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1 **TITLE**

2 Sex and hatching order modulate the association between MHC-II diversity and fitness in early-life
3 stages of a wild seabird

4 **RUNNING TITLE**

5 MHC-II diversity and fitness in kittiwake chicks

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14 **ABSTRACT**

15 Genes of the major histocompatibility complex (MHC) play a pivotal role in parasite resistance, and
16 their allelic diversity has been associated with fitness variations in several taxa. However, studies
17 report inconsistencies in the direction of this association, with either positive, quadratic or no
18 association being described. These discrepancies may arise because the fitness costs and benefits of
19 MHC-diversity differ among individuals depending on their exposure and immune responses to
20 parasites. Here, we investigated in black-legged kittiwake (*Rissa tridactyla*) chicks whether associations
21 between MHC class-II diversity and fitness vary with sex and hatching order. MHC-II diversity was
22 positively associated with growth and tick clearance in female chicks, but not in male chicks. Our data
23 also revealed a positive association between MHC-II diversity and survival in second-hatched female
24 chicks (two eggs being the typical clutch size). These findings may result from condition-dependent
25 parasite infections differentially impacting sexes in relation to hatching order. We thus suggest that it
26 may be important to account for individual heterogeneities in traits that potentially exert selective
27 pressures on MHC-diversity in order to properly predict MHC-fitness associations.

28 **KEYWORDS**

29 Divergent allele advantage; fitness; heterozygote advantage; immunity; *Ixodes uriae*; parasite-
30 mediated selection

31 **INTRODUCTION**

32 Identifying the genetic bases of fitness differences among individuals is a long-standing goal in
33 evolutionary biology (Chapman, Nakagawa, Coltman, Slate, & Sheldon, 2009; Ellegren & Sheldon,
34 2008; Merila & Sheldon, 1999). In this context, immune-related genes have drawn substantial
35 attention (Bateson et al., 2016; Froeschke & Sommer, 2005; Oliver, Telfer, & Piertney, 2009; Sepil,
36 Lachish, Hinks, & Sheldon, 2013) because parasite resistance often covaries with fitness in wild
37 populations (Asghar et al., 2015; Hamilton & Zuk, 1982; Moller, Arriero, Lobato, & Merino, 2009;

38 Willink & Svensson, 2017). The major histocompatibility complex (MHC) is a cluster of genes coding for
39 cell surface proteins that are essential for the adaptive immune system. The MHC plays a critical role
40 in modulating self/non-self discrimination and in activating immune response against parasites
41 (Murphy & Weaver, 2017). In past decades, several studies reported associations between MHC allelic
42 diversity and fitness, but with some major inconsistencies. For instance, depending on the considered
43 species or population, either maximal or intermediate MHC-diversity was found to maximize fitness
44 (Bonneaud, Mazuc, Chastel, Westerdahl, & Sorci, 2004; Kalbe et al., 2009; Lenz, Mueller, Trillmich, &
45 Wolf, 2013; Thoss, Ilmonen, Musolf, & Penn, 2011; Wegner, Reusch, & Kalbe, 2003).

46 The reported inconsistencies in the fitness consequences of MHC-diversity likely stem from
47 the variations in the trade-off between the different functions of the MHC. The fact that each MHC
48 protein can bind a limited set of antigens leads to the straightforward expectation that an increase in
49 MHC diversity increases the number of antigens recognized, thereby providing resistance to a wider
50 range of parasites (reviewed in Milinski, 2006). Higher MHC-diversity may also lead to more efficient
51 immune responses during infection (Behnke & Wahid, 1991; Doherty & Zinkernagel, 1975; McClelland,
52 Penn, & Potts, 2003). However, theoretical models have shown that high MHC-diversity can also incur
53 costs by limiting the potential for inducing an immune reaction (Nowak, Tarczyhornocho, & Austyn,
54 1992; Woelfing, Traulsen, Milinski, & Boehm, 2009; see also Migalska et al. 2019) or by increasing the
55 potential for autoimmune disorders (Borghans & De Boer, 2001).

56 Variation in the level of MHC-diversity maximizing fitness should be shaped by any selective
57 pressure associated with changes in exposure to parasites, immune response strength or susceptibility
58 to autoimmunity. Several studies have shown that MHC-diversity varies among species or populations
59 according to key life-history traits. For instance, increased mean MHC-diversity has been associated
60 with migratory behavior and female promiscuity, two traits that may increase exposure and/or reduce
61 immune response to parasites (Gohli et al., 2013; Minias, Pikus, Whittingham, & Dunn, 2019;

62 Whittingham, Dunn, Freeman-Gallant, Taff, & Johnson, 2018; Winternitz et al., 2013). In contrast,
63 studies investigating interindividual variation in the fitness consequences of MHC-diversity within a
64 population are scarce, although there is extensive evidence for interindividual variations in these
65 potential selective pressures (i.e. exposure to parasites, immune response strength or susceptibility to
66 autoimmunity). For instance, it has been recently hypothesized that sex differences in the effects of
67 immunosuppressive sex hormones on the strength of immune response and on the susceptibility to
68 autoimmunity should result in different optima of MHC diversity between males and females (Roved,
69 Westerdahl, & Hasselquist, 2017). Specifically, the authors argued that males should benefit from
70 higher levels of MHC-diversity than females because sex hormones reduce immune activation in males
71 and increase susceptibility to autoimmunity in females. Accordingly, the association between MHC-
72 diversity and reproductive success was positive in adult males but not in adult females in great reed
73 warblers (*Acrocephalus arundinaceus*) (Roved, Hansson, Tarka, Hasselquist, & Westerdahl, 2018). This
74 hypothesis may explain similar findings in other species (Huchard, Knapp, Wang, Raymond, &
75 Cowlshaw, 2010; Sauermaun et al., 2001; Schaschl et al., 2012). There may be other explanations for
76 why males benefit from higher levels of MHC-diversity than females. For instance, male-male contests
77 increase males' risk of wounds and thus infections (Huchard et al., 2010 and references therein), and
78 deplete males' energetic reserves, thereby possibly leading to less energy available for allocation to
79 immune functions (Schaschl et al., 2012 and references therein). While a few other studies investigated
80 sex-specific associations between MHC-diversity and fitness (Hablutzel et al., 2014; Jager et al., 2007;
81 Lenz, Eizaguirre, Scharsack, Kalbe, & Milinski, 2009), no studies have investigated whether other
82 individual traits may modulate these associations. Sex is not the only trait modulating exposure to
83 parasites or immune response strength. For instance, social status and personalities have been
84 associated with infection risks by influencing frequency and duration of interactions with conspecifics
85 (Boyer, Reale, Marmet, Pisanu, & Chapuis, 2010; Drewe, 2010; Habig & Archie, 2015).

86 Here, we investigated whether differences in sex and hatching order are associated with
87 variation in the fitness consequences of MHC class-II diversity during the nestling stage in a wild
88 population of the monogamous black-legged kittiwakes (*Rissa tridactyla*). In kittiwakes, female and
89 second-hatched chicks are smaller, grow slower (Merkling et al., 2012; Vincenzi, Hatch, Mangel, &
90 Kitaysky, 2013; Vincenzi, Hatch, Merklings, & Kitaysky, 2015) and suffer more from sibling aggressions
91 (Delaunay, 2018; White, Leclaire, et al., 2010) than other chicks, suggesting that they are less
92 competitive for food and in poorer condition. In several other species, including birds, food shortage
93 and reduced condition have been linked to reduced immune responses via energy trade-offs
94 (Beldomenico & Begon, 2010; Brzek & Konarzewski, 2007) or chronic stress (Glaser & Kiecolt-Glaser,
95 2005). In addition, in kittiwakes, second-hatched chicks hatch from eggs containing increased levels of
96 androgens compared to first-hatched chicks (Benowitz-Fredericks, Kitaysky, Welcker, & Hatch, 2013;
97 Gasparini et al., 2007). This may lead to reduced immune responses as these sex hormones are known
98 to be immunosuppressive in other species (Klein & Flanagan, 2016; Smyth, Caruso, Davies, Clutton-
99 Brock, & Drea, 2018). Thus, females and second-hatched chicks are predicted to be immunologically
100 disadvantaged compared to males and first-hatched chicks. Because individuals who have less efficient
101 immune response are hypothesized to be particularly advantaged by high MHC-diversity (Roved et al.,
102 2017), we expect, the fitness of females and second-hatched chicks to be more dependent on MHC-
103 diversity than the fitness of males and first-hatched chicks. We thus investigated whether the
104 association between fitness-related traits and MHC class-II diversity varied with sex and hatching
105 order. We tested several fitness-related traits, namely survival in the nest, growth rate and tick
106 infection during the nestling stage. Growth rate is an important component of fitness in kittiwakes
107 because faster growing chicks are more likely to recruit as breeders (Vincenzi et al., 2015). Ticks can
108 have strong deleterious effects on kittiwake chicks by reducing growth rate when food is scarce
109 (McCoy, Boulinier, Schjorring, & Michalakis, 2002), potentially leading to death in case of hyper-
110 infestation (Chastel, Monnat, Lelay, & Balouet, 1987). Antigens contained in tick saliva are recognized

111 by MHC class II molecules, which present them to T lymphocytes, thereby activating an immune
112 response that can reduce tick-feeding efficiency and eventually lead to tick detachment (Andrade,
113 Texeira, Barral, & Barral-Netto, 2005; Oliver et al., 2009; Owen, Nelson, & Clayton, 2010).

