




RESEARCH ARTICLE

Botfly infections impair the aerobic performance and survival of montane populations of deer mice, *Peromyscus maniculatus rufinus*

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Funding information

National Science Foundation, Grant/Award Number: IOS 1634219, OIA 1736249, IOS 1755411; University of Montana

Handling Editor: Craig White

Abstract

1. Elevations >2,000 m represent consistently harsh environments for small endotherms because of abiotic stressors such as cold temperatures and hypoxia.
2. These environmental stressors may limit the ability of populations living at these elevations to respond to biotic selection pressures—such as parasites or pathogens—that in other environmental contexts would impose only minimal energetic and fitness-related costs.
3. We studied deer mice (*Peromyscus maniculatus rufinus*) living along two elevational transects (2,300–4,400 m) in the Colorado Rockies and found that infection prevalence by botfly larvae (*Cuterebridae*) declined at higher elevations. We found no evidence of infections at elevations >2,400 m, but that 33.6% of all deer mice, and 52.2% of adults, were infected at elevations <2,400 m.
4. Botfly infections were associated with reductions in haematocrit levels of 23%, haemoglobin concentrations of 27% and cold-induced VO_{2max} measures of 19% compared to uninfected individuals. In turn, these reductions in aerobic performance appeared to influence fitness, as infected individuals exhibited 19–34% lower daily survival rates.
5. In contrast to studies at lower elevations, we found evidence indicating that botfly infections influence the aerobic capabilities and fitness of deer mice living at elevations between 2,000 and 2,400 m. Our results therefore suggest that the interaction between botflies and small rodents is likely highly context-dependent and that, more generally, high-elevation populations may be susceptible to additional biotic selection pressures.

KEYWORDS

carry-over effects, context-dependence, macroparasites, thermogenic capacity

1 | INTRODUCTION

Infection by a macroparasite—parasites with multiple life stages that do not multiply within their host—can influence the physiology and

behaviour of a host (Burns, Goodwin, & Ostfeld, 2005; Finnerty, Shine, & Brown, 2018; Smith, 1978). These infections can also amplify the effects of other environmental stressors and affect host fitness (Gooderham & Schulte-Hostedde, 2011; Juliana,

Khokhlova, Wielebnowski, Kotler, & Krasnov, 2014). For instance, young blue tits (*Parus caeruleus*) infected by ectoparasitic blowflies (*Protocalliphora*) have reduced haematocrit levels and heightened thermogenic requirements that inhibit their ability to withstand subsequent environmental stressors (Simon, Thomas, Blondel, Perret, & Lambrechts, 2004). In turn, macroparasites can even influence host population dynamics. For example, red grouse (*Lagopus lagopus scotica*) suffer reduced fecundity when infected by parasitic nematodes (*Trichostrongylus tenuis*), and as a result, population growth rates decline following years with a high prevalence of infections (Albon et al., 2002; Dobson & Hudson, 1992). Nonetheless, the effects of macroparasites on the population dynamics of their hosts are thought to be relatively small compared to the effects of other types of infections (e.g. pathogens; Buck & Ripple, 2017). This discrepancy may, however, result from our limited understanding of how the effects of macroparasitic infections differ across species and environmental contexts, and not the macroparasitic infections themselves.

In particular, environmental and biotic contexts can influence the severity of the consequences of a macroparasitic infection for a host. For example, nutritionally stressed capybaras (*Hydrochoerus hydrochaeris*) have higher infection intensities than unstressed individuals (Eberhardt et al., 2013). Similarly, in *Peromyscus leucopus* and *P. maniculatus*, food-supplemented individuals are better able to stave off infections by intestinal parasites (Pederson & Greives, 2008). Additionally, tree swallow (*Tachycineta bicolor*) nests in wetlands comprised of mining tailings are parasitized by 72% more blowflies (*Protocalliphora* spp.) than nests in natural wetlands (Gentes, Whitworth, Waldner, Fenton, & Smits, 2007). Nonetheless, relatively few studies have investigated the effects of macroparasitic infections in wild populations, and it is therefore unclear whether the consequences of infections are generally context-dependent (Jolles, Beechler, & Dolan, 2015).

Cuterebra botflies (hereafter, “botflies”) are obligate parasites that infect mammals throughout the western hemisphere from sea level to ~2,500 m.a.s.l. (Coquillett, 1898; Graham & Capelle, 1970). Botfly infections last 20–25 days, during which time the larva feeds on a host's interstitial fluids, cellular debris and necrotic tissues (Capelle, 1970; Cramer & Cameron, 2006; Slansky, 2007). The costs of accommodating the larval load—the proportion of a host's resources allocated to larval development—and immune response to botfly infections have been well documented at low elevations (Careau, Garant, & Humphries, 2012; Jaffe, Zegers, Steele, Merritt, & Solomon, 2005; Munger & Karasov, 1994; Timm & Cook, 1979). In general, infections lead to increased white blood cell counts, decreased haemoglobin concentrations and haematocrit levels (Brown & Fuller, 2006; Sealander, 1961; Weisbroth, Wang, & Scher, 1973) and impaired host nutrition and behaviour (Hunter & Webster, 1974).

Despite these effects, botflies are thought to only weakly affect the whole-organism performance and fitness of small mammals (Burns et al., 2005; Careau et al., 2012; Cramer & Cameron, 2006). As obligate parasites, botfly larvae rely heavily on their host's survival (Timm & Cook, 1979), leading to the hypothesis that botflies and some rodent species have co-evolved to minimize the consequences

for the host (Burns et al., 2005; Jaffe et al., 2005; Timm & Cook, 1979). However, while selection on both the host and the parasite may limit the costs of active infections, these pressures likely relax after larval emergence, and the costs of the infection may carry over to influence host fitness during subsequent life-history events without a direct cost to the parasite (Simon et al., 2004).

