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Morgane Tidière, Adèle Badruna, David Fouchet, Jean-Michel Gaillard,
Jean-François Lemaître Lemaître, Dominique Pontier

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1 Pathogens shape sex differences in mammalian aging

2 Morgane Tidière^{1,2*}, Adèle Badruna^{1,2}, David Fouchet^{1,2}, Jean-Michel Gaillard^{1,2}, Jean-
3 François Lemaître^{1,2}, and Dominique Pontier^{1,2}

4 ¹ Université de Lyon, F-69000, Lyon; Université Lyon 1; CNRS, UMR5558, Laboratoire de
5 Biométrie et Biologie Evolutive, F-69622, Villeurbanne, France.

6 ² LabEx ECOFECT, Université de Lyon, F-69000, Lyon, France.

7 *Correspondence: mtidiere@gmail.com (M. Tidière)

8

9 KEYWORDS: pathogen exposure; immunosenescence; lifespan; life history traits; medicine

10

11 ABSTRACT

12 Understanding the origin of sex differences in lifespan and aging patterns remains a salient
13 challenge in both biogerontology and evolutionary biology. Different factors have been
14 studied but the potential influence of pathogens has never been investigated. Sex differences
15 especially in hormones and resource allocation generate a differential response to pathogens
16 and thereby shape sex differences in lifespan or aging. We provide an integrative framework
17 linking host pathogenic environment with both sex-specific selections on immune
18 performance and mortality trajectories. We propose future directions to fill existing
19 knowledge gaps about mechanisms that link sex differences, not only to exposition and
20 sensitivity to pathogens, but also to mortality patterns, whilst emphasizing the urgent need to
21 consider the role of sex in medicine.

22 **Sex differences in mammalian lifespan**

23 In almost all human populations, and consistently throughout history, women live longer than
24 men [1]. This pattern is pervasive in mammals [2], although the difference in **lifespan** (see
25 Glossary) between sexes varies strikingly across species and populations facing contrasted
26 environmental conditions [2,3]. Currently, a large body of research is devoted to the
27 understanding of evolutionary, genetic, and physiological mechanisms that govern these sex
28 differences in lifespan [4,5]. Differences in life-history strategies between sexes driven by
29 **sexual selection** are among the most common explanations [6]. However, evidence that
30 sexual selection mostly shapes sex differences in lifespan remains equivocal [2]. Here, we
31 highlight that sexual selection, by selecting for traits and behaviors that increase male
32 reproductive success, also leads males to be more exposed to **pathogens** than females.
33 Moreover, earlier **aging** of the immune system can occur in males. This can lead to sex
34 differences in aging, which can be exacerbated in pathogen-rich environments.

35 Up to now, the literature on the deleterious consequences of infectious diseases has focused
36 on the deterioration of the immune system with increasing age (i.e. the **immunosenescence**
37 process; Box 1). In humans and wild vertebrate populations, aging of the **adaptive immune**
38 **system** may occur earlier in males [7,8]. These different patterns of immunosenescence could
39 occur between sexes due to a variety of interactions between physiological factors and the
40 local environmental context. For instance, more intense stimulation of immune defenses
41 through a greater pathogen exposure could contribute to earlier aging of the male immune
42 system, leading to an earlier onset of their **actuarial senescence**. In support, HIV-1-infected
43 individuals experience immunologic changes similar to uninfected elderly persons as a result
44 of the continuous stimulation of their immune system [9]. However, the contribution of
45 immunosenescence to the observed sex differences in lifespan and aging within and across
46 mammals is yet to be deciphered. We argue that sex-specific immune responses and sex

47 differences in energy allocation strategies driven by sexual selection, by leading to differences
48 in both exposure and susceptibility to pathogens, should result in an accelerated
49 immunosenescence in males through immune exhaustion. If this hypothesis is correct, sex
50 differences in lifespan, through either direct (host mortality) or indirect (faster
51 immunosenescence) effects, could be modulated according to the pathogenic environment of
52 populations [2] (Figure 1) and have direct consequences in human as well as veterinarian
53 medicine (Box 2). Although the sample size was limited, a preliminary analysis of currently
54 available data supports this hypothesis with sex differences of lifespan increasing in favor of
55 females when pathogen richness increases (Box 3).