114 **MATERIALS AND METHODS**

115 **Study site**

116 The study was conducted during the 2007-2013 and 2016-2017 breeding seasons (May–August) on a
117 colony of black-legged kittiwakes nesting on an abandoned U.S. Air Force radar tower on Middleton
118 Island (59°26'N, 146°20'W), Gulf of Alaska. The 400 nest sites created on the upper walls of the tower
119 can be observed from inside the building through sliding one-way mirrors and birds are individually
120 identified using color and metal bands (Gill & Hatch, 2002). All nest sites were checked twice daily (9:00
121 and 18:00) to record laying, hatching and death events. We focused on two-eggs clutches, which is the
122 typical clutch size in this kittiwake population (range 1-3; Gill & Hatch, 2002). There is generally a two-
123 day interval between laying of the first and second egg, which usually results in an asynchronous
124 hatching by a day or two (Coulson, 2011). On the day of laying, A- and B- eggs (first- and second-laid
125 eggs, respectively) were labeled individually with a non-toxic marker. Chicks were marked on the head
126 with similar markers for identification shortly after hatching.

127 **DNA collection and sexing**

128 Chicks were sexed molecularly using DNA extracted from eggshells, tissues from embryos (in case of
129 pre-hatching death) or blood collected from the metatarsal vein (see Merklings et al., 2012 for a
130 detailed sexing protocol). A few chicks (n = 18) were sexed *a posteriori* when they came back to the
131 colony as adults (identified with a numbered metal ring). We used DNA extracted from a blood sample
132 collected on adults with a syringe or capillaries from the brachial vein to determine sex using the same
133 molecular method as for chicks (Merklings et al., 2012). The sex of a few adults (n = 4) was determined

134 using sex-specific behavior (i.e. copulation and courtship feeding during the prelaying period; Danchin,
135 1991; Jodice, Lanctot, Gill, Roby, & Hatch, 2000).

136 **Molecular analysis of major histocompatibility complex**

137 *MHC genotyping*

138 The DNA samples were used to amplify 258 bp fragments (218 bp excluding primers) of the exon 2 of
139 the black-legged kittiwake MHC class-II_B. We used the MHC class-II_B specific primers (forward: 5'
140 GCACGAGCAGGGTATTTCCA and reverse: 5' GTTCTGCCACACTCACC) designed by Leclaire et al.
141 (2014), which amplify at least two MHC class-II_B loci. These loci are presumed to be functional as
142 shown by signs of positive selection, by the absence of stop codon or frame shift mutations in the
143 translated alleles and by at least three alleles being transcribed in each of the two individuals studied
144 (Leclaire et al., 2014). To discriminate samples after sequencing, the 5' end of both forward and reverse
145 primers included a combination of two different 8 bp tags. The PCR amplification was performed in 20
146 µl mixtures containing 2 µl of extracted DNA, 0.5 µM of each primer, 1x AmpliTaq Gold® 360 Master
147 Mix (Applied Biosystems, Foster City (CA) USA) and 3.2 µg of bovine serum albumin (Roche Diagnostics,
148 Basel, Switzerland). The PCR program consisted of 10 min initial denaturation at 95°C, followed by 30
149 cycles of 30 s denaturation at 95°C, 30 s annealing at 57°C and 1 min 30 s extension at 72°C. A final
150 elongation step was run at 72°C for 7 min. Amplicons were then purified using the MinElute PCR
151 Purification protocol (Qiagen, Hilden, Germany). Amplicons were sequenced in two runs with an
152 Illumina MiSeq platform, using the 2 × 300 bp protocol (Fasteris SA, Plan-les-Ouates, Switzerland). We
153 included PCR blank controls, as well as unused tag combinations, in the sequenced multiplex to detect
154 and withdraw potential mistagging biases (Esling, Lejzerowicz, & Pawlowski, 2015).

155 Amplicon sequences were analyzed with ampliSAS, a three-step pipeline that consists of read
156 demultiplexing, unique sequence clustering, and erroneous sequence filtering (Sebastian, Herdegen,
157 Migalska, & Radwan, 2016). First, the Illumina data were filtered to remove low-quality sequences

158 (sequences with Phred scores less than 50). Sequences were then clustered using the default ampliSAS
159 parameters for Illumina sequences (substitution errors: 1%, indel errors: 0.001%, minimum frequency
160 with respect to dominant: 25%), and sequences that were potential chimeras or that had less than 3%
161 frequency were discarded. We discarded samples with a depth inferior to 500 reads. Considering the
162 larger set of samples analyzed in the two MiSeq runs ($n = 2064$ samples, including 699 samples that
163 were part of this study), the reproducibility of genotype between the two runs ($n = 25$ DNA samples
164 that were split and processed in independent PCRs) was 100%. After processing, we had an average (\pm
165 s.d.) of 4735 ± 846 reads per individual (range: 509–5000 reads). We obtained 83 different MHC class-II
166 alleles. All detected alleles were of the same length. The number of alleles per individual was $3.38 \pm$
167 0.83 (mean \pm s.d.; range: 1–7), suggesting the presence of at least 4 functional loci.

168 *Chick MHC-II diversity*

169 Several measures of MHC-diversity have been used across studies (Lenz et al., 2013; Radwan et al.,
170 2012; Sepil, Lachish, & Sheldon, 2013). The most widely used proxy of MHC-diversity is the number of
171 different MHC alleles possessed by an individual (e.g. Huchard et al., 2010; Kalbe et al., 2009; Roved et
172 al., 2018). This measure relates to the “heterozygote advantage” (or overdominance) hypothesis. This
173 hypothesis posits that heterozygous individuals should have a selective advantage over homozygous
174 individuals, because they have a higher number of different MHC molecules, and thus can bind a higher
175 number of antigens (Doherty & Zinkernagel, 1975). Wakeland et al. (1990) later proposed the
176 “divergent allele advantage” hypothesis, which posits that, in heterozygous individuals, those with
177 higher degree of functional divergence between alleles should have a selective advantage because
178 their MHC molecules can bind a broader range of antigens. Several studies on a single MHC locus have
179 thus used the functional divergence between two alleles to estimate MHC-diversity (Pierini & Lenz,
180 2018). Studies considering several MHC loci and using functional divergence to estimate MHC diversity
181 are scarce. A few of them used the average functional divergence between all alleles and considered

182 that individuals with higher mean divergence should be advantaged (Lenz, Wells, Pfeiffer, & Sommer,
183 2009; Schwensow, Eberle, & Sommer, 2010). However, the "divergent allele advantage" is expected
184 to work in concert with the "heterozygote advantage" (Wakeland et al., 1990) and, when considering
185 several loci, this estimate of MHC-diversity is, therefore, unlikely to be strongly correlated with the
186 range of antigens bound by all alleles together. A few studies have thus used the degree of divergence
187 over all loci to estimate MHC-diversity (Grieves, Gloor, Bernards, & MacDougall-Shackleton, 2019;
188 Huchard, Baniel, Schliehe-Diecks, & Kappeler, 2013; Leclaire et al., 2019; Radwan et al., 2012). This
189 measure is expected to estimate the range of antigens recognized by MHC molecules, regardless of
190 whether a high range is due to the possession of many alleles that are somewhat divergent or to the
191 possession of a few alleles that are very divergent. In our study, we decided, therefore, to estimate
192 MHC-II diversity as the degree of divergence between alleles over all loci.