Peromyscus mice are commonly used in studies investigating the effects of botflies on mammalian hosts (see review in Slansky, 2007). Thus far, however, no study has investigated the potential context-dependence of the consequences of infections. Being that deer mice inhabit the broadest elevational range of any North American mammal (Hock, 1964), they encounter a diversity of potential environmental stressors that could mediate the costs of parasitic infections (Fuller, 1996). Accordingly, across their range, different populations of deer mice display an array of habitat-specific adaptations to biotic and abiotic factors. For instance, populations of the subspecies *P. m. rufinus* (hereafter: *P. maniculatus* or deer mice) at high elevations have evolved traits along the entire oxygen transport cascade that confer on individuals increased aerobic capacity and blood-oxygen loading capabilities (Chappell et al., 2007; Scott, Elogio, Liu, Storz, & Cheviron, 2015; Tate et al., 2017). Given the importance of haematocrit and haemoglobin concentrations to an individual's blood-oxygen carrying capacity, the known haematological effects imposed by botfly infections on *P. maniculatus* may have more pronounced consequences at higher elevations than in other contexts (Hayes & O'Connor, 1999).

We thus investigated how botfly infections influenced the blood composition and aerobic performance of deer mice over three years along two elevational transects that extended to the upper limits of the ranges of both botflies and deer mice in the Colorado Rocky Mountains, USA. Along these transects, we measured the effects of botfly infections on a suite of traits related to aerobic performance—including haemoglobin concentration (Hb), haematocrit level (Hct), resting metabolic rate (RMR), cold-induced VO_{2max} (summit metabolic rate; hereafter, M_{sum}) and absolute metabolic scope (difference between RMR and M_{sum} values; hereafter, metabolic scope)—as well as overwinter survival. We predicted that infected individuals would have diminished metabolic scope, with an elevated resting metabolic rate and decreased summit metabolic rate, reduced haemoglobin concentration and lower haematocrit, and that these effects would persist post-infection, leading to significant long-term fitness costs (e.g. increased overwinter mortality). By measuring such a wide range of traits thought to be under selection in deer mice at high elevations, as well as survival itself, our study will allow us to place the impacts of botfly infections on aerobic performance into a broader fitness context and further our understanding of the potential context-dependent costs of parasitic infections.

2 | MATERIALS AND METHODS

2.1 | Study site

We monitored two elevational transects in northcentral Colorado in September and October from 2016 to 2018 for botfly infections

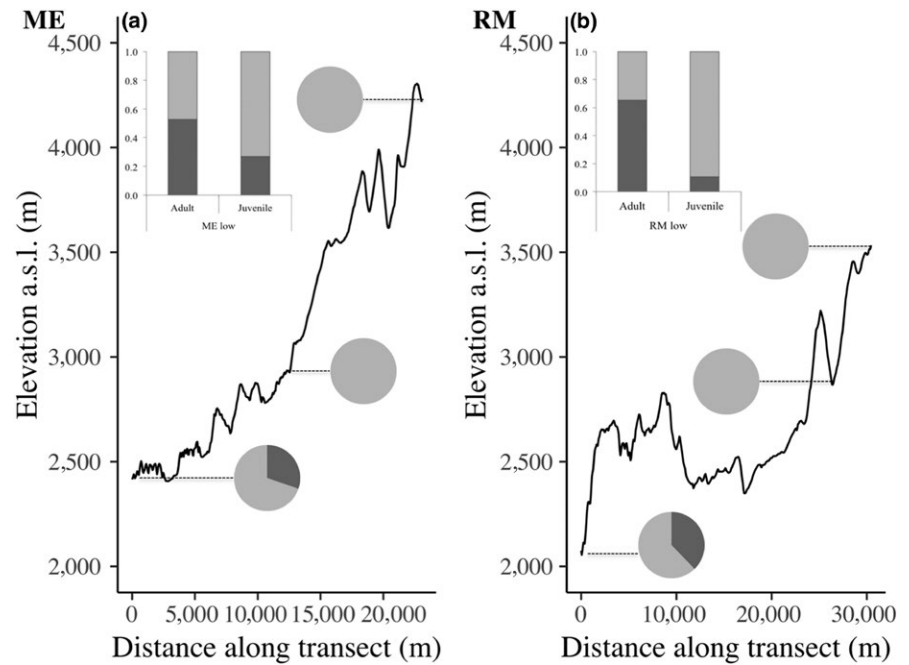


FIGURE 1 Cross-sectional view of the demographic transects ME (left; $ME_{low} = 2,400$ m, $ME_{mid} = 2,900$ m, $ME_{high} = 4,200$ m) and RM (right; $RM_{low} = 2,120$ m, $RM_{mid} = 2,870$ m, $RM_{high} = 3,660$ m). Infection prevalence at each site is shown as a pie chart depicting infected (dark grey) and uninfected (light grey). Age-specific infection prevalence for ME_{low} (a) and RM_{low} (b) is displayed as an inset using the same colouring format

in local deer mouse populations, and again in April and May in 2017 and 2018 to document overwinter deer mouse survival. These transects each consisted of three plots, with one transect following the Big Thompson River watershed in Rocky Mountain National Park and Roosevelt National Forest (RM; Supporting Information Appendix S2)—which was only monitored in 2017 and 2018—and the other following the Clear Creek watershed in the Mount Evans Wilderness and Arapahoe National Forest (ME). Each transect had a high- (~4,000 m a.s.l.), mid- (~2,900 m) and low-elevation (~2,300 m) site (Figure 1). Along the RM transect, these sites were located at 40.3989°N, 105.7031°W; 40.3926°N, 105.6566°W; and 40.2839°N, 105.3829°W, respectively. On the ME transect, they were located at 39.5852°N, 105.6379°W; 39.6796°N, 105.6576°W; and 39.7379°N, 105.5342°W, respectively. We chose plots based on the presence of open-ground habitats, as this is the preferred habitat of deer mice in the Colorado Rockies (Williams, 1955).

