also induce type-I or -II errors.

(6) Guidelines for studying sub-lethal effects in wildlife

Our results highlight how methodological variations may influence our perceptions of the influence of sub-lethal

parasites on wildlife populations. Going forward, researchers should explicitly state and model the context and importance of energetic condition ('health') metrics as they relate to individual and population fitness for the species. We suggest some general guidelines below.

For *semi-controlled field experiments*, it is preferable that individuals with known infection status (best practice to treat uninfected 'control' animals with anthelmintics paired with faecal analysis to confirm they are parasite free) be observed for differences in behaviour, reproductive output, or hormonal proxies (which can be measured *via* faeces), and if possible, re-captured for serological and morphometric energetic proxies. Since infection period is unlikely to be known, and faecal analysis often limits parasite quantification to presence/absence, it is best that analysis of the effect of anthelmintics or artificial infection be measured as change over time. Thus, re-capture of individuals is preferred over random sampling of a population where individual hosts cannot be confirmed as treated or not. Depending on the duration of the study, energetic proxies that respond quickly to energy availability should be used, such as time spent in an elective behaviour, metabolic parameters, concentrations of specific vitamins, etc. (Table S2).

For *cross-sectional studies*, animals should be sampled according to controlled experimental protocols whenever possible to ensure adequate sampling of the population depending on study goals. Opportunistic methods often introduce bias into the sample group and should be interpreted with caution. During data collection, considerations of both age class and sex should be included, along with consideration of the time of year and species-specific life-history traits. If this is logistically impossible, for opportunistically collected carcasses, researchers must explicitly model cause of death in the analysis to differentiate individuals that died of accidental (i.e. unnatural events such as roadkill or fishing bycatch) causes and those that died of natural causes (e.g. disease, age). Hosts that die of natural processes are more likely to be in poor condition regardless of parasitic infection, which reduces the sensitivity of the comparison between infected and uninfected individuals. Researchers should also comment on any possible compounding effects of parasite and natural cause of death. For example, in marine mammals opportunistically sampled from carcasses washed up on shore, it would be beneficial to include cause of death in the model to account for the variance in condition for the uninfected 'control' hosts between 'trauma', 'disease', and 'age'. Those that died from boat strike or other traumatic events, but in otherwise good condition, would constitute a better uninfected control group than those that died of old age or starvation and may obfuscate more subtle effects of infection.

Relying upon a single energetic proxy may lead to type-II errors, which can be avoided by combining different proxies. For example, when infection period is unknown, using a mix of proxies with some that respond quickly and others that take longer to respond to energetic challenge (for example cortisol stress response and a nutritional status proxy such as muscle depth) will provide a more complete and less-biased picture of the effects of infection. If using a proxy like fat (nutritional status), use multiple body locations such as subcutaneous and organ fat, as different host species may deplete their fat stores at different points during the infection period. Explicitly modelling the effect of infection on each would document infection effects better and help avoid type-II errors if a species, for example, depletes their organ fat first when energetically challenged. Proxies should also be chosen according to species-specific host life history. For example, for a host that does not tend to store large quantities of fat, even when healthy, and instead pours all excess energy into reproduction or metabolism, condition would be best measured by reproductive output, core systemic functioning, or 'optional' activities such as time spent patrolling or exploration.

Overall, it is difficult to quantify unequivocally the effects of sub-lethal infection on host fitness in any single study. Due to methodological inconsistencies and other constraints/limitations, data are often limited, and our conclusions biased by incomplete information. Going forward, studies aiming to assess parasite influence on mammal hosts should aim to use multiple condition proxies, clear methodology, and account for the potential limitations of host and parasite sampling.

(7) Helminths matter

Our meta-analysis shows that contrary to some assumptions, mammals are significantly affected by sub-lethal infections of helminth parasites. Generally, infection lowers host energetic condition, which may be directly related to fitness. Methodological factors strongly influence our ability to detect and quantify infection effects and the significance of helminth parasites on host health. Cross-sectional studies relying on opportunistic sampling may have contributed to a perception that these parasites do not influence host health or fitness. However, our results show that this is not the case. Similarly, differences such as host species, age, sex, and the condition proxy assessed also influence the significance of the negative effects of helminth infection. The strength of effect is also likely linked to duration of infection, as there were no strong differences between intensity and presence/absence. This is consistent with Sanchez *et al.* (2018), who noted a similar lack of differentiation between presence/absence and intensity data. Energetic proxies more likely to change quickly, or those that explicitly included time (such as growth rate), showed slightly stronger negative effects of infection on host energetics.