193 We used the Faith's diversity index to estimate MHC-II diversity as the degree of divergence of
194 alleles across all loci (as in Grieves et al., 2019 and Leclaire et al., 2019). We first translated MHC-II DNA
195 sequences into amino acid sequences, and considered DNA sequences as functionally identical if they
196 had the same amino-acids in the peptide-binding regions (PBRs; inferred from Leclaire et al., 2014).
197 Non-PBR sites were characterized by a low nucleotide diversity and codons with no significant excess
198 of non-synonymous substitutions (Leclaire et al., 2014). We obtained a total of 68 functional alleles.
199 The mean number of functional alleles per individual was 3.31 ± 0.78 (mean \pm s.d.; range: 1-7;
200 supporting information Figure S1) and did not significantly vary among years (Kruskal–Wallis, $U = 4.89$,
201 $df = 8$, $p = 0.77$; supporting information Figure S2). Then, following the approach of Schwensow et al.
202 (2007), we described the chemical binding properties of each amino acid in the PBRs with the
203 Sandberg's five physico-chemical descriptors (z-descriptors; Sandberg, Eriksson, Jonsson, Sjostrom, &
204 Wold, 1998). Following an approach adapted from Strandh et al. (2012), we used this Sandberg matrix
205 to construct an alternative maximum-likelihood phylogenetic tree with "Rcontml" in the R package
206 *Rphylip* (Revell & Chamberlain, 2014). This tree represents clusters of functionally-similar MHC-II

207 sequences (see supporting information Figure S3) and was used as a reference to calculate the
208 functional diversity of an individual as the minimum total length of all the branches required to span
209 its MHC-II alleles (i.e. Faith's phylogenetic diversity; Faith, 1992) with the R function "pd" in the *picante*
210 R package (Kembel et al., 2010). In other words, for each additional allele, only the part of the peptide-
211 binding characteristics that is not shared with other alleles is summed. Chick Faith's MHC-II diversity
212 varied from 0.89 to 9.81 (mean \pm s.d.: 6.01 ± 1.19 ; supporting information Figure S4) and did not
213 significantly vary among years (Kruskal–Wallis, $U = 4.24$, $df = 8$, $p = 0.83$; supporting information Figure
214 S5).

215 For comparison with Faith's MHC-II diversity, we also carried out analyses on the association
216 between fitness traits and the number of functional MHC-II alleles or the mean MHC-II divergence. We
217 calculated the number of functional MHC-II alleles as the number of amino acid PBR sequences per
218 individual. To calculate mean MHC-II divergence, we used the Sandberg matrix to compute the
219 Euclidean distance between all possible pairs of functional alleles (Lenz, Wells, et al., 2009) with the R
220 function "distance" in the *phylentropy* R package (Drost, 2018). Then for each individual, we calculated
221 MHC-II divergence as the sum of Euclidean distances between each pair of alleles possessed by this
222 individual, divided by the number of allele pairs. It was thus not possible to calculate MHC-II divergence
223 for chicks carrying only one MHC-II allele ($n = 2$ individuals). Chick functional MHC-II divergence varied
224 from 6.57 to 21.93 (mean \pm s.d.: 17.32 ± 1.79 ; Figure S6) and did not significantly vary among years
225 (Kruskal–Wallis, $U = 10.22$, $df = 8$, $p = 0.24$; Figure S7).

226 **Chick fitness parameters**

227 *Survival*

228 To record disappearance and death, all nests were checked twice daily (9:00 and 18:00) throughout
229 the season until we left the study site (August 15th).

230 *Morphological measurements and growth*

231 Chicks were measured every 5 days from hatching to the age of 35 days. We measured body mass to
232 the nearest 0.1 g using an electronic scale, tarsus length to the nearest 0.1 mm with a caliper and wing
233 length to the nearest 1 mm with a wing ruler.

234 We estimated body mass and size growth rates over 35 days by calculating the maximum slope
235 of a logistic growth curve between morphological measures and age (Merkling et al., 2012) using the
236 *grofit* package in R (Kahm, Hasenbrink, Lichtenberg-Frate, Ludwig, & Kschischo, 2010). Chick size was
237 estimated by taking the scores of the first principal component analysis on wing and tarsus length at
238 0, 5, 10, 15, 20, 25, 30 and 35 days together. Because such measurement necessarily excludes chicks
239 that were not measured up to 35 days old, we also estimated growth rates over the first 10 days by
240 calculating the slope of the linear regression between the morphological measures and age (Merkling
241 et al., 2014; Merkling et al., 2016).

242 *Tick infection*

243 For each chick hatched in the 2008, 2009 and 2010 breeding seasons, we recorded the number of
244 attached ticks (*Ixodes uriae*) every 5 days from 5 to 30 days through visual examination and palpation
245 (Danchin, 1992). *I. uriae* is the only tick species known to infect kittiwakes on Middleton Island (BM
246 Williams, personal communication). Ticks generally start to feed on 5-day-old chicks and parasitism
247 may continue until fledging (Boulinier & Danchin, 1996).

248 **Statistical analysis**

249 *Sample size*

250 In all statistical analyses, eggs were excluded when their handling for other experimental purposes
251 could have affected fitness. Because our study aimed at investigating the effect of chick (or embryo)
252 sex on MHC-II-fitness relationships, we excluded unsexed chicks (or embryos) from the analyses (n =
253 94 individuals). These filters, together with the fact that tick infections were checked only over 3 years,

254 led to different sample sizes for each fitness parameter: 17 non-hatched embryos and 429 chicks were
255 used for survival analyses, 680 chicks for the analyses on condition and size at hatching, 292 chicks for
256 growth rate analyses over the first 10 days, 209 chicks for growth rate analyses over 35 days and 138
257 chicks for tick infection analyses.

258 *Model selection*

259 We used an AICc-based information-theoretic approach to test how Faith's MHC-II diversity was
260 associated with fitness-related traits (Burnham & Anderson, 2004; Burnham, Anderson, & Huyvaert,
261 2011). For each fitness-related trait, we built a set of candidate models corresponding to biologically
262 plausible hypotheses explaining the response variable. Each set of candidate models also included a
263 null model (intercept only) and when a model included an interaction, we always considered an
264 additive model (i.e. without the interaction). We selected the best models based on their ΔAICc (i.e.
265 the difference between the AICc of a given model and the AICc of the best model) by keeping every
266 model with $\Delta\text{AICc} \leq 4$. This cut-off can be considered as conservative and retains the true best model
267 with an approximate 95% confidence (Richards, 2005). Using these best models, we computed natural
268 model-averaged parameter estimates, standard errors and 95% confidence intervals without
269 shrinkage; i.e. parameter estimates of each variable were averaged using only the models with ΔAICc
270 < 4 in which they appear (Nakagawa & Freckleton, 2011). Model selection and averaging were
271 conducted using the *MuMIn* package (Bartoń, 2018) and based on maximum likelihood estimation (see
272 supporting information for an outline of all models). All statistical analyses were performed with R
273 3.5.2 (R Core Team, 2018).

274 For each fitness-related trait, we built a set of models that included Faith's MHC-II diversity,
275 the square of Faith's MHC-II diversity, sex, hatching order and two- and three-way interactions
276 between sex, hatching order and Faith's MHC-II diversity. We standardized continuous variables in all
277 analyses and checked for collinearity issues. We detected a significant association between sex and

278 Faith's MHC-II diversity at hatching (see results), and thus ran separate models for male and female
279 chicks for all analyses. We included clutch identity (ID), pair ID and year as random effects in the models
280 and checked for normal distribution of random effects using the best model in model selection. The
281 pair ID random effect was however removed from models because associated variance estimates were
282 virtually zero.

283 *Survival at the nest*

284 We tested for the effect of Faith's MHC-II diversity on chick survival at the nest using Cox proportional
285 hazard mixed-effect models in the R package *coxme* (Therneau, 2018). We considered chick survival
286 between 0 and 35 days (i.e. before fledging; Coulson & White, 1958; Maunder & Threlfall, 1972).
287 Sixteen chicks younger than 35 days (mean \pm s.d. : 30.6 \pm 4.3 days old) were still alive when we left the
288 study site. To be confident that survivors included in analyses fledged after our departure, we excluded
289 those sixteen chicks because chicks' likelihood to fledge is very high once they reach 35 days old
290 (Barrett & Runde, 1980; Merklings et al., 2014).

291 *Body condition and size at hatching and growth*

292 We used linear mixed models (LMMs) in the *lme4* R package (Bates, Machler, Bolker, & Walker, 2015)
293 to test for the effects of Faith's MHC-II diversity on body condition and size at hatching and on body
294 mass and size growth rates. Chick size at hatching was included in the model built for body mass at
295 hatching, which can thus be interpreted as size-adjusted body mass, or body condition (Garcia-
296 Berthou, 2001). We checked for normality and homoscedasticity of residuals using the best model in
297 model selection.

298 *Tick infection*

299 We investigated the association between Faith's MHC-II diversity and three variables linked to tick
300 infection. First, we determined whether Faith's MHC-II diversity was associated with the probability

301 and the timing of first infection by ticks during the nestling stage (between 5 and 30 days old; n = 138
302 chicks) by fitting Cox proportional hazard mixed-effect models in the R package *coxme* (Therneau,
303 2018). Chicks that were not infected by ticks during this period were right-censored (n = 28). Second,
304 we focused on quantitative resistance by testing whether Faith's MHC-II diversity was associated with
305 the maximum number of ticks chicks had during the nestling period (n = 110 chicks, excluding those
306 without ticks) using zero-truncated models with a Poisson distribution using the *glmmTMB* R package
307 (Brooks et al., 2017). If models with a zero-truncated Poisson distribution were overdispersed, we
308 compared their fit to the fit of models with zero-truncated negative binomial 1 and zero-truncated
309 negative binomial 2 distributions. We pooled the values over 15 to "15+" to reduce overdispersion (i.e.
310 four chicks had more than 15 ticks). Finally, we determined whether Faith's MHC-II diversity was
311 associated with the probability and the timing of tick clearance during the nestling stage (n = 86 chicks)
312 by fitting Cox proportional hazard mixed-effect models in the R package *coxme* (Therneau, 2018).
313 Chicks without ticks (n = 28) or discontinuously infected by ticks (n = 24) were excluded from this
314 analysis. Chicks that still had ticks at the end of the observation period were right-censored. We
315 removed the clutch ID random effect from models because associated variance estimates were
316 virtually zero.

