Survival is reduced when endogenous period deviates from 24 h in a non-human primate, supporting the circadian resonance theory

Clara Hozer1, Martine Perret1, Samuel Pavard2 & Fabien Pifferi1

Circadian rhythms are ubiquitous attributes across living organisms and allow the coordination of internal biological functions with optimal phases of the environment, suggesting a significant adaptive advantage. The endogenous period called \(\tau\) lies close to 24 h and is thought to be implicated in individuals’ fitness: according to the circadian resonance theory, fitness is reduced when \(\tau\) gets far from 24 h. In this study, we measured the endogenous period of 142 mouse lemurs (\(Microcebus murinus\)), and analyzed how it is related to their survival. We found different effects according to sex and season. No impact of \(\tau\) on mortality was found in females. However, in males, the deviation of \(\tau\) from 24 h substantially correlates with an increase in mortality, particularly during the inactive season (winter). These results, comparable to other observations in mice or drosophila, show that captive gray mouse lemurs enjoy better fitness when their circadian period closely matches the environmental periodicity. In addition to their deep implications in health and aging research, these results raise further ecological and evolutionary issues regarding the relationships between fitness and circadian clock.
season (or summer-like season), characterized by long photoperiod and abundance of resources corresponds to high levels of metabolic activity, as well as reproductive behavior. Rather, during the cooler dry season (or winter-like season), food scarcity and low temperatures force the gray mouse lemur to considerably slow down its metabolism inducing a global fattening and frequent daily phases of hypometabolism24,25. These seasonal phenotypic changes are only triggered by the photoperiod: when exposed to photoperiod shorter than 12 h, the gray mouse lemurs exhibits a winter phenotype, whereas it displays a summer phenotype when exposed to a photoperiod greater than 12 h17,26.

Recently, we reported that mouse lemurs raised under light–dark cycles of 26 h exhibited higher daily body temperature and metabolic rate than animals kept in natural lighting conditions (24 h), demonstrating the existence of potential metabolic and physiological costs of clock synchronization when endogenous and external rhythms deviate27. Do these costs affect the survival of adult individuals? We analyzed how affected survival in 142 mouse lemurs. In males, the deviation of \( \tau \) from 24 h substantially increased mortality, particularly during the inactive season (winter), whereas it did not affect mortality in females.

**Results**

**Distribution of \( \tau \) and correlation with age.** As found in many nocturnal species8, the gray mouse lemur clock oscillates with a period of less than 24 h (Fig. 1). Only 2 males and 2 females had an endogenous period greater than 24 h. Mean endogenous periods were 23.09 ± 0.58 h and 23.10 ± 0.64 h in males and females respectively. There was no significant correlation between \( \tau \) and age at \( \tau \) measurement neither in males (\( r = 0.13, p = 0.20 \)), nor in females (\( r = − 0.22, p = 0.12 \)) (Fig. 2). These two results suggest that endogenous period is both specific to individuals and independent of age in this species.

**The relationship between \( \tau \) and survival depends on sex and season.** Best selected models for the female and male samples are presented in Table 1. They incorporate only variables Dev.\( \tau \), season, the interaction between Dev.\( \tau \) and season and body mass. All models incorporating the variable lineage had larger AICc such that delta(AICc) > 2. Individual, maternal and cohort effects did not change the effect sizes of the models. Schoenfeld residuals show that the selected models satisfy the proportionality assumption and martingale residuals did not reveal departure from a linear effect of Dev.\( \tau \) on mortality. As the effect of Dev.\( \tau \) remains unchanged among the different selected models and is not modified by other covariates than season, we chose to treat Dev.\( \tau \) as a categorical variable into a Kaplan–Meier analysis in order to allow graphic representation. We split each sample (males and females) into three categories, corresponding to tertiles of Dev.\( \tau \) values.

![Figure 1. Endogenous period repartition in the 51 female (A) and 91 male (B) mouse lemurs tested. Most of the endogenous periods were less than 24 h, only 4 individuals had a \( \tau \) higher than 24 h.](image-url)
such as every category included an equal number of individuals greater than 15). For females, the tertiles were 0–40 min (17 individuals), 40 min–1 h (17 individuals) and ≥ 1 h (17 individuals). For males, tertiles values were 0–42 min (31 individuals), 42 min–1h04 (30 individuals) and ≥ 1h04 (30 individuals) (Fig. 3).