2.2 | Peromyscus trapping

Each study site was comprised of a rectangular plot ranging in size from 2 to 4 ha, depending on the extent of contiguous open habitat. At each site, we deployed Sherman live traps (7.62 × 8.89 × 22.86 cm) in a geometric grid. We trapped at each plot for 3–6 days or until ≥30 unique individuals had been completely processed. Trapping was suspended on nights with wet and cold conditions to minimize mouse mortalities. Each trap was set nightly (between 15:00 and 19:00 hr), baited with peanut butter and oats and filled with Poly-fil® polyester fibre. We checked traps the following morning (between 07:00 and 09:00 hr) and released non-target species immediately; all traps then remained closed from 09:00 to 15:00 hr.

2.3 | Animal processing

For each new mouse captured, we first recorded the presence or absence of botflies (Smith, 1978). Infection status was divided into infected, recovering—skin lesions or substantial scarring in the inguinal, scrotal or dorsal region, indicating larval emergence within the previous ~9 days (Payne & Cosgrove, 1966)—and uninfected. Preliminary analyses indicated that multiple larvae (i.e. in addition to the first infection) had only a weak effect on an individual's haematological values (Hb and Hct). As a result, we chose to pool individuals with a single larva or multiple larvae ($n_{Hb} = 5$, $n_{Hct} = 4$, $n_{RMR, Msum} = 3$) in our analyses. Although two species of rodent-infecting botflies commonly co-occur in the Colorado Rockies (*C. fontinella* and *C. approximata*), the differentiation of the two requires observation of the adult flies; we therefore only identified the larvae to genus (Boggs, Lochmiller, McMurry, Leslie, & Engle, 1991; Capelle, 1970).

Additionally, for each mouse, we recorded the individual's anogenital distance (male: ≥4 mm), mass and age class (adult: ≥16 g, see below). We also inserted a 12.5 mm, 134.2 kHz PIT tag (HPT-12, Biomark, Boise, ID, USA) into the interscapular region of each mouse for identification. We then collected an ear clip as a genetic sample and an ≤75 μl blood sample from the maxillary vein to measure Hb and Hct (Hct: 2017 and 2018 only). We immediately quantified an individual's Hb concentration with a HemoCue Hb 201 + analyser (HemoCue AB, Angelholm, Sweden) and their Hct value by measuring the column height of packed red blood cells relative to the whole blood column height in a heparinized capillary tube following centrifugation. Morphological measurements and body mass were taken immediately upon capture for animals that did not undergo respirometry trials or after 30 min following the termination of an M_{sum} trial.

All experimental protocols were performed in accordance with the guidelines of the American Society of Mammalogists (Sikes & Gannon, 2011) as documented in IACUC Protocol 029-16ZCDBS-051016 from the University of Montana, scientific permit ROMO-SCI-2017-0034 from Rocky Mountain National Park, collecting permit CLC772 from the U.S. Forest Service and licence #17TR2168b from Colorado Parks and Wildlife.

2.4 | Metabolic rate measurements

As deer mice are primarily nocturnal, we measured RMR during daylight hours while mice were resting (2016–2017; no metabolic measures were collected in 2018). To do this, we pumped ambient air through a darkened cabinet that housed a Peltier device to regulate the temperature and keep the internal air at 27°C, which is within the thermoneutral zone of deer mice. We used mass flow controllers (Sable Systems Inc., Las Vegas, NV, USA) that maintained in-current air at a flow rate of 500 ml/min (Cheviron, Bachman, & Storz, 2013). We scrubbed the in-current air of H₂O using drierite before it entered either the airtight baseline or animal respirometry chambers (polypropylene, 180 ml). Once the air had passed through the chambers, we scrubbed it of CO₂ with ascarite and then re-dried it before pumping it through an oxygen analyser (FoxBox, Sable Systems Inc.). We recorded the oxygen consumption of each individual over a series of 15-min intervals allowing for alternation of measurements between the animal and baseline chambers. This process was repeated until a stable measure—10-min period with no significant change in slope of oxygen consumption—was collected for each individual (1–4×, 15-min intervals). We calculated RMR using equation 10.1 in Lighton (2008) and measured as the minimum rate of oxygen consumption averaged over a continuous 5-min period.

For measures of M_{sum} , we followed the methods of Cheviron et al. (2013), using the respirometry set-up described above for RMR with the following differences: We pumped a heliox mixture (21% O₂, 79% He ± 0.5%) equilibrated to local atmospheric pressure at the capture elevation into a temperature-controlled cabinet at a rate of 700 ml/min. Flow rates were controlled using an Alicat Flow Meter calibrated for a heliox environment. Rates of heat loss in a heliox environment are greater than ambient air, allowing M_{sum} to be measured without subjecting individuals to an increased risk of cold injuries (Rosenmann & Morrison, 1974); all M_{sum} trials were conducted at -5°C. After a 5-min baseline, we monitored the excurrent O₂ of a single experimental animal for a maximum of 30 min. This animal was removed when oxygen consumption declined, at which point we collected a second, five-minute baseline. A rectal thermocouple was used to measure the body temperature of each individual before and after the half-hour trial to confirm a hypothermic state (e.g. internal temperature ≤90% of initial temperature) and verify that M_{sum} had been reached for each animal. M_{sum} was calculated using equation 10.1 in Lighton (2008) and measured as the maximum rate of oxygen consumption averaged over a continuous 3-min period.

2.5 | Statistical analysis

For our analyses, we assigned each mouse to an infection group, as well as an age class and sex. An uninfected or recovering individual with a mass of ≥16 g was considered an adult; the same was true of an infected individual with a mass ≥16 g + 5% of total mass to account for the additional mass of the bot larva(e) (Cramer & Cameron, 2006; Slansky, 2007). To assess how infection prevalence varied across years, between transects and among sites, and depended on demographic factors, we used generalized linear models (GLM) with a binomial distribution in the package “MuMIn” (Bartoń, 2015) in Program R (v. 3.3.2) with year, elevation, sex, age class, transect and site as predictor variables and infection status as the dependent variable. Because we only detected infections at our two low-elevation sites, transect was excluded as a variable from further analyses.