317 *Comparison of MHC measures*

318 To test the association between fitness-related traits and the number of functional MHC-II alleles or
319 MHC-II divergence, we used the same statistical approach as for Faith's MHC-II diversity. MHC-
320 divergence is theoretically not related to the number of alleles but, in our dataset, there was a negative
321 correlation between these measures (Pearson correlation, $t = -5.67$; $r = 0.21$; $p < 0.001$; $n = 697$, as in
322 Roved, 2019). Including both measures into the same models leads to VIF values > 5 , indicating
323 collinearity issues (Zuur, Ieno, & Elphick, 2010). We therefore carried out separate analyses for the
324 number of functional MHC-II alleles and MHC-II divergence. Because most chicks had 3 or 4 alleles in

325 the restricted dataset used for tick analyses, we transformed the “number of MHC-II alleles” in a binary
326 variable with number of MHC-II alleles ≤ 3 or ≥ 4 for analyses on ticks. The square of number of MHC-
327 II alleles and the interactions that included this variable were thus removed from the corresponding
328 models. Full models including either Faith’s MHC-II diversity, MHC-II divergence or number of MHC-II
329 alleles were compared according to the Akaike information criterion (AICc) to explore the relative
330 importance of these three different MHC-measures.

331 **RESULTS**

332 **Sex-difference in Faith’s MHC-II diversity**

333 There was a significant association between sex and Faith’s MHC-II diversity at hatching (t-test: $t = -$
334 2.75 ; $p = 0.006$; $n = 680$ chicks) and at 35 days old (t-test: $t = -2.10$; $p = 0.037$; $n = 209$ chicks). At
335 hatching and at 35 days-old, male chicks were less MHC-II diverse than female chicks (mean \pm s.d.:
336 males at hatching: 5.90 ± 1.48 ; males at 35 days old: 5.98 ± 1.20 ; females at hatching: 6.14 ± 1.31 ; and
337 females at 35 days old: 6.30 ± 1.15).

338 **Survival at the nest**

339 Among 430 monitored eggs, 142 chicks (33%) died before reaching 35 days of age. In single-sex models,
340 the interaction between Faith’s MHC-II diversity and hatching order was significant only in females
341 (estimate \pm s.e. = -0.58 ± 0.28 , 95% CI: $-1.13, -0.04$; supporting information Tables S1, S2). Mortality
342 significantly decreased with increasing Faith’s MHC-II diversity in female B-chicks, but not in female A-
343 chicks, while we detected no significant effect of Faith’s MHC-II diversity on mortality in males (Figures
344 1, S8).

345 **Body condition and size at hatching**

346 Body condition at hatching was not significantly associated with Faith’s MHC-II diversity (Tables S3,
347 S4). Although there was a negative trend in males, size at hatching was not significantly associated

348 with Faith's MHC-II diversity (females: estimate \pm s.e. = 0.01 ± 0.06 , 95% CI: -0.10, 0.12; males: estimate
349 \pm s.e. = -0.10 ± 0.05 , 95% CI: -0.20, 0.01; Tables S5, S6).

350 **Growth**

351 In females only, body mass growth rate (females: estimate \pm s.e. = 0.26 ± 0.09 , 95% CI: 0.08, 0.43;
352 males: estimate \pm s.e. = -0.001 ± 0.08 , 95% CI: -0.15, 0.15; Tables S7, S8, Figure 2A) and body size
353 growth rate over the first 10 days (females: estimate \pm s.e. = 0.24 ± 0.09 , 95% CI: 0.06, 0.42; males:
354 estimate \pm s.e. = 0.06 ± 0.07 , 95% CI: -0.08, 0.20; Tables S9, S10, Figure 2B) were significantly and
355 positively associated with Faith's MHC-II diversity. There was also a significant effect of the interaction
356 between the square of Faith's MHC-II diversity and hatching order on body size growth rate in females
357 (estimate \pm s.e. = 0.26 ± 0.11 , 95% CI: 0.05, 0.47; Table S9). However, this interaction became non-
358 significant after removing one A-female with high Faith's MHC-II diversity and moderate size growth
359 rate (estimate \pm s.e. = 0.20 ± 0.13 , 95% CI: -0.06, 0.46; Table S11). Similar results were obtained for
360 growth rates over 35 days (Tables S12-S15; Figure S9).

361 **Tick infection**

362 In single-sex models, there was no significant association between Faith's MHC-II diversity and the age
363 of first infection by ticks (females: estimate \pm s.e. = -0.15 ± 0.14 , 95% CI: -0.43, 0.12; males: estimate \pm
364 s.e. = -0.10 ± 0.14 , 95% CI: -0.37, 0.17; Tables S16, S17) or the maximum number of ticks (females:
365 estimate \pm s.e. = -0.29 ± 0.22 , 95% CI: -0.73, 0.15; males: estimate \pm s.e. = -0.01 ± 0.26 , 95% CI: -0.51,
366 0.51; Tables S18, S19). However, in females only, tick clearance was positively and significantly
367 associated with Faith's MHC-II diversity (females: estimate \pm s.e. = 0.54 ± 0.20 , 95% CI: 0.14, 0.94;
368 males: estimate \pm s.e. = -0.07 ± 0.21 , 95% CI: -0.49, 0.34; Tables S20, S21). The more females were
369 MHC-II diverse, the more likely and the faster they were to clear ticks (Figures 3, 4). There was no
370 significant effect of any other parameter on these three response variables (Tables S16-S21).

371 **Comparison of MHC measures**

372 Faith's MHC-II diversity was significantly and positively correlated with both the number of functional
373 MHC-II alleles (Pearson correlation, $t = 8.90$; $r = 0.32$; $p < 0.001$; $n = 699$) and MHC-II divergence
374 (Pearson correlation, $t = 2.89$; $r = 0.11$; $p = 0.004$; $n = 697$). No effects of functional MHC-II allele number
375 or mean MHC-II divergence on fitness traits were detected except for a sex-specific effect of allele
376 number on tick infection, with females, but not males, possessing three MHC-II alleles or less being
377 more likely to get infected than females with four MHC-II alleles or more (see supporting information
378 for more details). There was also a weak effect of the square of MHC-II divergence on body mass
379 growth rate, with chicks harboring intermediate MHC-II divergence growing faster than those with low
380 or high MHC-II divergence (see supporting information for more details). For fitness traits associated
381 with Faith's MHC-II diversity, full models including Faith's MHC-II diversity had lower AICc than similar
382 models including MHC-II divergence or MHC-II allele number (Table S22). This suggests that Faith's
383 MHC-II diversity is a better predictor of these different fitness traits than MHC-II divergence or the
384 number of MHC-II alleles in kittiwake chicks.

385 **DISCUSSION**

386 Although fitness advantages have been associated with different levels of MHC-II diversity in a wide
387 range of species and populations (Bonneaud et al., 2004; Brouwer et al., 2010; Lenz et al., 2013; Thoss
388 et al., 2011; Wegner et al., 2003), only a handful of studies have investigated the possibility that
389 individuals within a population might benefit from different levels of MHC-II diversity. Yet, individuals
390 can differ greatly in exposure and immune responses to parasites, leading to the expectation that they
391 might not benefit from MHC-II diversity the same way. In this study, we investigated whether, in
392 kittiwake chicks, MHC-II-fitness associations depended upon sex and hatching order, two factors
393 expected to modulate exposure and immune response to parasites. As expected, we detected positive
394 associations between MHC-II diversity and female chick survival, but only in second-hatched female
395 chicks. In contrast, no association between MHC-II diversity and survival was detected in male chicks.

396 High MHC-II diversity was also associated with faster growth and tick clearance in female chicks only.
397 Our results suggest, therefore, that female chicks, especially those hatched in second position, benefit
398 from maximal levels of MHC-II diversity while male chicks do not.