56 **How biological differences between males and females contribute to disease** 57 **dimorphism?**

58 As a general rule, **prevalence**, **intensity**, and **pathogenesis** of infections caused by diverse
59 pathogens (i.e. viruses, bacteria, parasites, and fungi) are higher in males than in females in
60 humans, domesticated animals, companion animals, laboratory rodents, and numerous species
61 in the wild (see review in [10]). For example, in adult mice (*Mus musculus*) males display
62 more symptoms of sickness than females when they are exposed to bacteria that cause an
63 illness with symptoms similar to the flu [11]. Women have more than 40% less HIV-1 RNA
64 loads than men [12], while Italian men infected by the SARS-CoV-2 are approximately twice
65 more likely to die than infected women [13]. Beyond obvious morphological, anatomical, and
66 behavioral differences (e.g. aggressiveness) that might affect exposure to pathogens, many
67 other biological differences may contribute to observed sex differences in the susceptibility or
68 disease progression [14]. Yet these differences remain little studied and data on the
69 underlying biological mechanisms are surprisingly scarce, while they lead to different
70 responsiveness to treatment between sexes [14] (see Box 2).

71 *Sex, hormones and immunity*

72 It has become increasingly clear that males and females differ in immune responses [15]. As a
73 general rule, females exhibit greater capability of producing antibodies than males [16]. They
74 are less susceptible to infectious diseases [15] but can develop a stronger predisposition to
75 autoimmune or inflammatory diseases than males [15]. However, the consequences in terms
76 of sex differences in lifespan and aging are yet to be accurately quantified [17].

77 Differences in disease prevalence and expression between males and females are mainly
78 attributed to sex steroids (e.g. estrogens, testosterone, progesterone), which, by binding to
79 hormone receptors on the surface of immune cells, modulate the phenotype of immunological
80 cells [7,15]. Most of them express multiple sex hormone receptors that drive sex-specific
81 immune responses following antigen stimulation [7]. Males and females differ in steroid
82 concentrations: males have a higher concentration of testosterone and females a greater
83 concentration of estrogen and progesterone. Estrogen receptors are detected in immune cell
84 populations, including lymphocytes, monocytes and macrophages [18], and have an immuno-
85 enhancing effect as well as diverse protective effects [19]. On the contrary, progesterone and
86 testosterone have mainly immunosuppressive effects [20]. Folstad and Karter [21] proposed
87 that testosterone has, in fact, a double-sword effect that increases the probability of mating for
88 a male while decreasing its ability to fight over pathogens. For instance, territorial male
89 chamois (*Rupicapra rupicapra*) have almost six times more fecal androgen metabolites and
90 are three times more parasitized during the rut period than non-territorial males [22]. Hence,
91 we may expect that males will develop stronger disease symptoms resulting in a lower
92 probability to survive and thereby increased between-sex differences of lifespan in pathogen-
93 rich environments. However, inconsistencies among studies of vertebrate species (e.g. Cape
94 ground squirrels, *Xerus inauris* [23]) suggest that testosterone is not all story.

95 *Immune system and reproduction*

96 Major physiological changes occur during reproductive seasons or cycles. Typically,
97 testosterone production is increased in males when competing for fecund females, while
98 pregnancy induces a decrease in estrogen and an increase in progesterone concentration to
99 avoid the immunologic aggression of the fetus [24]. However, infectious diseases that are
100 acquired during pregnancy or lactation are often associated with lower birth mass and reduced
101 breast-milk in humans, suggesting that females reactivate the formally quiescent immune
102 system [25] to combat infection at the expense of reproduction. For example, women who
103 contract malaria during pregnancy have higher circulating levels of pro-inflammatory
104 cytokines, which in turn are associated with lower birth mass [26]. This suggests that females
105 should show a lower **lifetime reproductive success** in an environment with high pathogenetic
106 load, but their lifespan should be much less affected than that of males.