After pooling data from both low sites, we used GLMs to investigate the physiological effects of botfly infections on their hosts using linear models with an individual's physiological trait value—Hb, Hct, RMR, M_{sum} or metabolic scope—as the dependent variable, and year, site, infection status, age and sex as predictor variables. For our metabolic data, we used an individual's uncorrected values in all of our models, but additionally included mass as a covariate to account for the known effects of mass on metabolic rate. We then calculated an individual's metabolic scope as the difference between the uncorrected measures of RMR and M_{sum} (Stager et al., 2016) and tested for differences among individuals based on their infection status, sex, site, sample year and age class as above. Finally, given our limited sample sizes, we did not include interaction terms in any of our models.

For all models, we performed model selection using Akaike's information criterion corrected for small sample sizes (AIC_c; Burnham & Anderson, 2001). The model with the lowest AIC_c score was considered the most well-supported model; when no single model had a model weight (w_i) > 0.90, we used model averaging. Predictor variables whose 95% confidence intervals did not include zero were considered biologically relevant. We report the conditional average—with the adjusted standard error to include the effect of model uncertainty—to denote the importance of each predictor variable (Grueber, Nakagawa, Laws, & Jamieson, 2011).

Additionally, we assessed the effects of botfly infections on over-winter survival. To do this, we calculated survival as the percentage of individuals that were recaptured from the previous fall while accounting for variation in encounter probabilities among individuals. Because the trapping periods at the two sites did not fully overlap, and because we monitored ME_{low} for two consecutive winters but RM_{low} for only one, we elected to analyse the sites separately. For these analyses, we first used a goodness-of-fit test in U-CARE (Choquet, Lebreton, Gimenez, Reboulet, & Pradel, 2009) to test for evidence of over-dispersion in our dataset and determined that no corrections were necessary. We then used a Cormack-Jolly-Seber model performed in “RMark” (Laake,) to calculate estimates of apparent survival, ϕ , and encounter probability, p . We included detections of marked individuals from both fall and spring capture periods and considered the effects

of botfly infection, sex and age on ϕ and p . We included sex and age effects, as these demographic features have been shown to influence multi-season survival in small mammals (Burns et al., 2005). Given the small sample size of recaptured mice, we excluded additional covariates (Supporting Information Appendix S1: Table S3). We performed model selection and averaging as described above.

3 | RESULTS

3.1 | Botfly infection prevalence

Along our two transects, we assessed 390 mice ($\mu = 65$ individuals per site) for the presence of *Cuterebra* larva. We found no evidence of infections above an elevation of 2,400 m (Figure 1). Below 2,400 m, infection prevalence—the proportion of the population exhibiting active infections—averaged 33.6% and did not differ between sites ($RM_{low} = 37.8\%$, $n = 45$ individuals; $ME_{low} = 30.3\%$, $n = 56$ individuals; Supporting Information Appendix S1: Table S1). Additionally, neither sex (females: 34.7%, $n = 49$ individuals; males: 32.7%, $n = 52$ individuals; Supporting Information Appendix S1: Table S1) nor year (2016:21.7%, $n = 23$ individuals, 2017:40.0%, $n = 45$ individuals, 2018:33.3%, $n = 33$; Supporting Information Appendix S1: Table S1) affected infection status. However, infection prevalence did differ between age classes, with only 17.9% of juveniles ($n = 56$ individuals), but 52.2% of adults exhibiting infections ($n = 46$ individuals; adults: $\beta = 1.72$, $SE = 0.47$, $CI = 0.79, 2.64$).

3.2 | Botfly effects on haematology

Haemoglobin concentration was best predicted by age class and infection status (Figure 2, Supporting Information Appendix S1: Table S1). Mice with an active infection had Hb concentrations averaging 4.17 g/dl lower ($\mu = 11.62 \pm 2.16$ g/dl, $n = 34$; all means [$\mu \pm SD$]) than those without an infection ($\mu = 15.79 \pm 1.59$ g/dl, $n = 62$; Infected: $\beta = -3.41$, $SE = 0.39$, $CI = -4.18, -2.64$; Supporting Information Appendix S1: Table S2). Although recovering mice had higher Hb concentrations than actively infected mice, they still exhibited a 3.25 g/dl reduction in haemoglobin ($\mu = 12.54 \pm 1.74$ g/dl, $n = 5$; Recovering: $\beta = -2.57$, $SE = 0.79$, $CI = -4.12, -1.03$) compared to uninfected individuals. Furthermore, adult mice also had 3.06 g/dl less haemoglobin ($\mu = 12.55 \pm 2.51$ g/dl, $n = 45$; Adults: $\beta = -1.52$, $SE = 0.39$, $CI = -2.29, -0.75$; Supporting Information Appendix S1: Table S2) than did juveniles ($\mu = 15.60 \pm 1.93$ g/dl, $n = 56$).

Haematocrit levels were also best predicted by age class and infection status (Figure 2, Supporting Information Appendix S1: Table S1). Infected individuals had, on average, 0.11 lower Hct levels ($\mu = 0.41 \pm 0.08$, $n = 23$) than uninfected mice ($\mu = 0.52 \pm 0.04$, $n = 42$; infected: $\beta = -0.10$, $SE = 0.01$, $CI = -0.13, -0.07$; Supporting Information Appendix S1: Table S2). Recovering mice had lower Hct as well, although this difference was not significant ($\mu = 0.48 \pm 0.06$, $n = 3$; recovering: $\beta = -0.01$, $SE = 0.03$, $CI = -0.07, 0.05$). As with haemoglobin, adult mice exhibited haematocrit levels 0.08 lower