399 Several underlying mechanisms may explain the sex- and hatching rank-dependent effects of
400 MHC-II diversity on fitness in kittiwake chicks. Because high MHC-II diversity provides resistance to a
401 wider range of parasites and is associated with more efficient immune response, the fitness benefits
402 associated with high MHC-II diversity in female chicks, particularly when hatched in second position,
403 might be explained by weaker immune responses and/or higher exposure to parasites compared to
404 males and A-chicks. Decreased immune response may result from higher levels of immunosuppressive
405 sex hormones, such as androgens (Klein & Flanagan, 2016). Although higher levels of androgens have
406 been found in the yolk of B-eggs compared to A-eggs in kittiwakes (Benowitz-Fredericks et al., 2013;
407 Gasparini et al., 2007), sex-differences in circulating levels of androgens have not been investigated in
408 kittiwake chicks. However, female chicks have been found to have higher levels of androgens than
409 male chicks in several other species (Fargallo, Martinez-Padilla, Toledano-Diaz, Santiago-Moreno, &
410 Davila, 2007 and references therein). Non-exclusively, weaker immune responses might also result
411 from a trade-off between immunity and other competing functions that require metabolic resources
412 (Zuk & Stoehr, 2002). In kittiwakes, female- and B-chicks are smaller (Merkling et al., 2012), in poorer
413 condition (this study; see supporting information Tables S3-S4, S23, S24; Figure S10) and suffer more
414 from sibling aggression than other chicks (Delaunay, 2018; White, Leclaire, et al., 2010) suggesting that
415 they might be less competitive for food, and thus have a lower amount of resources to allocate to
416 immune functions (Beldomenico & Begon, 2010; Beldomenico et al., 2008). Interestingly, when
417 restricting our MHC-II-fitness analyses to broods where one egg did not hatch, thereby excluding the
418 role of competition and aggression between siblings in driving MHC-II-fitness associations, we did not
419 find any significant effect of MHC-II diversity on survival in female B-chicks (n = 49 females) or on
420 growth rate (n = 34 females) or tick clearance (n = 14 females) in female chicks (supporting information

421 Tables S25-S28). Although these results must be taken with caution because of the reduced sample
422 size, they suggest that sibling interactions are a potential driver of sex- and rank-specific effects of
423 MHC-II diversity on fitness in this species.

424 A surprising finding of our study was that female chicks had, on average, a higher MHC-II
425 diversity than male chicks at hatching (mean \pm s.d.: 6.14 ± 1.31 vs. 5.90 ± 1.48). Yet, females and males
426 should exhibit the same level of MHC-diversity as they share the genetic architecture of the MHC (i.e.
427 MHC genes are located on autosomes; Murphy & Weaver, 2017). Sex-difference in mean MHC-
428 diversity has already been reported in humans, rats and mice, with increased MHC-diversity in
429 newborn males compared to newborn females (Dorak, Lawson, Machulla, Mills, & Burnett, 2002, and
430 references therein). Proposed mechanisms include selective fertilization, egg resorption and embryo
431 loss (Dorak et al., 2002). Selective fertilization and embryo loss have been associated with both the
432 degree of MHC-similarity between parents (Lenz, Hafer, Samonte, Yeates, & Milinski, 2018; Ober,
433 Hyslop, Elias, Weitkamp, & Hauck, 1998; Wedekind, Chapuisat, Macas, & Rulicke, 1996; Zhu, Wan,
434 Zhang, & Fang, 2019) and with the sex of the embryo (or the sex chromosome of the gametes; Navara,
435 2018). However, whether they can be affected by these two parameters in interaction remains largely
436 unknown. In our dataset, female hatchlings were still more MHC-II diverse than males when we
437 considered only clutches with no egg loss (mean \pm s.d.: 6.20 ± 1.12 vs 5.93 ± 1.15 ; t-test: $t = -2.55$; $p =$
438 0.01 ; $n = 448$ chicks), suggesting that the sex-difference in hatchlings MHC-II diversity is not triggered
439 by a sex-specific effect of MHC-II diversity on post-laying embryo mortality. Regardless of the
440 underlying mechanism, MHC-II-similar parents, that are more likely to produce chicks with low MHC-
441 II diversity (Setchell, Abbott, Gonzalez, & Knapp, 2013), might benefit from avoiding the fitness costs
442 associated with the production of low MHC-II diverse daughters.

443 While our results are consistent with a direct effect of MHC-II on fitness-related traits, some
444 methodological limitations and alternative explanations must be acknowledged. First, we amplified

445 exon 2 of the MHC-II because it codes for the majority of amino acids that form the peptide-binding
446 groove in model species like humans (Brown et al., 1993; Saper, Bjorkman, & Wiley, 1991) and because
447 it has been the focus of most MHC research in non-model avian species (Minias, Pikus, Whittingham,
448 & Dunn, 2018). However, both exon 2 and exon 3 encode the peptide binding grooves on MHC-II
449 molecules. Second, we cannot rule out the possibility that variation at other genes may partly explain
450 our results. For instance, MHC-II alleles might be in linkage disequilibrium with other MHC genes (e.g.
451 MHC class I genes), owing to the compact architecture of the avian MHC (Hess & Edwards, 2002). Third,
452 our results may possibly be explained by a broader effect of inbreeding on fitness, as variations at MHC
453 genes can be correlated with genome-wide genetic variation depending on the life history, the
454 dispersal ability and the breeding system of the study species (Sommer, 2005). Several studies
455 reported sex-specific effects of inbreeding on fitness related traits (Billing et al., 2012; T. Coulson,
456 Albon, Slate, & Pemberton, 1999; Rioux-Paquette, Festa-Bianchet, & Coltman, 2011). In his
457 (*Notiomystis cincta*), the loss of inbred female embryos at a very early stage was proposed to explain
458 increased heterozygosity in females later in the development (Brekke, Bennett, Wang, Pettorelli, &
459 Ewen, 2010). When testing for an association between MHC-II diversity and an estimate of genome-
460 wide diversity (i.e. standardized heterozygosity; Coltman, Pilkington, Smith, & Pemberton, 1999) in a
461 collection of 614 adults for which we had both MHC-II and microsatellite data (nine microsatellite loci;
462 see Pineaux et al., 2019 for details), we found however no significant correlation (Pearson correlation:
463 $t = 0.27$; $r = 0.01$; $p = 0.79$; supporting information Figure S11). In future, these potential effects on
464 fitness could be disentangled by studies including multiple MHC genes and other immune genes
465 alongside a better measure of overall inbreeding status.

466 This study underscores the importance of considering traits that are expected to shape an
467 individual's exposure and immune responses to parasites when predicting the association between
468 MHC-diversity and fitness. Sex-specific effects of MHC-diversity on fitness have been mostly studied in
469 polygynous species, with a positive association between MHC-diversity and survival or reproductive

470 success found in adult males (Huchard et al., 2010; Roved et al., 2018; Sauermaun et al., 2001; Schaschl
471 et al., 2012). Here, we provide evidence for sex-specific associations between MHC-II diversity and
472 fitness in the early life of a monogamous species, thus calling for further research in species or
473 populations with differing life-history strategies. A recent study in adult Leach's storm-petrels
474 (*Oceanodroma leucorhoa*), a monogamous seabird, found a positive association between MHC-
475 diversity and reproductive success in adult females but not in males (Hoover et al., 2018). The
476 underlying explanation was that males avoided low MHC-diverse females during mate choice but it
477 was unclear whether reduced reproductive success of low MHC-diverse females also partly resulted
478 from a direct, detrimental effect of reduced female quality on offspring viability. For instance, female
479 petrels may be more likely to suffer from sexually transmitted infections than males, as shown in
480 kittiwakes (Van Dongen et al., 2019; White, Mirleau, et al., 2010), thereby explaining sex-specific
481 effects of MHC-diversity on fitness. Future investigations of sex-specific associations between MHC-II
482 diversity and post-fledging survival or reproductive success in kittiwakes represent an interesting
483 avenue to explore whether the benefits of high MHC-II diversity found in female chicks persist in adult
484 females. Importantly, ignoring early-life stages may yield only a partial picture of how MHC affects
485 fitness if selection removes the less fit genotypes early in life, leaving only relatively high-quality
486 individuals that survived long enough to be sampled. Such biased picture may in turn lead to a
487 misunderstanding of the evolution of reproductive strategies.