Dev.tau did not influence survival in females (Table 1 and Fig. 3A). In males, however, Dev.tau affected negatively and significantly the survival. Our best model predicted that every supplementary hour of Dev.tau (i.e. every supplementary hour of \( \tau \) deviation from 24 h) multiplied the risk of death by 2.82 (\( = e^{1.04} \), Table 1). Dividing the sample into tertiles of Dev.tau, median survival ages were 2637 days (7.22 years), 2170 days (5.94 years) and 1704 days (4.67 years) in the three represented groups respectively, i.e. a reduction of 35% of median survival between the two extreme curves. Maximum longevities were 3363 days (9.21 years), 3772 days (10.33 years), and 3915 days (10.72 years) in the three groups respectively (Fig. 3B).

Besides, the interaction between Dev.tau and season in males was significant as well (Table 1). When only considering the winter-like season, the negative effect of Dev.tau in males on survival was amplified: every supplementary hour of Dev.tau multiplied the risk of death by 3.22 (\( = e^{1.17} \), Table 1). Dividing the sample into tertiles of Dev.tau, median survival ages were 3180 days (8.71 years), 2844 days (7.79 years) and 1413 days (3.87 years) in the three represented groups respectively, i.e. a reduction of 56% of median survival between the two extreme curves. Maximum longevities were 3363 days (9.21 years), 3772 days (10.33 years), and 3871 days (10.60 years) in the three groups respectively (Fig. 3C).

Parametric AFT models were equally but not better supported by the data than proportional hazard model (data not shown).

Discussion
This study aimed at exploring the relationship between the endogenous period \( \tau \) and survival in a non-human primate. Our results show no impact of endogenous period on survival in female mouse lemurs. On the other hand, male individuals with endogenous period close to 24 h were those experiencing a better survival. This effect was particularly significant in winter-like season, corresponding to the non-mating and inactive season. Individuals with \( \tau \) far from 24 h had a reduction of median survival up to 56% compared to individuals with closer \( \tau \), suggesting a high adaptive value of maintaining an endogenous period close to 24 h. It is still not clear, however, why \( \tau \) exhibits such important inter-individual variance but the deviation of \( \tau \) from 24 h may bring some advantage in seasonal adaptation by stabilizing the phase angle. So far, the relationship between
endogenous period and survival had been assessed in fruit flies and mice. Only one study found a similar relationship in primates, but it applied a totally different experimental protocol, based on interspecific comparisons and maximum lifespans taken from the literature. To our knowledge, our results are the only ones to report a relationship between \( \tau \) and survival in a single primate species.

Why are the endogenous period and survival related to each other? Pittendrigh and Minis suggested that the daily resetting of the biological clock onto the 24 h of the environment would engender daily marginal metabolic costs that would accelerate aging and affect survival: the impact of these costs on longevity would be proportional to the deviation of \( \tau \) from 24 h. In that respect, the median survival ages found in our experiment show clearly that the more \( \tau \) gets far from 24 h, the more the survival is low. Recently, we observed that mouse lemurs kept in light–dark cycles far from their endogenous period (26 h) exhibited higher resting body temperature and higher energy expenditure, associated with lower cognitive performances. This study suggests that living under photoperiodic regimen far from endogenous rhythms leads to physiological, metabolic and cognitive costs for

---

**Figure 3.** Effect of Dev.\( \tau \) on the survival of females (A), males (B) and males in winter-like season (C) with increasing age. Individuals were distributed in tertiles to allow graphic representation, corresponding to specific cut-off of absolute deviation of \( \tau \) from 24 h. Dotted lines correspond to median survivals. Small solid vertical bars correspond to censored data.
the organism. It could partially explain the link between tau, longevity and aging. Indeed, biological clock and aging processes are assumed to influence one another. Aging is often associated with rhythm fragmentation, phase advance, sleep disorders, decrease of rhythm amplitude, SCN atrophy59-32. Besides, the deterioration of the biological clock is alleged to accelerate and stand at the heart of aging mechanisms33-35. In this context, the endogenous period could modulate the rate of aging and indirectly influence organisms’ mortality. For example, it was reported that plasma level of interferon-γ, a well-known biomarker of aging, was negatively correlated to survival in gray mouse lemurs. Interestingly, the plasma level of interferon-γ was also negatively correlated with the endogenous period, i.e. the individuals with tau close to 24 h displayed lower aging biomarkers and greater survival36. These observations, along with our results, underline the relevance of an acute and coordinated circadian pacemaker, including endogenous rhythms resonating with the environment cycles, to enhance survival.