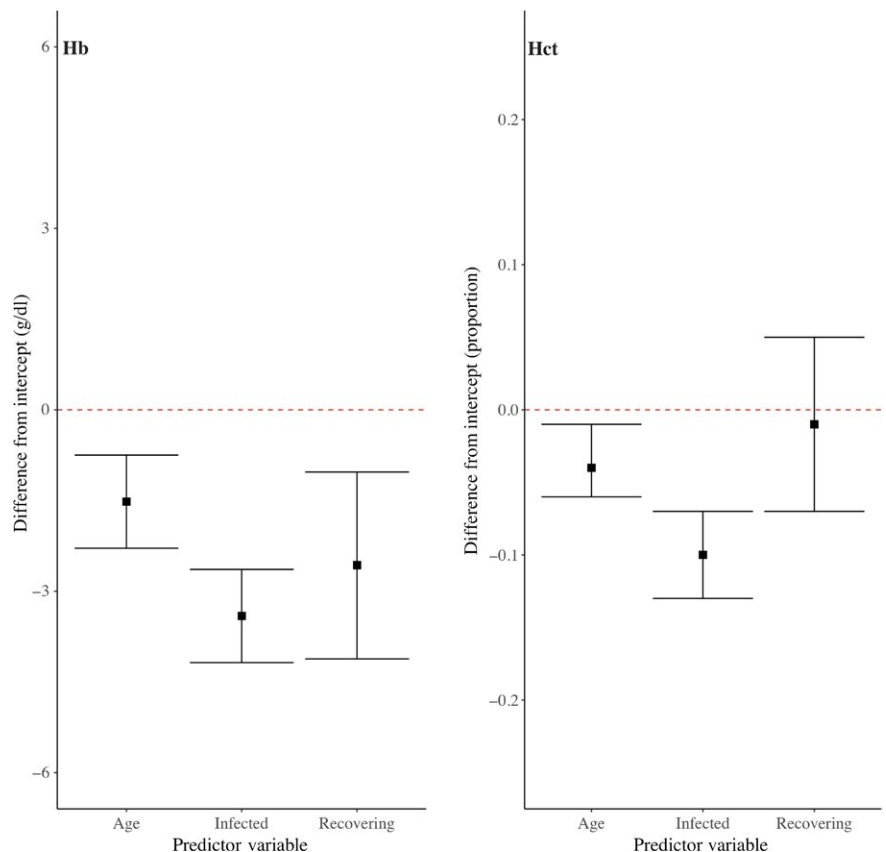


FIGURE 2 Estimated effects of predictor variables on haematological parameters Hb (left) and Hct (right) in relation to the model intercept (dotted red line). Age class (Hb: $n_{adult} = 45$, $n_{juvenile} = 51$; Hct: $n_{adult} = 36$, $n_{juvenile} = 35$) and infection status (Infected, $n_{Hb} = 32$, $n_{Hct} = 23$; recovering, $n_{Hb} = 5$, $n_{Hct} = 3$) effects are reported