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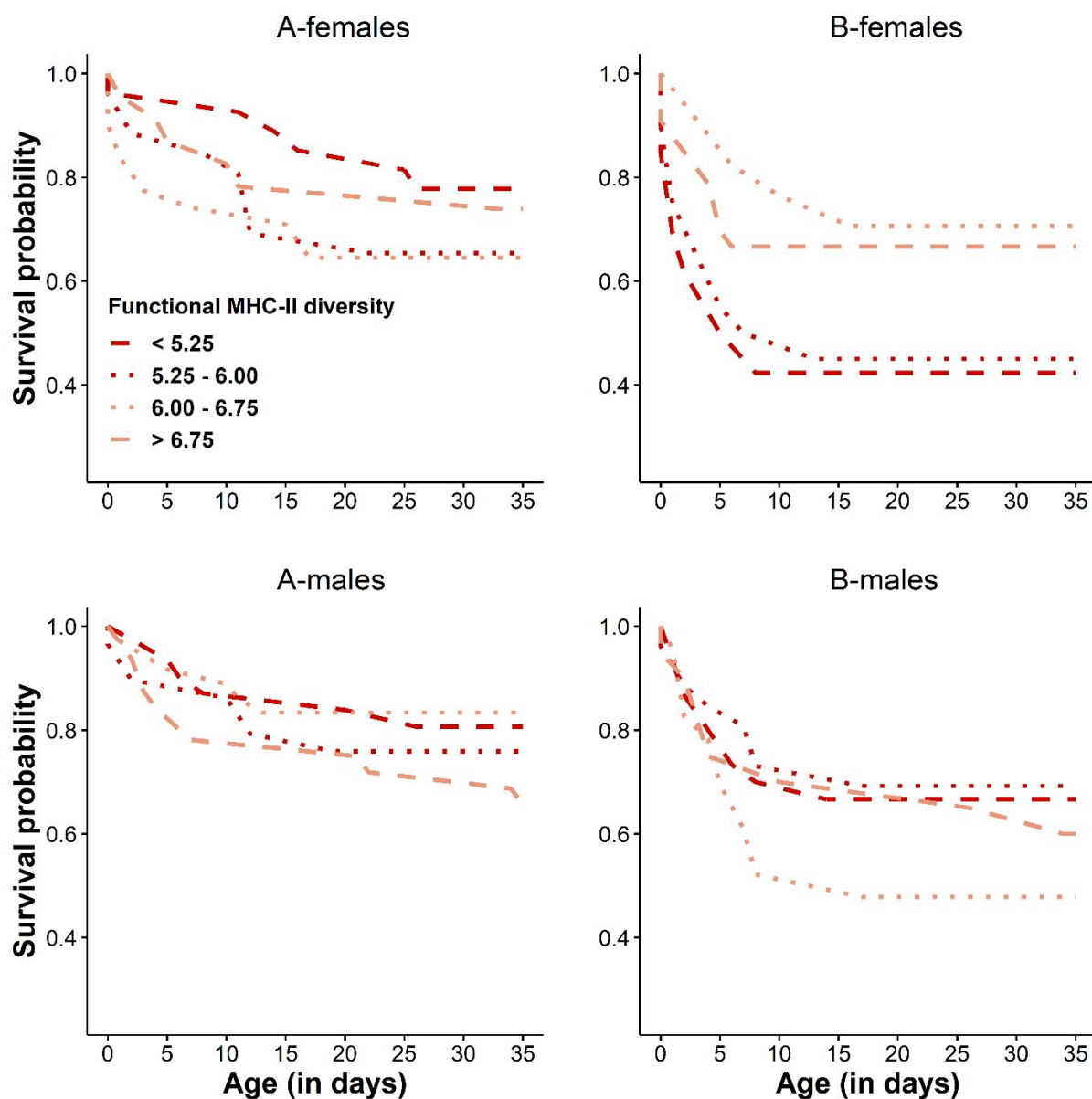
846 **DATA ACCESSIBILITY**

- 847 Data are available on Open Science Framework. Pineaux, M., et al. (2020). MHC-II fitness associations
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 849 (https://osf.io/dn5y8/?view_only=97ddd8f65a264c62bd540b1e4e9148a5).

850 **AUTHOR CONTRIBUTIONS**

- 851 MP, PB and SL conceived and designed the study. ED, MP, PB, SL and TM collected the data. MP, SL
 852 and TM carried out the molecular analyses. SAH is responsible of the long-term monitoring on
 853 Middleton Island and gave access to the study area. MP and TM performed the statistical analyses. MP
 854 wrote the manuscript and all authors contributed comments. All authors gave final approval for
 855 publication.

856 FIGURES

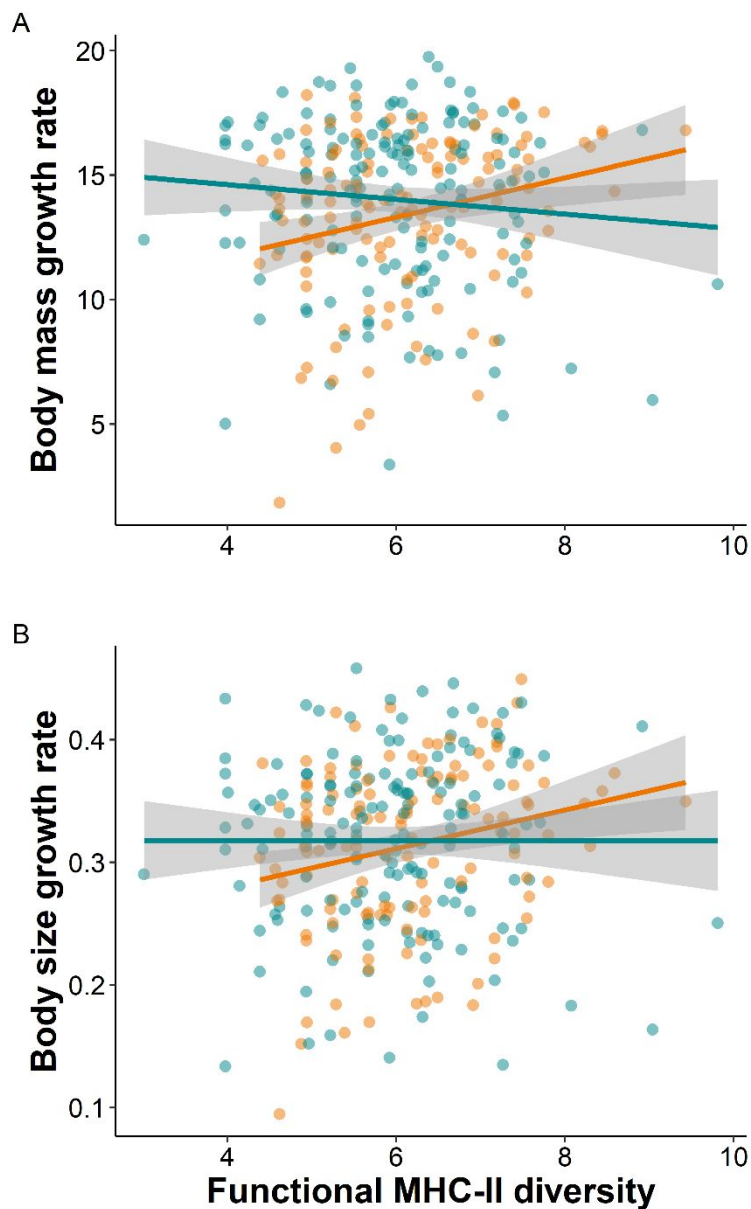


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858 **Figure 1.** Chick survival probability during the nestling stage according to functional MHC-II diversity
 859 for female A- ($n = 107$), female B- ($n = 96$), male A- ($n = 128$) and male B-chicks ($n = 99$). Although
 860 functional MHC-II diversity was analyzed as a continuous variable (see text), it is displayed here as a
 861 categorical variable for illustrative purposes. We categorized MHC-II diversity in four groups using
 862 quartiles of the whole data set used for survival analyses ($n = 430$). The colors and line types represent
 863 MHC-II diversity, with red corresponding to the first (dashed line) and second (dotted line) quartiles
 864 (i.e. low MHC-II diversity) and pink to the third (dotted line) and fourth (dashed line) quartiles (i.e. high
 865 MHC-II diversity). See supporting information (Figure S10) for a different display (heatmap).

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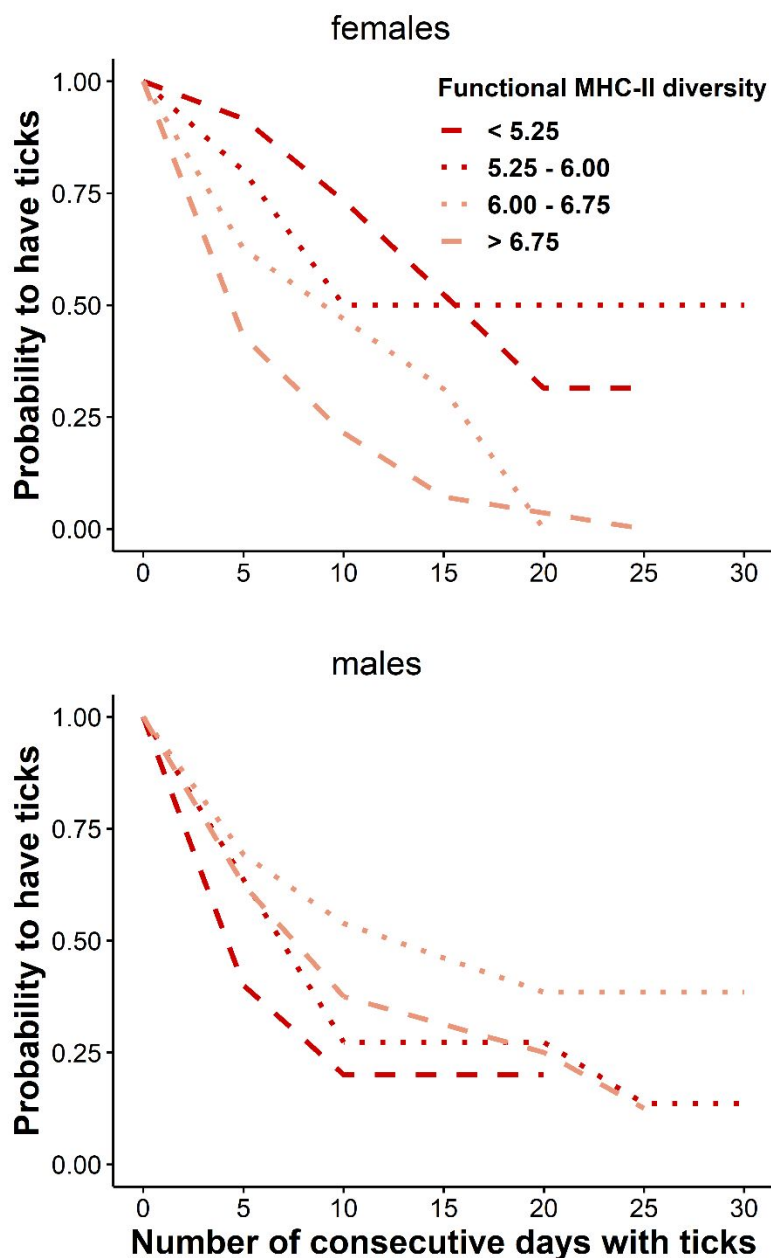
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868