Why does the endogenous period correlate with survival in males but not in females? Libert’s study focused exclusively on males, but curiously, Pittendrigh and Minis found similar results on males and females. This is intriguing, regarding our results, since insect and mammal clocks are known to display significant similarities37,38. We have no clear explanation, but it should not be forgotten that the study included more males than females, increasing the risk of type II statistical error in females. Otherwise, this difference between sexes may be related to mammal sexual circadian specificities, even though a bias towards research on male’s circadian clock makes exhaustive comparisons between sexes difficult39. Some studies report though that the influence of internal desynchronization on sleep–wake disorders is considerably greater in females than in males, some other mentioned a slower synchronization in females40,41. The daily costs of resynchronization due to tau deviation may be negligible in females compared to more important circadian alterations. Unfortunately, sexual comparisons in circadian parameters are little studied in the gray mouse lemur. However it is known that female mouse lemurs deal with seasonal transitions and metabolic costs differently than males, particularly during aging42. Facing an environmental metabolic stress, female mouse lemurs seem to better manage their energy expenditure and exhibit more flexible physiological response44-46. During aging, males body weight variations collapse whereas females keep displaying clear seasonal mass variations, suggesting a better management of resources21,47. Therefore, females may better deal with generated daily metabolic costs due to circadian clock reset and thus would not display survival impairments.

Why does tau correlate with survival in winter-like more than in summer-like? The explanation could lie in the huge physiological and metabolic changes experienced by the gray mouse lemurs between winter-like and summer-like photoperiods. The species has the particularity of being heterothermic, allowing daily phases of hypometabolism (torpor) that occur almost exclusively during the winter-like season, in order to cope with environmental food scarcity and to save substantial amount of energy, even in captive conditions48,49. It has been shown that circadian clock and torpor use are closely related50. For example, light pollution significantly modifies circadian expressions, with negative repercussions on torpor51. If the circadian clock oscillates too far from environmental periodicity, it may imply affectations of torpor efficiency and be deleterious in the long run. Inversely, in summer-like season, during which torpor hardly ever happens, the activation of reproduction investments may require so much energy that reproduction investments in males could overwhelm daily costs engendered by clock synchronization. In addition, IGF-1 (Insulin-like Growth Factor 1) rates exhibit an age-related decrease in male mouse lemurs only during the winter-like season, whereas they remain high and stable during the summer-like season. Interestingly, the winter-like IGF-1 rates are also predictive of survival52. It could thus be worthwhile to combine data from tau and IGF-1 in this species, as it is known that circadian rhythms and IGF-1 are closely related45,46.

In this study, we showed that Dev.tau was not influenced by age between individuals, but we made the hypothesis that tau was constant over each individual lifetime. It is however not clear if time and more specifically aging do influence the endogenous period or not. In several mammals, even within the same species, increasing, decreasing or constant endogenous periods with age have been found45,53-58. In the gray mouse lemur, the same conflicting observations lead to suggest that tau evolution during aging is due to epigenetic variations between individuals and underline once again that aging is an individual-dependent phenomenon18,59. A longitudinal approach is necessary to bring further exhaustive information on the relationship between tau and aging.

These experiments were performed in captive animals, but one may wonder if the endogenous period substantially impacts fitness in nature. Indeed, wild individuals often die before aging45 and captive animals are not submitted to predation, food scarcity and less to diseases. Furthermore, the fact that the tested mouse lemurs had such inter-individual variability in tau values might suggest weak selection pressures of tau on survival. Very few studies actually carried out such protocols in natural conditions. It was reported that mice with a mutation in the enzyme casein kinase 1ε exhibited a short tau (~22 h) and displayed lower survival and reproduction performances when released in outdoor enclosures60. However, the authors could not rule out a potential pleiotropic effect of the mutation, rather than a direct effect of shorter endogenous period to explain reduced lifespans in mutant mice. In natural populations of pitcher-plant mosquitos (Wyeomyia smithii), exposition to light–dark cycles that are integral multiples of the endogenous period maximized fitness by increasing fecundity but surprisingly not by enhancing adult’s longevity61. In the light of these observations, an interesting study would be to place wild type individuals in semi natural conditions, and to monitor their survival depending on their endogenous period. In captive gray mouse lemurs, an interesting perspective could also be to investigate the relationship between tau and reproduction performances, such as reproductive events or juveniles’ recruitment.