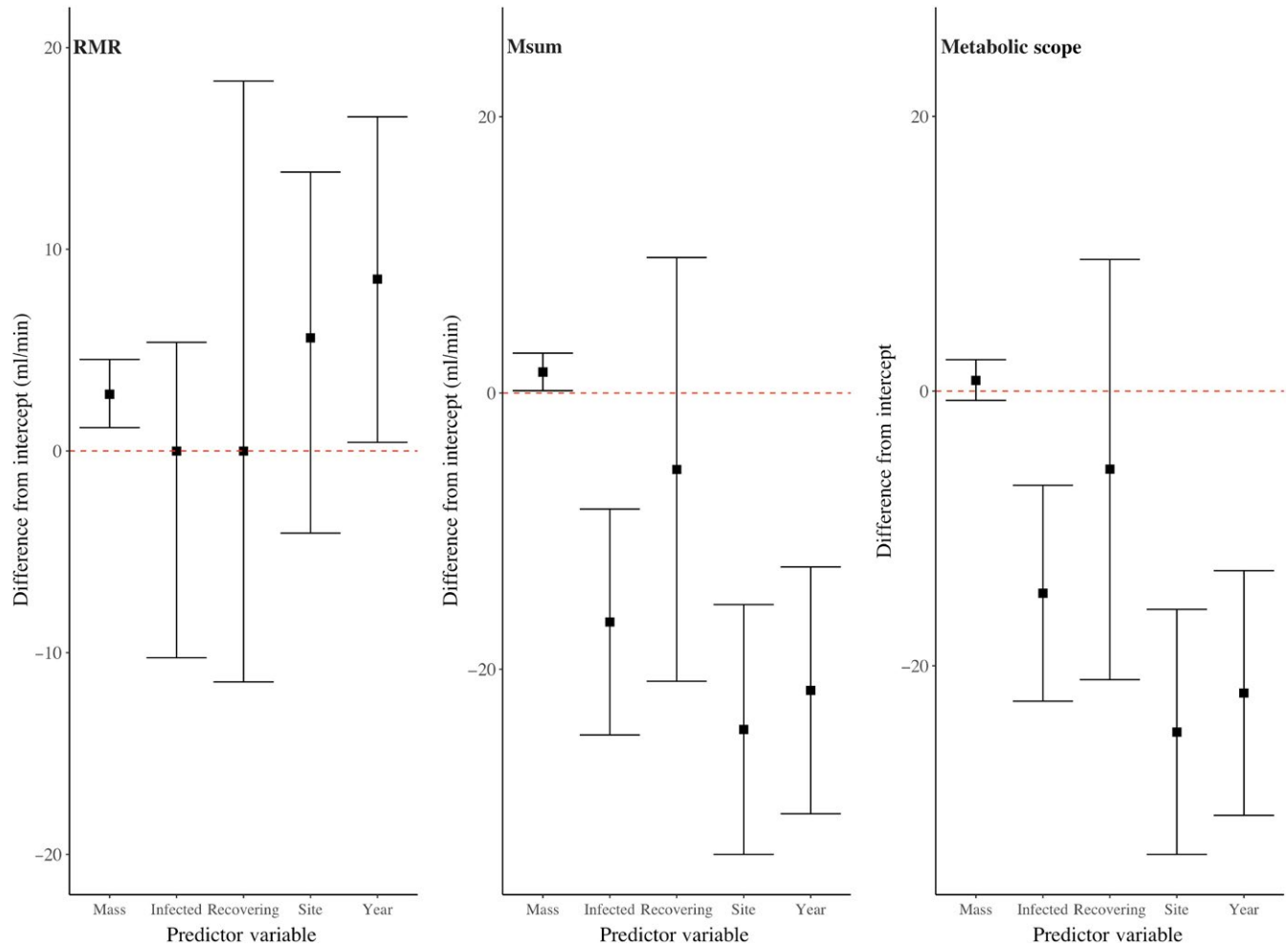


FIGURE 3 Estimated effects of predictor variables on metabolic measurements RMR (left), M_{sum} (middle) and metabolic scope (right) in relation to the model intercept (dotted red line). Mass ($n_{\text{RMR}} = 59$, $n_{\text{Msum}} = 58$, $n_{\text{scope}} = 57$), site (RM: $n_{\text{RMR}} = 24$, $n_{\text{Msum}} = 23$, $n_{\text{scope}} = 23$; ME: $n_{\text{RMR}} = 35$, $n_{\text{Msum}} = 35$, $n_{\text{scope}} = 34$), year (2016: $n_{\text{RMR}} = 22$, $n_{\text{Msum}} = 21$, $n_{\text{scope}} = 21$; 2017: $n_{\text{RMR}} = 37$, $n_{\text{Msum}} = 36$, $n_{\text{scope}} = 36$) and infection status (all: infected, $n = 19$; recovering, $n = 3$) effects are reported

($\mu = 0.44 \pm 0.08$, $n = 32$; adults: $\beta = -0.04$, $SE = 0.01$, $CI = -0.06$, -0.01) than did juveniles ($\mu = 0.52 \pm 0.05$, $n = 36$).

3.3 | Botfly effects on metabolic rate

Year and mass both affected RMR (Figure 3, Supporting Information Appendix S1: Table S1). Individuals sampled during 2016 had lower RMR ($\mu = 0.66 \pm 0.20$ ml O_2/min , $n = 22$; 2016: $\beta = 8.52$, $SE = 4.11$, $CI = 0.43$, 16.57 ; Supporting Information Appendix S1: Table S2) than those sampled in 2017 ($\mu = 0.90 \pm 0.29$ ml O_2/min , $n = 37$). Additionally, individuals with a larger mass ($\mu = 0.79 \pm 0.27$ ml O_2/min , $n = 59$; mass: $\beta = 2.81$, $SE = 0.85$, $CI = 1.16$, 4.54) had slightly higher RMR values. None of our other predictor variables were correlated with RMR (Supporting Information Appendix S1: Table S2).

Site, infection status, year and mass all affected M_{sum} (Figure 3, Supporting Information Appendix S1: Table S1). Individuals from our ME_{low} site had a lower M_{sum} ($\mu = 3.76 \pm 1.05$ ml O_2/min , $n = 35$; ME_{low}: $\beta = -24.36$, $SE = 4.61$, $CI = -33.40$, -15.32 ; Supporting Information Appendix S1: Table S2) than those from our RM_{low} site

($\mu = 5.09 \pm 1.93$ ml O_2/min , $n = 24$). Furthermore, infected mice had, on average, a 0.85 ml O_2/min lower M_{sum} ($\mu = 3.72 \pm 1.49$ ml O_2/min , $n = 19$; infected: $\beta = -16.58$, $SE = 4.17$, $CI = -24.75$, -8.40 ; Supporting Information Appendix S1: Table S2) than uninfected individuals ($\mu = 4.57 \pm 1.61$ ml O_2/min , $n = 38$). Recovering individuals, however, did not have a significantly different M_{sum} than uninfected ones ($\mu = 4.00 \pm 1.45$ ml O_2/min , $n = 3$; Supporting Information Appendix S1: Table S2). Measures of M_{sum} were also 1.28 ml O_2/min higher in 2016 ($\mu = 4.23 \pm 0.90$ ml O_2/min , $n = 21$) than in 2017 ($\mu = 2.95 \pm 0.79$ ml O_2/min , $n = 13$; 2017: $\beta = -21.53$, $SE = 4.56$, $CI = -30.46$, -12.59 ; Supporting Information Appendix S1: Table S2) at Spring Gulch, the only site for which we had two years of M_{sum} data. Finally, as with measures of RMR, individuals with larger masses had slightly higher M_{sum} values ($\mu = 4.29 \pm 1.59$ ml O_2/min , $n = 58$; $\beta = 1.52$, $SE = 0.69$, $CI = 0.17$, 2.88 ; Supporting Information Appendix S1: Table S2).

Metabolic scope was best predicted by site, year and infection status. Individuals from ME_{low} had a lower metabolic scope ($\mu = 3.04 \pm 1.13$, $n = 34$; ME_{low}: $\beta = -24.83$, $SE = 4.54$, $CI = -33.73$,

-15.89; Supporting Information Appendix S1: Table S2) than those from RM_{low} ($\mu = 4.18 \pm 1.91$, $n = 23$). Mice sampled in 2017 also exhibited a reduced metabolic scope ($\mu = 3.43 \pm 1.88$, $n = 36$; 2017: $\beta = -21.99$, $SE = 4.53$, $CI = -30.89$, -13.08 ; Supporting Information Appendix S1: Table S2) in comparison with those sampled in 2016 ($\mu = 3.63 \pm 0.88$, $n = 21$). Finally, mice with an active infection had a lower metabolic scope ($\mu = 2.84 \pm 1.34$, $n = 19$; infected: $\beta = -14.72$, $SE = 4.00$, $CI = -22.58$, -6.86 ; Supporting Information Appendix S1: Table S2) than uninfected individuals ($\mu = 3.84 \pm 1.63$, $n = 38$), but recovering mice did not ($\mu = 3.12 \pm 1.37$, $n = 3$; Supporting Information Appendix S1: Table S2).