Historical assumptions that helminths do not significantly influence mammal health, unless they occur in overwhelming numbers (Appendix S1), may derive from both sampling limitations and common emphasis on disease in the literature (Fig. S9). However, we should not draw conclusions on complex host–parasite interactions based solely on pathogenicity or intensity of infection (Samuel *et al.*, 2001). Indicators of wildlife health need to go beyond death and disease and

consider host individual and population fitness. Similar to non-consumptive predator effects and the ecology of fear (Clinchy *et al.*, 2013), or the stress of anthropogenic disruptors on energy budgeting (Bennett *et al.*, 2009), sub-lethal helminth infections should be considered influencers of host fitness. Helminths can disrupt digestive functions, suppress the immune system, activate a stress response, and alter other physiochemical processes (Irvine, 2006; Beldomenico *et al.*, 2008*a*; Parker *et al.*, 2009; Tompkins *et al.*, 2011; Stephen, 2014; Shanebeck & Lagrue, 2020). Concomitant infections, lower competitiveness, and stress on already resource-limited systems may also be linked to sub-lethal helminth effects on mammal health (Samuel *et al.*, 2001; Stevenson & Woods, 2006; Beldomenico *et al.*, 2008*a*). As such, they clearly have the potential to be significant influencers of host fitness and ecological functioning. While the significance of these effects may depend on specific systems, host and parasite species, and situations, helminths should be considered guilty until proven innocent.

IV. CONCLUSIONS

(1) Mammal energetic condition is significantly negatively affected by sub-lethal helminth parasites, across all major groups (including ungulates, carnivores, primates, and rodents).

(2) Methodological limitations and disparities in wildlife research can reduce the resolution of these effects and may have driven previous assumptions of insignificance. Cross-sectional observational studies produced weaker effect sizes compared to experimental or semi-controlled studies. Sampling protocols also explained inter-study variance in wildlife research; opportunistic sampling of carcasses led to reduced effect sizes and increased variance compared to studies using active sampling protocols of live animals.

(3) There was no difference in parasite effects on host condition between infections measured by intensity or presence/absence, suggesting that duration of infection may be more important when analysing sub-lethal infections. This contradicts assumptions that only high-intensity infections are relevant, highlighting an important limitation of observational studies where infection period is unknown.

(4) We hope this review and meta-analysis will instruct ongoing research and provide a comprehensive context for the inclusion of sub-lethal parasites into ecological and management models. We strongly recommend that sub-lethal parasites be considered a significant potential threat to wildlife populations and ecosystem structure and functioning.

V. ACKNOWLEDGEMENTS

VI. REFERENCES

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VII. SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Relevant quotes from textbooks with reference to the effects of helminths on wildlife health.

Table S1. Glossary of terms.

Appendix S2. Inclusion and exclusion criteria.

Table S2. All energetic proxies included in the meta-analysis and binned by categories of scale: (A) morphological; (B) physiological; and (C) observational (external).

Fig. S1. Hierarchy decision tree for calculation of Cohen's *d*.

Fig. S2. Phylogenetic tree of included species by clade.

Appendix S3. Additional information on the data set.

Fig. S3. Point counts of included studies by the year in which they were published.

Fig. S4. Orchard plot showing effect of infection on host energetics according to parasite taxonomic group: trematodes, nematodes, cestodes and mixed infections (i.e. hosts infected by more than one taxonomic group).

Fig. S5. Orchard plot showing effect of infection on host energetics according to tissue location.

Fig. S6. Orchard plot showing effect of infection on host energetics according to energetic condition proxy and parasite quantification.

Fig. S7. Orchard plot showing effect of infection on host energetics according to study design and parasite quantification.

Table S3. Effect sizes and meta-regression statistics for infections by gastrointestinal helminths using only the common body condition metrics sub-set.

Fig. S8. Contour funnel plots: (A) intercept-only model; (B) best-fit meta-regression model (host sampling origin: energetic proxy).

Fig. S9. Word cloud of literature search abstracts.

Datafile S1. Full data set used in the analysis with calculated effect sizes, confidence intervals and standard error, and with a separate sheet providing explanatory information.