To conclude, our results highlighted the negative correlation between great deviation of tau from 24 h on survival in adult captive male mouse lemurs, even if further investigations are needed to elucidate the ecological implications of sex and season dependence. Our findings show that resonating circadian clocks seem to be highly adaptive features of living organisms and underlie the importance of correct clock resetting to enjoy better health. They may have some interesting applications in human societies, where light pollution and drifted ways of life modulate circadian clock adjustments to external world.
### Methods

#### Animals and ethical statement.
All data integrated in the study were taken from the database of the mouse lemur colony of Brunoy (MECADEV, MNHN/CNRS, IBISA Platform, agreement F 91.114.1, DDPP, Essonne, France). These data have been collected between 1996 and 2013. All experiments were performed in accordance with the Principles of Laboratory Animal Care (National Institutes of Health publication 86-23, revised 1985) and the European Communities Council Directive (86/609/EEC). The research was conducted under the approval of the Cuvier Ethical Committee (Committee number 68 of the "Comité National de Réflexion Ethique sur l’Expérimentation Animale") under authorization number 12992-2018011613568518 v4. Animals were raised in the laboratory under identical nutritional and social conditions. They were all treated using the same experimental methodology, as described below.

#### Housing conditions.
All animals were housed in cages equipped with wood branches for climbing activities as well as wooden sleeping boxes mimicking the natural sleeping sites of mouse lemurs, *i.e.* tree holes or cavities. The temperature and the humidity of the rooms were maintained at 25–27 °C and at 55–65%, respectively. In captivity, the artificial daily light-dark cycles within the housing rooms are changed to mimic season alternation, with periods of 6 months of summer-like long days (14 h of light and 10 h of darkness, denoted 14:10) and 6 months of winter-like short days (10 h of light and 14 h of darkness, denoted 10:14). Animals were fed ad libitum (with fresh fruits and a homemade mixture, see Dal-pan et al., 2011[^2] for details).

#### Telemetry implants.
Recording of locomotor activity (LA) was obtained by telemetry at a constant ambient temperature of 25 °C. A small telemetric transmitter weighing 2.5 g (model TA10TA-F10, DataScience Co. Ltd, Minnesota, USA) was implanted into the visceral cavity under ketamine anesthesia (lmalgène, 100 mg/kg ip). After surgery, animals returned to their home cage and were allowed to recover for 15 days before start of experiment and continuous recordings of LA. Total recovery was checked by visual inspection of the complete healing of the surgical incision. A receiver was positioned in the cage. Locomotor activity was continuously recorded by the receiver plate, which detected vertical and horizontal movements (coordinate system, DataquestLab Prov.3.0, DataScience Co.Ltd, Minnesota, USA).

#### Endogenous period measurement.
In order to measure the endogenous period $\tau$, individuals included in the survey were isolated and submitted to free-running conditions *i.e.* total darkness during 7–30 days. Feeding and weighing were planned at random times of the day, so that no bias could be introduced by human activity in the animals’ facility. After circadian activity measurements, the light regimen was returned to 10:14 light–dark cycles. Endogenous periods were assessed using Clocklab software (Actimetrics, Evanston, IL, USA).

#### Mortality data.
In total, 142 animals, with 91 males and 51 females were integrated in the study. Thirty-six of them were right-censored (Table 2) because they were alive at the end of the study (*i.e.* 23 march 2020), had been transferred to another laboratory or had been euthanized during experiments requiring sacrifice. The remaining 106 died natural deaths. Dates of birth and natural death or censoring of each individual as well as the dates of season change were known.