3.4 | Botfly effects on survival

Across all individuals, the daily survival rate at RM_{low} was 0.992 ± 0.002 ($n = 31$ individuals), leading to an extrapolated overwinter survival rate of $12.25 \pm 1.29\%$. There was no single best model explaining survival, although the top two models both included an effect of infection status on survival (Supporting Information Appendix S1: Table S3). Accordingly, our model-averaged estimates indicated that infected individuals experienced a >15% reduction in daily survival rates ($\varphi = 0.846 \pm 0.120$ vs. 0.992 ± 0.002 , $n_{\text{infected}} = 14$; infected: $\beta = -2.85$, $SE = 0.84$, $CI = -4.49$, -1.21 ; Supporting Information Appendix S1: Table S4). Thus, few, if any, infected individuals survived the winter (extrapolated overwinter survival = $9.95 \times 10^{-10} \pm 2.40 \times 10\%^{-13\%}$), while an estimated $18.80 \pm 1.29\%$ of uninfected individuals ($n = 17$) did. Additionally, we found that age positively influenced the probability of detection, although its effects were not as large as those of infection status on survival (Supporting Information Appendix S1: Table S4).

At ME_{low}, the daily survival rate was lower ($\varphi = 0.987 \pm 0.003$, $n = 42$), leading to an extrapolated overwinter survival rate of $6.6 \pm 0.7\%$ across all individuals. As with our RM_{low} site, there was no single best model, but sex and infection status both affected survival, while age affected the recapture probability (Supporting Information Appendix S1: Tables S3 and S4). Between the two sexes, females ($\varphi = 0.989 \pm 0.003$, $n = 21$) had significantly higher survival rates than males ($\varphi = 0.702 \pm 0.225$, $n = 21$; males: $\beta = -3.88$, $SE = 0.99$, $CI = -5.82$, -1.95), while adults had higher recapture probabilities (Supporting Information Appendix S1: Table S4). Infected mice had daily survival rates ($\varphi = 0.652 \pm 0.300$, $n = 13$; $\beta = -3.44$, $SE = 1.65$, $CI = -6.67$, -0.21 ; Supporting Information Appendix S1: Table S4) that were reduced by 33.6% from those of uninfected mice ($\varphi = 0.989 \pm 0.003$, $n = 29$). Therefore, an estimated $9.3 \pm 1.4\%$ of all uninfected mice survived the winter, while no infected mice likely did. Post hoc, we also simultaneously tested the effects of sex and infection status on survival: Sex had a larger effect than did infection status (sex, males: $\beta = -4.04$, $SE = 0.85$, $CI = -5.70$, -2.37 ; Supporting Information Appendix S1: Table S5), but both were significant (infected: $\beta = -3.40$, $SE = 1.53$, $CI = -6.39$, -0.41). Thus, while infected females had a 20% reduction in daily survival ($\varphi = 0.790 \pm 0.251$ vs. 0.991 ± 0.003),

infected males had a nearly 60% reduction ($\varphi = 0.062 \pm 0.098$ vs. 0.666 ± 0.178).

4 | DISCUSSION

We surveyed two elevational transects, ranging from 2,300 to 4,400 m, for evidence of botfly infections in deer mice. We only found infected mice at elevations <2,400 m. At these elevations, mice exhibited significant parasite-associated performance costs, including decreases in haemoglobin concentrations, haematocrit levels, summit metabolic rates, metabolic scopes and overwinter survival compared to uninfected individuals. Although similar reductions in haematological values have been documented before in botfly infected mice (Dunaway, Payne, Lewis, & Story, 1967; Sealander, 1961), ours is among the first studies to document reductions in whole-organism aerobic performance and subsequent overwinter survival resulting from these infections in any species. Our study thus corroborates previous work indicating that variation in aerobic performance and thermogenic capacity influences survival in high-elevation populations of deer mice (Hayes & O'Connor, 1999) and suggests that the effects of the selection pressures inherent to high elevations may be strongly mediated by biotic interactions. We therefore provide further evidence that context-dependent environmental stressors influence the nature of and costs imposed by host-parasite interactions (Patterson, Neuhaus, Kutz, & Ruckstuhl, 2013).

Previous investigations in *P. leucopus* and *P. maniculatus* have found reductions in haematocrit levels of ~20% and haemoglobin concentrations of ~25%, but no effect on RMR resulting from botfly infections (Dunaway et al., 1967; Robar, Murray, & Burness, 2011; Sealander, 1961). These are similar to the reductions in haematocrit (~23%) and haemoglobin (~27%), but minimal effects on RMR, that we observed in actively infected individuals compared to uninfected individuals. However, no previous study in *Peromyscus* mice, and only one study of four individuals in eastern chipmunks (*Tamias striatus*; Careau et al., 2012), had assessed the effects of botfly infections on M_{sum} or metabolic scope. We found that infected mice exhibited a 19% reduction in M_{sum} and 26% reduction in metabolic scope, suggesting a link between the infections' haematological effects and whole-organism performance. Additionally, of the numerous studies investigating the effects of botflies on *Peromyscus* mice, only two studies had previously reported any whole-organism or fitness-related effects resulting from botfly infections: Jaffe et al. (2005) found a pattern of longer residency and decreased home-range size in *P. maniculatus* and *P. leucopus*, while Burns et al. (2005) documented a reduction in the number of litters produced by *P. leucopus* that was counterbalanced by an increased adult life span. Our results, though limited to elevations between 2,000 and 2,400 m, suggest that the haematological effects of botfly infections may be more likely to affect a host's performance when the host is constrained by additional abiotic selection pressures such as hypoxia.

Furthermore, we found a 19%–34% decrease in daily survival in infected deer mice, with those reductions being especially

pronounced for males at our ME_{low} site. These reductions in survival meant that, overall, survival rates at our low-elevation sites were considerably lower than those at our higher elevation sites, where overwinter survival averaged $17.89 \pm 6.63\%$ ($n = 4$ sites; N.R. Senner et al., unpublished data). These findings stand in contrast with previous studies in small mammals and suggest that botfly infections can have strong fitness effects on deer mice under at least some circumstances (Burns et al., 2005), and may even influence their population dynamics. However, we should note that our survival analyses were potentially limited by two factors: (a) Overall, we had low recapture rates in the spring across all individuals at our low-elevation sites, limiting the power of our dataset. (b) The acute stress of animal handling and undergoing an M_{sum} trial may have affected infected individuals, already poorly equipped to handle stress, more negatively. Despite these caveats, the degree to which botfly infections reduced the aerobic performance of infected individuals, coupled with the magnitude of the difference in survival that we did detect, suggests that our conclusions about the context-dependency of the consequences of infections are robust.