107 **The evolutionary roots of sex differences in response to pathogens**

108 From an evolutionary viewpoint, the immune response is a key fitness-related trait, but the
109 energy it requires should inevitably be traded for allocation to life-history traits governing
110 other biological functions [27]. For instance, the growth and maintenance of secondary sexual
111 traits impair male immune performance through a resource-based allocation trade-off [28],
112 making them more sensitive to pathogens [29] (Figure 1). Many observations in rodents,
113 birds, and insects document substantial energetic, reproductive, and survival costs of immune
114 activation [30]. Hence, organismal responses to pathogens should involve sex differences
115 given that the optimal solution to the trade-off between reproduction and survival differs
116 between sexes, with females allocating more than males to their immune responses to not
117 jeopardize their survival and increase thereby their lifetime reproductive success [27]. We can
118 even expect that iteroparous females should rapidly redirect their energy to immune functions

119 at the expense of fetus/offspring survival when exposed to a pathogen during pregnancy. The
120 optimal strategy should be radically different in semelparous females who only have one
121 opportunity to reproduce. For example, parasite removal reduces reproducing female survival
122 in the Taiwan field mouse (*Apodemus semotus*), possibly by allowing breeding females to
123 increase maternal investment (i.e. allocation at the cost of their future survival [31]). By
124 contrast, in males, immune performance is impaired by the growth and maintenance of
125 secondary sexual traits, which makes them more sensitive to pathogens [28]. In mice,
126 increased aggression is costly and is associated with reduced resistance to disease [32]. As a
127 consequence, sex differences of lifespan should increase in favor of females when pathogen
128 load increases (Box 3).

129 Finally, males and females correspond to markedly different environments for pathogens,
130 which may shape their evolution. Hence, the observed sex-biased disease prevalence and/or
131 severity might be the result of the parasite having adapted to grow in specific host sex [33].
132 Úbeda and Jansen [34] formalized this idea and suggested that natural selection can act
133 differently on pathogens in males and females depending on the transmission route of the
134 pathogen. In Japan, where the transmission of HTLV-1 (Human T-cell Lymphotropic Virus
135 Type 1) occurs through breast-feeding rather than through sexual transmission, the
136 progression to Adult T-cell Leukemia is slower in women than men. Sex-specific adaptation
137 of HTLV-1 to preserve women as a viral route could be a potential explanation for this
138 puzzling observation [34].

139 **The need to consider sex-specific immune performance and pathogen exposure in**
140 **evolutionary biology**

141 *Challenges within species*

142 The immune system includes many different immune cell types, each having its unique
143 function, and collectively protecting the host against pathogens. The reliable measurement of
144 multiple markers of both immunity (e.g. cellular components, T cell repertoire) and aging
145 (e.g. epigenetic markers of biological age [35]) remains challenging. However, such metrics
146 are required to allow a better understanding of the ecological (pathogen exposure) and
147 evolutionary forces that shape the sex-specific decline of immune responses and between-sex
148 differences in lifespan. Ideally, these measures should be made in wild populations, which
149 display a large variation in the magnitude of sex differences in lifespan (see [2]) because of
150 differential risk-taking behavior, food requirements, mortality due to direct sexual
151 competition, or exposition to commensal and pathogenic organisms. Longitudinal studies are
152 thus required to assess how immunosenescence patterns are shaped according to sex (see for
153 example [36], and references in [8]) and also to identify mortality causes, which allows
154 deciphering the different ways through which pathogens reduce individuals' lifespan (through
155 early deaths from lethal diseases or through advanced immunosenescence due to immune
156 exhaustion). This has yet rarely been investigated in wild populations (but see [37]).

157 Even though studies of rodents (reviewed in [38]) show that reaching this aim is possible in
158 wild populations, it remains a complex task. Populations living in protected conditions (e.g.
159 wild species in zoos, domestic animals and companion animals living with humans,
160 laboratory animals) would offer excellent simplified systems to explore more deeply the
161 deterioration of immune functions with increasing age and its role in between-sex mortality
162 patterns (see [39] for an example in mice). This would allow an investigation into how the
163 level of pathogen exposure as well as the virulence of pathogens to which hosts are exposed
164 shape the immunosenescence profile and thus the mortality rate and lifespan of males and
165 females.

166 Captive mammalian populations could also provide insightful information on the potential
167 effect of chronic and putatively asymptomatic infections on the differential rates of
168 immunosenescence between sexes, which is currently totally underestimated. Research on
169 human health has provided important and somewhat unexpected results in this field. Notably,
170 the chronic infection by the common CMV (cytomegalovirus) is involved in the remodeling
171 of the immune system. Hence chronic exposition to any microbial agent (i.e. not only known
172 pathogens) could be both implied in shaping sex-specific immunosenescence [40]. Only long-
173 term monitoring of individuals from birth to death, in which molecular and cellular markers of
174 adaptive and innate functions can be recorded repeatedly throughout their lifetime, and a
175 reliable estimate of the infection date becomes available at the individual level, will allow a
176 deeper understanding of immunosenescence according to age and sex concerning microbial
177 agent exposure.