#### Statistical analyses.
Because complex interactions exist between sex, season and mortality[^17,63], we treated males and females separately (for an analysis incorporating males and females together, see supplementary materials Table S1 and Figure S1). We first assessed if there was a relationship between $\tau$ and the age at $\tau$ measurement, using a Pearson correlation test. For each individual, we then calculated a “Dev.$\tau$” value, which is the absolute deviation of the individual’s endogenous period from 24 h ($\text{Dev.}\tau = |24 - \tau|$). The individuals entered the study at $\tau$ measurement, and were left truncated at this age. We then investigated the influence of Dev.$\tau$ on survival using multi-variate Cox proportional hazard survival analysis[^64]. The hazard function (defined as the instantaneous risk that the event of interest, *i.e.* death, happens) links a baseline hazard function and a vector of covariates via the following function: $h(t|y) = h_0(t).e^{\beta^Ty}$, with $h_0(t)$ being the baseline hazard function of unspecified distribution, $t$ being the age, and $\beta$ being the parameter quantifying the impact (effect size) of covariate $y$. We first treated Dev.$\tau$ as a continuous variable and we included other additional covariates, that are known to affect mortality in this species: season (integrated as a time-varying covariate), and the age at $\tau$ measurement, identities of individuals and their mothers entered as random variables. We considered all interactions two by two between fixed parameters. We selected the best

|                | Males  | Females |
|----------------|--------|---------|
| Mean age at death (in years) | 5.98 ± 2.35 | 5.69 ± 2.03 |
| Mean age at $\tau$ measurement (in years) | 3.10 ± 1.85 | 3.81 ± 2.20 |
| Death from natural causes | 66 | 40 |
| Censored | 25 | 11 |

Table 2. Mean age at death, age at $\tau$ measurement, number of natural deaths and censored individuals in male and female mouse lemurs. Data are presented as mean ± SD.
models using a backward elimination rule by calculating second-order Akaike’s Information Criterion (AICc), conserving only models with delta(AICc)<2. Since the use of AICc is not appropriate to predict significance of random effects, we compared the effect sizes of models incorporating the random variables vs models that did not, to potentially adjust for interindividual heterogeneity, maternal effects or cohort effects. Verification of the proportionality and the linearity of the models was made using Shapenveld and martingale residuals. Finally, we constructed parametric Accelerated Failure Time (AFT) models equivalent to the selected Cox models in term of incorporated covariates, to test whether Dev.tau accelerate the speed at which mortality increase with age. We compared them to equivalent parametric Proportional Hazard (PH) models. Both methods assume a Gompertz baseline distribution. This procedure allowed to test whether Dev.tau was related to mortality patterns by changing the rate of aging.