Additionally, we found that age had an effect on two of our physiological parameters, with young mice having higher haemoglobin concentrations and haematocrit levels. Similarly, mass—a metric highly correlated with age in mice—had a slight effect on some of our metabolic parameters, with heavier mice having higher resting and summit metabolic rates. However, with the exception of RMR, infection status had an equivalent or stronger effect on all of these parameters than did age or mass. Furthermore, while age had a small effect on an individual's recapture probability, it had no effect on their estimated overwinter survival, and juvenile and adult mice survived the winter at similar rates. Aerobic performance therefore appears to change over the course of development in mice, but these changes have a more limited effect on performance and survival than do botfly infections.

Given these results, the question becomes—How do botfly infections actually affect the fitness of infected mice? We hypothesize that infections could potentially affect host survival in one of (at least) three ways: First, during the active infection, infected mice could be susceptible to the direct effects of early fall cold snaps and snowstorms as a result of their reduced thermogenic performance and metabolic scope (Careau et al., 2012). Second, as hypothesized for multiple other host taxa, an individual's impaired aerobic performance during an active infection could influence their movements and mobility, and thus their ability to avoid predators (Cramer & Cameron, 2010; Sealander, 1961). And, third, the effects of an infection could carry over after the infection has passed and impact an individual's performance during subsequent life-history events (Simon et al., 2004; Juliana, Khokhlova, Wielebnowski, Kotler, & Krasnov, 2014).

Which of these three hypotheses is most likely to explain the effects of botflies on deer mice living at higher elevations? For deer mice, the peak incidence of Cuterebrid infections occurs from September to October (Hunter, Sadleir, & Webster, 1972; Jaffe et al., 2005; Wolf & Batzli, 2001). Snow begins to accumulate in the Colorado Rockies as early as mid-October, and autumn is the period of time when small mammals are building food caches to last them

through the subsequent winter months (Careau et al., 2012; Sears, Hayes, O'Connor, Geluso, & Sedinger, 2006). It is thus possible that a botfly infection during early autumn could disrupt an individual's short-term energy balance and—via their reduced aerobic capabilities and mobility—home-range size, constraining their ability to acquire sufficient stores to ensure survival until the following spring (Cramer & Cameron, 2010; Van Sant & Hammond, 2008; Wolf & Batzli, 2001). Accordingly, our sample of recovering individuals ($n = 5$), though small, suggests that the effects of infections persist post-infection for at least nine days—that is, the point at which scarring from infections becomes undetectable (Payne & Cosgrove, 1966)—if not longer, indicating that the costs of botfly infections could carry over to affect overwinter survival. Nonetheless, we were unable to directly assess any of these three hypotheses. Future work should therefore focus on developing a better understanding of the full range of costs associated with botfly and other parasitic infections in small mammals, especially across environmental gradients encompassing a wider range of conditions and infection prevalences than our elevational transects.

More broadly, botflies are ubiquitous throughout most of North America and their range overlaps substantially with that of deer mice (Slansky, 2007). As a result, previous investigators have suggested that the two taxa may represent a highly co-evolved host-parasite system that results in few fitness consequences for the host (Brown & Fuller, 2006; Burns et al., 2005). Nonetheless, some level of antagonism between a parasite and its host is to be expected, and the degree to which this affects the host's performance and fitness may vary with the environmental context. Given that the identity and strength of selection pressures can vary strongly across a species' range, especially one as large and environmentally varied as that of deer mice (Cheviron et al., 2013; Cheviron, Connaty, McClelland, & Storz, 2014; Pfeifer et al., 2018; Storz, Scott, & Cheviron, 2010), it is not surprising that the costs of host-parasite interactions would vary among different environments (Eberhardt et al., 2013; Hall, Vettiger, & Ebert, 2013). This potential context-dependency becomes more important, however, in light of projections of rapid future environmental changes—because the context of host-parasite interactions will likely continue to change, it may be difficult to predict the outcome of these interactions under future environmental conditions. This may especially be true for high-elevation populations that face consistently strong, invariant selection pressures (Storz & Cheviron, 2016). As evidence mounts that botflies and other parasites and pathogens continue to expand their range to higher elevations with increasing global temperatures (Zamora-Vilchis, Williams, & Johnson, 2012), the host species occupying these environments may have to adjust their distributions or face novel selection pressures to which they may have only a limited capability of responding over short time-scales.

ACKNOWLEDGEMENTS

We are indebted to D. Buttke, R. Mahar, J. Shapiro and J. Velotta for their efforts in the field and to members of the Cheviron laboratory

for comments on earlier versions of this manuscript. We thank Rocky Mountain National Park and Denver University for field accommodations and Amos the rat for access to our RMLow site. This work was supported by grants from the National Science Foundation (IOS 1634219, OIA 1736249, IOS 1755411) to ZAC and the University of Montana to NRS and ZAC.

AUTHORS' CONTRIBUTIONS

N.R.S., L.R.W. and Z.A.C. conceived of the project and, with S.M.P. & C.J.W., conducted the fieldwork; L.R.W., M.S. and N.R.S. designed the statistical analyses; L.R.W. and N.R.S. wrote the manuscript, with contributions from C.J.W., M.S. and Z.A.C. All listed authors contributed substantially to the revision drafts and gave final approval for publication.

DATA ACCESSIBILITY

Raw data used in this research are deposited in the Dryad Digital Repository: <http://doi.org/10.5061/dryad.5s12fr6> (Wilde et al., 2018).

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How to cite this article: Wilde LR, Wolf CJ, Porter SM, Stager M, Cheviron ZA, Senner NR. Botfly infections impair the aerobic performance and survival of montane populations of deer mice, *Peromyscus maniculatus rufinus*. *Funct Ecol*. 2019;00:1–11. <https://doi.org/10.1111/1365-2435.13276>

SUPPORTING INFORMATION

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