178 Additionally, the comparative analysis of populations within a single species occupying
179 multiple habitat types can offer important insights into the intraspecific variation in
180 immunosenescence and its consequences on life history traits such as lifespan in both sexes.
181 Selection is expected to produce the immune response that maximizes individual fitness, in
182 interaction with other selection pressures imposed by the environmental context (i.e. resource
183 availability, weather conditions), the social and mating systems, and the pathogen exposure.
184 Thus, the immune system of rodents from different populations and environments in the wild
185 differs from that of laboratory rodents, the former being continuously exposed to commensal
186 and pathogenic organisms (reviewed in [38]). It would be thus interesting to evaluate how
187 such excessive energetic demands to activate the immune system compromise other fitness
188 components of laboratory rodents according to their pathogenic environment, notably the
189 differential actuarial senescence rates between males and females.

190 *Inter-specific comparisons*

191 Taking into account the evolutionary history of mammals, their pathogen species richness,
192 which varies largely across species [41], may help explain between-sex differences in
193 lifespan. In presence of numerous pathogens, males from species subjected to strong sexual
194 selection should be more exposed to pathogens compared to females than males from species
195 with a low sexual selection [42]. This could partly explain sex differences in
196 immunosenescence (see for example [8]) and highlight how these differences are likely
197 determined by fine scale interactions between sex-specific physiological pathways and the
198 local environment in pathogens [2].

199 Variation in pathogen richness, infection rate, and pathogen load correlates with numerous
200 morphological and ecological traits, mostly driven by sexual selection, which are also related
201 to the lifespan variation in mammals [43]. Among these traits, variation in host body size
202 [44], mating system and sexual size dimorphism [42], MHC allelic diversity [45],
203 geographical range [46], social group size [47], population density [48], and phylogeny [6,41]
204 have been identified as playing a role. However, most cross-species studies that investigate
205 the interaction between pathogens and host ecological and life-history traits performed to date
206 did not include between-sex differences in pathogens nor their consequences in terms of sex-
207 specific lifespan (e.g. [49]). Although male-biased parasitism is positively correlated with the
208 level of polygyny in mammals [42], the level of polygyny also correlates with a shorter
209 lifespan and a more pronounced aging in males compared to females, at least across captive
210 populations of large herbivores [6].

211 All these challenges will be made possible thanks to databases gathering longitudinal data that
212 measure accurately sex differences in lifespan, which are becoming increasingly available
213 (e.g. [2]). Besides, several databases recording the number of pathogen species found in
214 mammals, such as the World Register of Marine Species [50], Pathogen-Host Interactions
215 (Phi-Base) [51] or the Database of Bat-associated Viruses (DBatVir) [52] have been

216 developed. These databases provide a large amount of information about the diversity and the
217 richness of parasites across mammalian species displaying contrasted life styles. Combining
218 these databases should allow better understanding the role of pathogens in between-sex
219 differences of lifespan and aging (e.g. in terms of both onset and rate of actuarial and/or
220 **reproductive senescence** patterns) across mammalian species (see Box 3). In our view, this
221 information should inform on how pathogens shape sex differences rather than how sex
222 differences shape responses to pathogens because the magnitude of sex differences seems to
223 be context-specific (see [2] for a study of mortality patterns). It might be thus difficult to
224 envision mammals evolving differential responses to parasites mediated by sex differences if
225 the magnitude of sex differences is so labile.

226 **Concluding remark**

227 Understanding the determinants of differences in male and female outcomes is becoming a
228 crucial recognized challenge in infectious disease research in humans as well as in veterinary
229 clinical research, such as identifying the true contribution of pathogens to overall mammalian
230 mortality (see Outstanding Questions). Available information so far calls for an appropriate
231 inclusion of sex differences over the whole human life span to anchor medicine in the real
232 world (see Box 2). Longitudinal studies combining detailed immunological and non-
233 immunological follow-ups for individuals of each sex should help to understand aging of the
234 immune processes and how it differs between sexes and environments (see Outstanding
235 Questions). By taking into account the evolutionary history of mammalian species, such a
236 holistic approach could help explain between-sex differences in lifespan. For instance, studies
237 should focus on consequences of resistance and tolerance of pathogens on lifespan across
238 mammals (see Outstanding Questions). We encourage the scientific community to adopt this
239 holistic approach, which is necessary to embrace all the methodological, theoretical and

240 conceptual challenges raised by pathogens regarding sex differences in lifespan. The
241 increasing availability of required data offers great opportunities to formulate and test new
242 hypotheses.