869 **Figure 2.** Growth rate of (A) chick body mass and (B) chick body size over the first 10 days according to
 870 functional MHC-II diversity in females ($n = 131$, in orange) and males ($n = 160$, in blue). Chick size was
 871 estimated by taking the scores of the first principal component analysis on wing and tarsus length.
 872 Growth rate was calculated as the slope of a linear regression between morphological measures and
 873 age (see methods for more details). One male with a very low MHC-II diversity (i.e. 0.88) has been
 874 removed to improve clarity of the figure (see Figure S12 for a figure including this male). Removing this
 875 male from analyses did not change the results. Regression lines were derived from single-sex models
 876 including functional MHC-II diversity of chicks as a fixed effect. Random effects (year and clutch ID)
 877 were not considered in the models used for graphic representations. Shaded areas represent
 878 confidence intervals.

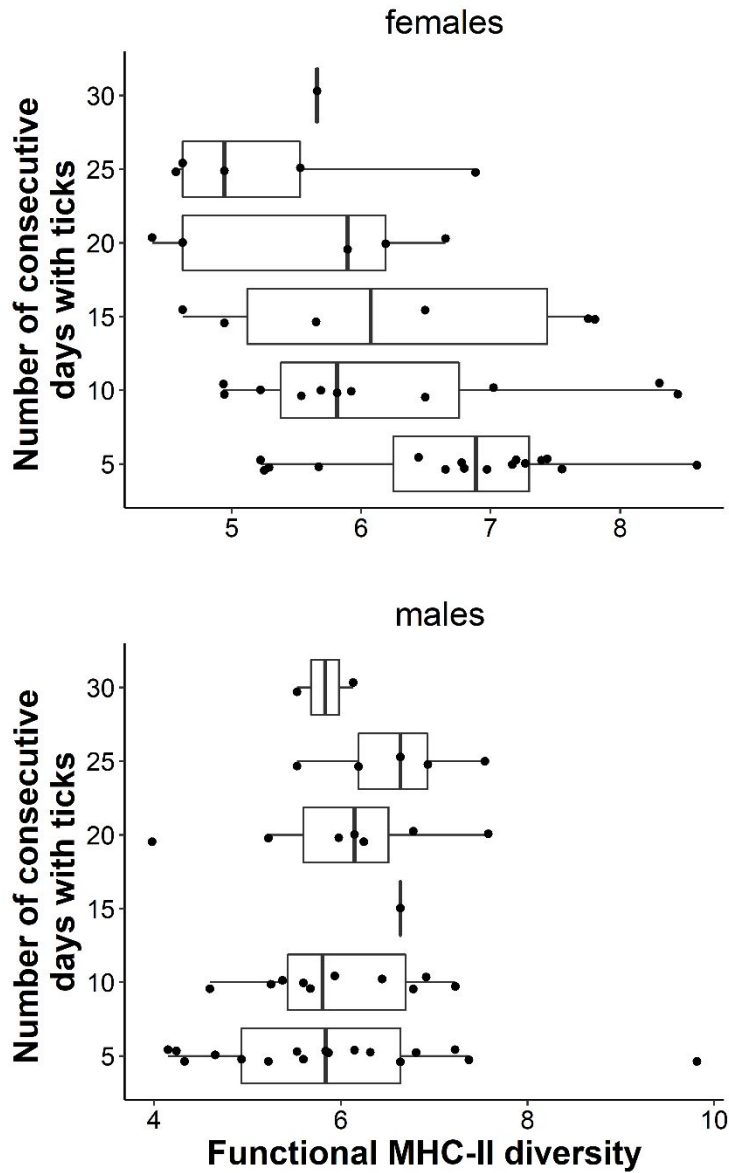
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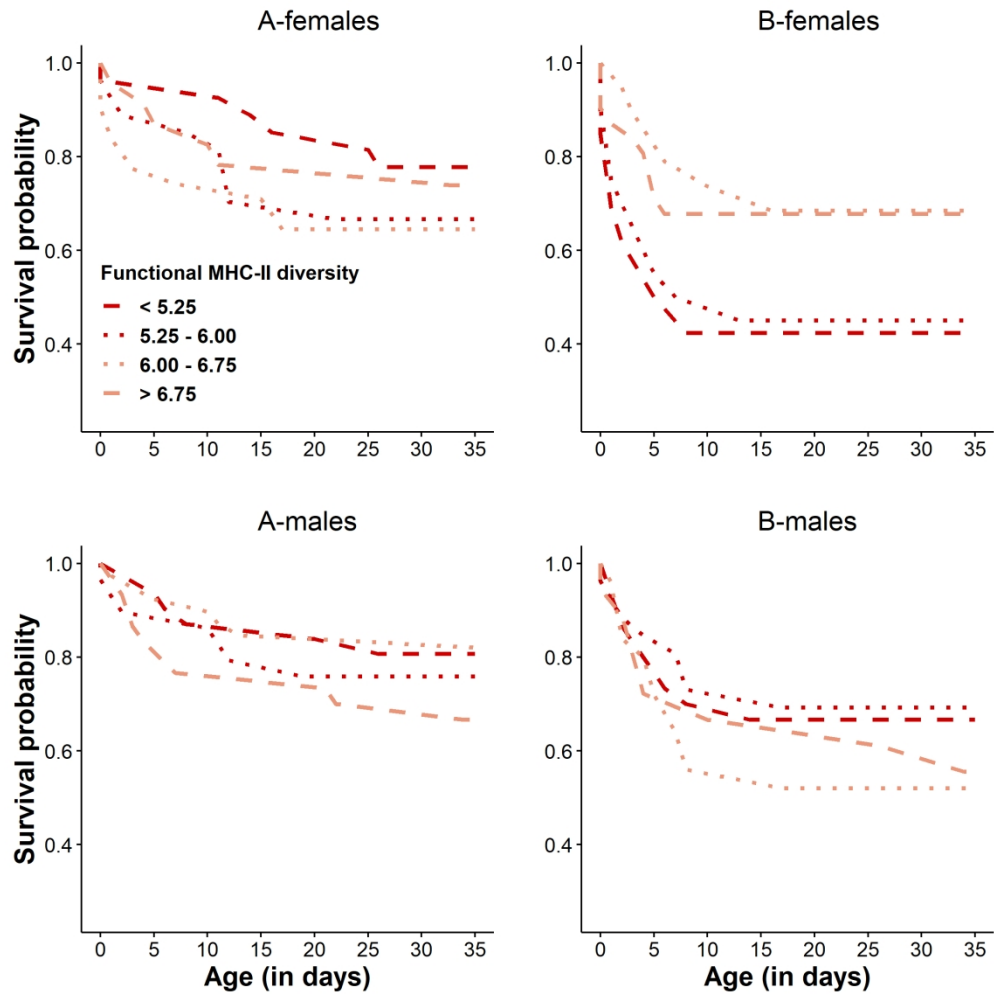
881 **Figure 3.** Probability of chicks to be infected according to infection duration and functional MHC-II
 882 diversity for females (n = 44) and males (n = 42). Although functional MHC-II diversity was analyzed as
 883 a continuous variable (see text), it is displayed here as a categorical variable for illustrative purposes.
 884 We categorized MHC-II diversity in four groups using quartiles of the whole data set used for tick
 885 analyses (n = 86). The colors and line types represent MHC-II diversity, with red corresponding to the
 886 first (dashed line) and second (dotted line) quartiles (i.e. low MHC-II diversity) and pink to the third
 887 (dotted line) and fourth (dashed line) quartiles (i.e. high MHC-II diversity).