Received: 3 July 2020; Accepted: 8 October 2020

References

1. Barclay, J. L., Tsang, A. H. & Oster, H. Interaction of central and peripheral clocks in physiological regulation. In Progress in Brain Research, Vol. 199, 163–181 (Elsevier, 2012).
2. Kyriacou, C. P. & Hastings, M. H. Circadian clocks: genes, sleep, and cognition. Trends Cogn. Sci. 14, 259–267 (2010).
3. Reineke, H. & Asher, G. Circadian clock control of liver metabolic functions. Gastroenterology 150, 574–580 (2016).
4. Kalsbeek, A., La Fleur, S. & Fliers, E. Circadian control of glucose metabolism. Mol. Metabol. 3, 372–383 (2014).
5. Richards, J. & Gumz, M. L. Mechanism of the circadian clock in physiology. J. Comp. Physiol. A 106, 291–331 (1976).
6. Duong, H. A., Robles, M. S., Knutti, D. & Weitz, C. A Molecular mechanism for circadian.
7. Lande-Diner, L., Boyault, C., Kim, J. Y. & Weitz, C. J. A positive feedback loop links circadian clock factor CLOCK-BMAL1 to the
8. Pittendrigh, C. & Daan, S. A functional analysis of circadian pacemakers in nocturnal rodents: I—The stability and lability of
9. Richards, J. & Gumz, M. L. Mechanism of the circadian clock in physiology. Am. J. Physiol. Regul. Integr. Comp. Physiol. 304, (2013).
10. Karatsoreos, I. N., Bhagat, S., Bloss, E. B., Morrison, J. H. & McEwen, B. S. Disruption of circadian clocks has ramifications for
11. Aschoff, J. Exogenous and endogenous components in circadian rhythms. Cold Spring Harb. Symp. Quant. Biol. 25, 11–28 (1960).
12. Pittendrigh, C. & Daan, S. A functional analysis of circadian pacemakers in nocturnal rodents: II—The stability and lability of
13. Richards, J. & Gumz, M. L. Mechanism of the circadian clock in physiology. Am. J. Physiol. Regul. Integr. Comp. Physiol. 304, (2013).
14. Libert, S., Bonkowski, M. S., Pointer, K., Pletcher, S. D. & Guarente, L. Deviation of innate circadian period from 24h reduces
15. van Saint Paul, U. & Aschoff, J. Longevity among blowflies Phormia terraenovae R.D. kept in non-24-h light-dark cycles.
16. Kyriacou, C. P. & Hastings, M. H. Circadian clocks: genes, sleep, and cognition.
17. Languille, S.
18. Hozer, C., Pifferi, F., Aujard, F. & Perret, M. The biological clock in gray mouse lemur: adaptive, evolutionary and aging considera-
19. Perret, M. Change in photoperiodic cycle affects life span in a prosimian primate (Microcebus murinus). Chronobiol. Int. 23, 451–460 (2006).
20. Pifferi, F. et al. Effects of dietary resveratrol on the sleep-wake cycle in the non-human primate gray mouse lemur (Microcebus murinus). Chronobiol. Int. 29, 261–270 (2012).
21. Perret, M. Change in photoperiodic cycle affects life span in a prosimian primate (Microcebus murinus). J. Biol. Rhythms 12, 136–145 (1997).
22. Pifferi, F. et al. Caloric restriction increases lifespan but affects brain integrity in grey mouse lemur primates. Commun. Biol. 1, 1–8 (2018).
23. Lutermann, H., Schmelting, B., Radespiel, U., Ehresmann, P. & Zimmermann, E. The role of survival for the evolution of female philopatry in a solitary forager, the grey mouse lemur (Microcebus murinus). J. Therm. Biol. 30, 71–81 (2003).
24. Zhdanova, I. V. et al. Aging of intrinsic circadian rhythms and sleep in a diurnal nonhuman primate Macaca mulatta. J. Biol. Rhythms 26(4), 159 (2011).
25. Jazwinski, S. M., Belancio, V. P. & Hill, S. M. Circadian Rhythms and Their Impact on Aging (Vol. 7) (2017).
26. Yang, G. et al. Timing of expression of the core clock gene Bmal1 influences its effects on aging and survival. Sci. Transl. Med. 8, (2016).
35. Banks, G., Nolan, P. M. & Peirson, S. N. Reciprocal interactions between circadian clocks and aging. Mamm. Genome 27, 332–340 (2016).
36. Cayetanot, F., Nygård, M., Perret, M., Kristensson, K. & Aujard, F. Plasma levels of interferon-γ correlate with age-related disturbances of circadian rhythms and survival in a non-human primate. Chronobiol. Int. 26, 1587–1601 (2009).
37. Stanewsky, R. Genetic analysis of the circadian system in Drosophila melanogaster and mammals. J. Neurobiol. 54, 111–147 (2003).
38. Helfrich-Förster, C. The circadian clock in the brain: A structural and functional comparison between mammals and insects. J. Comp. Physiol. A. 190, 601–613 (2004).
39. Kriou, J. A. & Mintz, E. M. Sex differences in behavioral circadian rhythms in laboratory rodents. Front. Endocrinol. 5, 3–6 (2015).
40. Weger, R. A. Sex differences in human circadian rhythms: Intrinsic periods and sleep fractions. Exp.erienda 40, 1226–1234 (1984).
41. Duffy, J. F. et al. Sex difference in the near-24-h intrinsic period of the human circadian timing system. Proc. Natl. Acad. Sci. USA 108, 15602–15608 (2011).