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373

374 GLOSSARY

375 **Adaptive immune system:** antigen-specific immune responses characterized by
376 immunological memory that makes future responses against a specific antigen more efficient.

377 **Aging:** decline in the age-specific contribution to fitness throughout life. As a consequence,
378 the aging process is mostly studied in the two main fitness components: survival and
379 reproduction. Survival ageing (also called **actuarial senescence**) corresponds to the decrease
380 in survival rates with increasing age and reproductive ageing (also called **reproductive**
381 **senescence**) corresponds to the decrease in reproductive rates with increasing age.

382 **Immunosenescence:** decline of immune parameters with increasing age, associated with
383 detrimental clinical outcome (e.g. high risk of contracting and dying from infectious diseases).

384 **Intensity of infection:** pathogen load within an individual at a given time.

385 **Lifetime reproductive success:** number of offspring alive produced by an individual at some
386 life stage (usually birth, weaning, or one year of age) during its entire lifetime.

387 **Lifespan:** time interval between the birth and the death of a given individual.

388 **Pathogens:** organisms that cause disease to the host. They include in particular ectoparasites,
389 protozoan, helminths, virus, bacteria and fungi.

390 **Pathogenesis:** progression of the disease. It encompasses the complete sequence of events
391 accompanying acute and persistent infections.

392 **Prevalence:** proportion of infected individuals within a population at a given time, which
393 encompasses both old and new cases.

394 **Sexual selection:** evolutionary process arising either through mating choice (i.e. preference
395 by one sex for certain characteristics (e.g. form, color, or behavior) in individuals of the other
396 sex) or through intra-sex competition (i.e. competition among mature individuals of one sex to
397 monopolize access to mate with individuals of the other sex). Both ways select for a large
398 sexually size dimorphism and extravagant sexually secondary characters such as ornaments or
399 weapons when sexual selection is strong.

400 **Box 1. Sex-specific immunosenescence**

401 A decline in immune defense with increasing age, defining the immunosenescence process,
402 has been highlighted in numerous species across the tree of life [8]. However, the few results
403 available so far do not support that a sex difference of immunosenescence pattern would
404 cause the observed sex differences of adult mortality [8,36].

405 Progressive deterioration of the organism results from concomitant retention (or exacerbation)
406 of innate immunity coupled with a dysregulation (or dysfunction) of adaptive immunity [53].
407 For now, in all studies conducted so far in humans, a universal age-associated immune
408 alteration is consistently observed. The numbers and proportions of naive peripheral blood
409 CD8+ T cells are reduced as a consequence of the developmentally-programmed thymic
410 involution [53]. Moreover, as the establishment of the innate immune response causes
411 inflammation and ROS production that induce collateral tissue damage, we can hypothesize
412 that the more an organism is subject to a repeated innate immune response (e.g. due to high
413 exposure to pathogens), the more permanent the damage will be. This potentially accelerates
414 an organism's deterioration, ultimately leading to its death. Similarly, the adaptive immune
415 system is particularly affected by the effect of long-term exposure to a variety of antigenic
416 stimuli. Accordingly, an adaptive immune system highly exposed to pathogens will quickly
417 lose efficiency, leading it to exhaustion with dramatic consequences such as high mortality.

418 As increased solicitation of the immune system leads to an acceleration of its dysregulation
419 and efficiency, we suggest that in presence of pathogens, males undergo stronger
420 immunosenescence than females, because of their higher exposure and tolerance to infectious
421 agents. This results in the observed higher mortality rate and shorter lifespan of males
422 compared to females. For example, Zeng et al. [54] highlighted that two immune pathways,
423 the cytokine IL-6 and TLR3 proinflammatory signaling pathways, are positively associated

424 with the lifespan of centenarian men but not women. This suggests that dysregulation of these
425 proinflammatory pathways with age makes elderly men more susceptible to infectious
426 pathogens than elderly women. However, while numerous researchers asked for more
427 longitudinal studies to define more accurately immunosenescence profiles and identify the
428 underlining mechanisms [53], sex remains overlooked in biological research despite its
429 critical consequences in the veterinarian and human medicine.