888

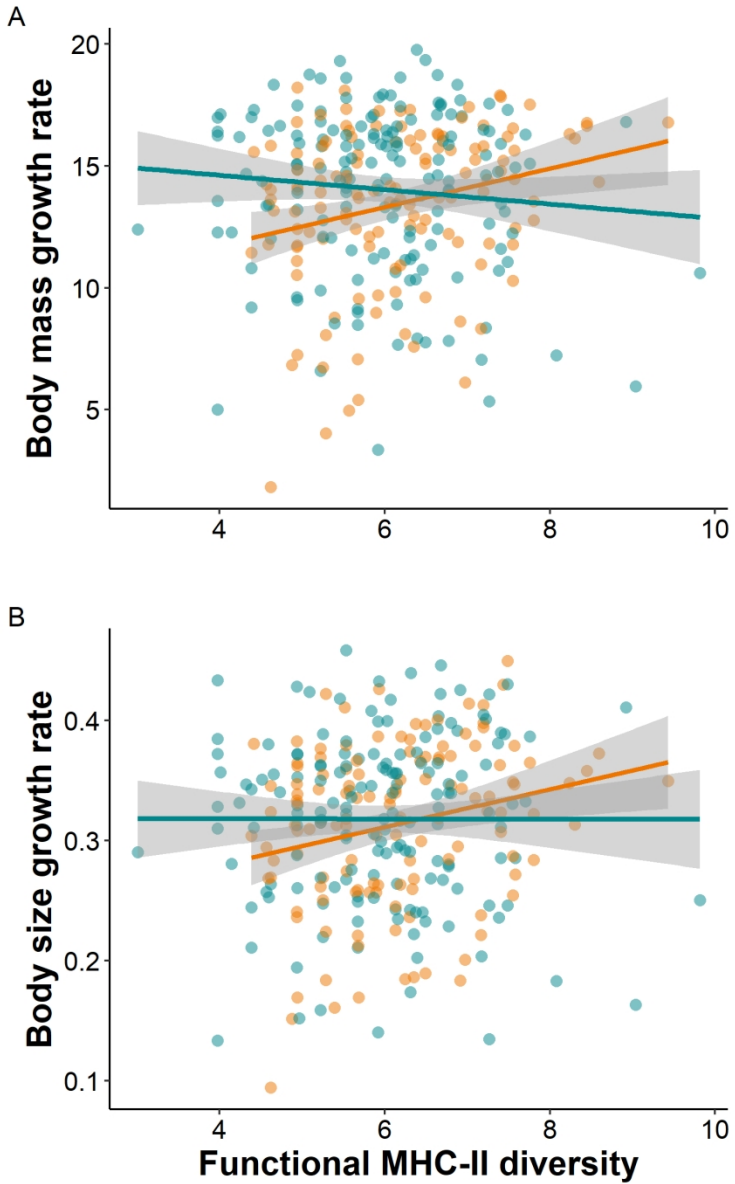


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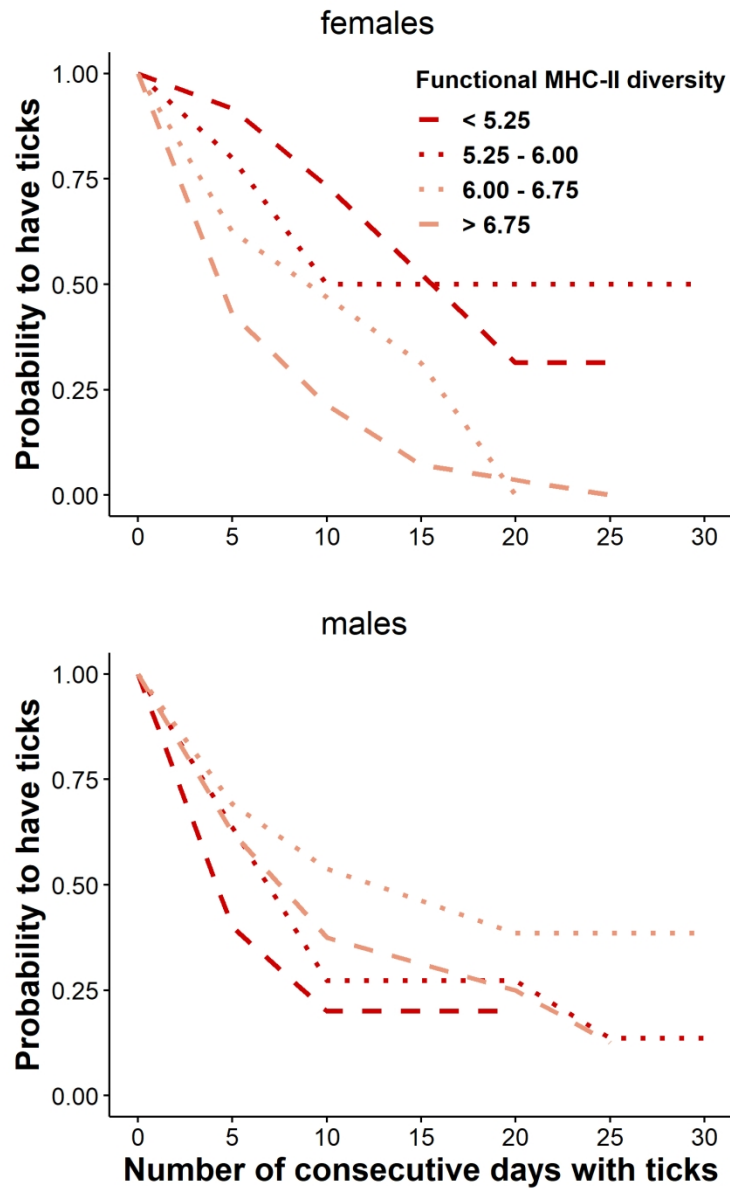
890 **Figure 4.** Boxplots of functional MHC-II diversity according to the number of consecutive days chicks
 891 were observed with ticks for females ($n = 44$) and males ($n = 42$).



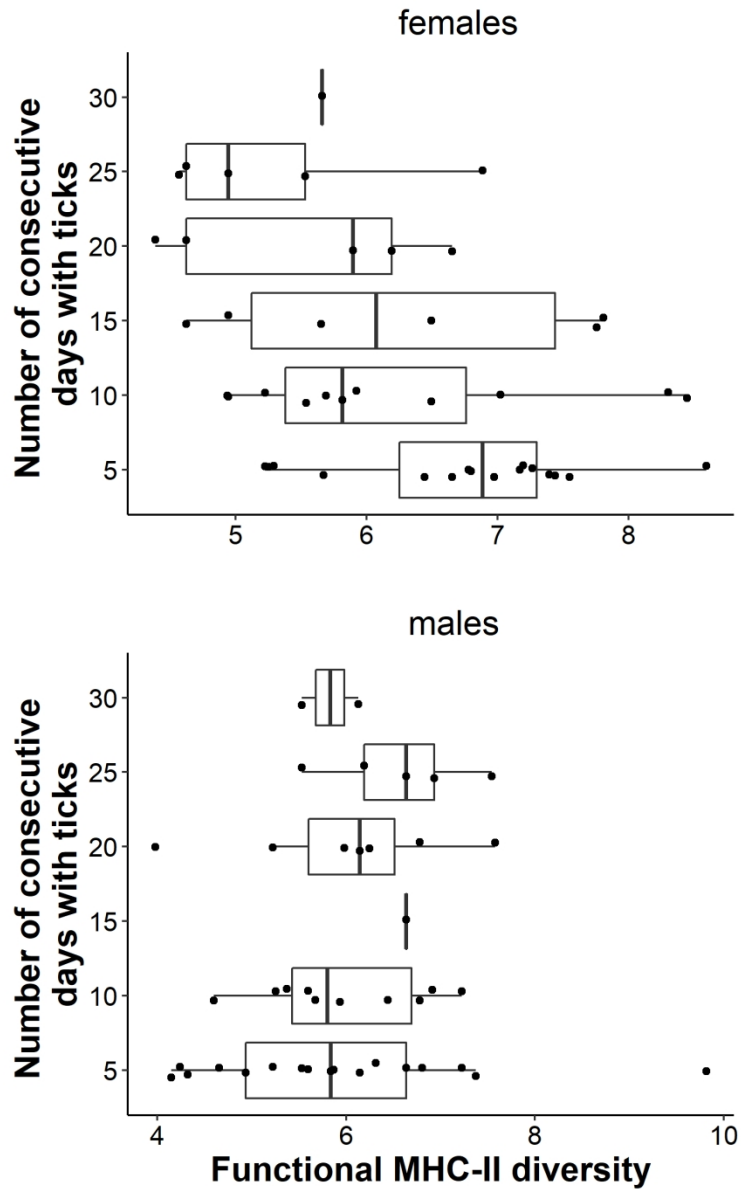
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