42. Bailey, M. & Silver, R. Sex differences in circadian timing systems: Implications for disease. Front. Neuroendocrinol. 35, 111–139 (2014).
43. Goel, N. & Lee, T. M. Sex differences and effects of social cues on daily rhythms following phase advances in Octodon degus. Physiol. Behav. 58, 205–213 (1995).
44. Schmid, J. Sex-specific differences in activity patterns and fattening in the gray mouse lemur (Microcebus murinus) in Madagascar. J. Mammal. 80, 749–757 (1999).
45. Terrien, J., Perret, M. & Aujard, F. Gender markedly modulates behavioral thermoregulation in a non-human primate species, the mouse lemur (Microcebus murinus). Physiol. Behav. 101, 469–473 (2010).
46. Noiret, A. et al. Sex-specific response to caloric restriction after reproductive investment in Microcebus murinus: an integrative approach. Front. Physiol. 11, 506 (2020).
47. Perret, M. & Aujard, F. Aging and season affect plasma dehydroepiandrosterone sulfate (DHEA-S) levels in a primate. Exp. Gerontol. 40, 582–587 (2005).
48. Aujard, F., Perret, M. & Vannier, G. Thermoregulatory responses to variations of photoperiod and ambient temperature in the male lesser mouse lemur: a primitive or an advanced adaptive character? J. Comp. Physiol. B Biochem. Syst. Environ. Physiol. 168, 540–548 (1998).
49. Perret, M. Energetic advantage of nest-sharing in a solitary primate, the lesser mouse lemur (Microcebus murinus). J. Mammal. 79, 1093–1102 (1998).
50. Perret, M. & Aujard, F. Daily hypothermia and torpor in a tropical primate: Synchronization by 24-h light-dark cycle. Physiol. Behav. 101, 469–473 (2010).
51. Le Tallec, T., Perret, M. & Théry, M. Light pollution modifies the expression of daily rhythms and behavior patterns in a nocturnal primate. PLoS ONE 8, e79250 (2013).
52. Aujard, F., Blué-Justhay, M. T., Zizzari, P., Perret, M. & Epelbaum, J. IGF-1: a marker of individual life-span in a primate. Ageing Res. 1, 2 (2010).
53. Brit, A. et al. Insulin-like growth factor-1 acts as a zeitgeber on hypothalamic circadian clock gene expression via glycogen synthase kinase-3 signaling. J. Biol. Chem. 293, 17278–17290 (2018).
54. Crosby, P. et al. Insulin/IGF-1 drives PERIOD synthesis to entrain circadian rhythms with feeding time. Cell 177(896), e20-909. e20 (2019).
55. Kendall, A. R., Lewy, A. J. & Sack, R. L. Effects of aging on the intrinsic circadian period of totally blind humans. J. Biol. Rhythms 16, 87–95 (2001).
56. Monk, T. H. & Moline, M. L. The timing of bedtime and waketime decisions in free-running subjects. Psychophysiology 26, 304–310 (1989).
57. Possidente, B., McEldowney, S. & Pabon, A. Aging lengthens circadian period for wheel-running activity in C57BL mice. Physiol. Behav. 57, 575–579 (1995).
58. Davis, F. C. & Viswanathan, N. Stability of circadian timing with age in Syrian hamsters. Am. J. Physiol. Regul. Integr. Comp. Physiol. 275, 6–10 (1992).
59. Schilling, A., Richard, J. P. & Servière, J. Effect of aging on circadian activity in gray mouse lemurs. Int. J. Primatol. 22, 25–42 (2001).
60. Spoelstra, K., Wikelski, M., Daan, S., Loudon, A. S. I. & Hau, M. Natural selection against a circadian clock gene mutation in mice. Proc. Natl. Acad. Sci. USA 113, 686–691 (2016).
61. Emerson, K., Bradshaw, W. E. & Holzapfel, C. M. Concordance of the circadian clock with the environment is necessary to maximize fitness in natural populations. Evolution (NY). 62, 979–983 (2008).
62. Dal-pan, A. et al. Caloric restriction or resveratrol supplementation and ageing in a non-human primate: first-year outcome of the RERIKAL study in Microcebus murinus. Age (Omaha). 33, 15–31 (2011).
63. Landes, J. et al. State transitions: a major mortality risk for seasonal species. Ecol. Lett. 20, 883–891 (2017).
64. Cox, D. R. & Oakes, D. Analysis of Survival Data. Monographs on Statistics and Applied Probability. (Chapman&Hall, London, 1984).
65. Kraus, C., Eberle, M. & Kappeler, P. M. The costs of risky male behaviour: Sex differences in seasonal survival in a small sexually monomorphic primate. Proc. R. Soc. B Biol. Sci. 275, 1635–1644 (2008).

Acknowledgements
We are grateful to Aude Anzeray and Isabelle Hardy for their participation in the data collection.

Author contributions
Conceptualization, C.H., F.P. and M.P. Investigation, C.H. and M.P. Methodology and Formal Analysis, C.H., S.P. and F.P. Writing-Original Draft, C.H.; Writing-Review and Editing, C.H., M.P., S.P. and F.P. Supervision, F.P.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information is available for this paper at https://doi.org/10.1038/s41598-020-75068-8.

Correspondence and requests for materials should be addressed to F.P.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