430 **Box 2. The urgent need to consider sex in medicine**

431 Investigating the role of pathogens on sex differences in aging highlighted how much males
432 and females differ regarding their immune system and their response to infectious diseases. In
433 spite of this, physicians still tend to prescribe the same treatment to both male and female
434 patients for a given diagnostic. One reason for this is that sex differences in immune functions
435 are not well understood yet.

436 During the last thirty years, most biomedical research has routinely used only males in both
437 cohort and animal model studies because the cyclic hormonal fluctuations of females
438 introduce additional experimental variation [55]. This could explain the higher number of
439 secondary effects observed in women than in men following the commercialization of a given
440 drug [56]. Upon vaccination, women develop a higher antibody immune response, but also
441 more frequent and severe adverse side effects than men [57]. The application of sex-specific
442 medicine is thus urgently required [56]. The American National Institute of Health recently
443 declared that clinical trials not taking sex-specific responses into account will no longer be
444 funded [58].

445 A great deal of knowledge about sex differences in immune functions comes from laboratory
446 animals, notably the mouse model, which have been used extensively to develop research and
447 test therapies before they are used in humans. However, very little is known about how much
448 information from inbred and laboratory-adapted mice can be extrapolated to mammalian
449 immune responses in the wild [59]. First, the selection of laboratory mice has resulted in the
450 alteration of life-history traits (such as reproduction or lifespan, see [60]) and immunological
451 traits of individuals. Second, as argued above, animals' immune responses are just one
452 dimension of a wider life-history strategy to maximize fitness within the constraints of the
453 environmental context. Laboratory conditions strongly differ from the environment

454 individuals face in the wild, which can have serious consequences on the immune response
455 they mount. Comparison between male and female immune functions in wild and laboratory
456 animals is thus crucially needed to reveal both the relevance and limitations of laboratory
457 animals as immunological models. Linking wild and laboratory animal immunology by using
458 tools and concepts of immunology, but also of ecology and evolutionary biology, is badly
459 needed. In that respect, companion animals, which live in the same environment as their
460 owners and are exposed to similar pathogens [61], may potentially serve as bridges between
461 laboratory and wild species. The affordability of new 'omic' approaches and the availability
462 of new trusted biomarkers (e.g. antibodies, cytokines, cellular responses) and immunological
463 reagents (e.g. monoclonal antibodies) will help to quantify male and female exposition to
464 microbes and the dysregulation of immune parameters with increasing age in a wider range of
465 mammalian species, aiding immunologists, ecologists and evolutionary biologists to work
466 altogether.

467 **Box 3. Relationship between sex differences in mean adult lifespan and increased**
468 **pathogen richness**

469 Using between-sex differences of mean adult lifespan in 13 mammalian species (8 carnivores
470 and 5 primates, see more details in supplemental Table S1), a preliminary analysis (Figure I)
471 reveals that between-sex differences of lifespan increases (0.335 ± 0.139 , $p = 0.03$) in favor of
472 females when pathogen richness increases. The mean adult lifespan for the 13 species was
473 obtained from [2]. Pathogen richness is defined as the cumulative number of pathogen species
474 inventoried (arthropods, helminths, protozoans, virus, and bacteria) for each carnivore and
475 primate species, males and females combined (extracted from literature and standardized for a
476 given sampling effort). Linear models have been fitted with between-sex differences of mean
477 adult lifespan as the response variable, and pathogen richness and ‘family’ (Carnivora or
478 Primates as factors) as explanatory variables. For each species considered, the number of
479 studies inventorying one or several pathogen species was recorded as an indication of the
480 sampling effort exerted on the species and included in the analysis: pathogen richness values
481 correspond to the residuals of the linear model with real pathogen richness in response
482 variable and the sampling effort as an explanatory variable.

483
484 **Figure I. Increase of sex differences of mean adult lifespan in favor of females when**
485 **pathogen richness increases for 8 carnivore (full circle) and 5 primate (open circle)**
486 **species.**

487

488 **Figure legend**

489 **Figure 1. Different selective strength between sexes driving the evolution of sex**
490 **differences.** These differences include those in life-history traits (blue boxes), in physiology
491 and the immune response to pathogens (yellow boxes), and in aging and lifespan (red boxes).
492

