

Chronic resveratrol supplementation has health benefits during aging but does not mimic the positive effects of calorie restriction on lifespan in male grey mouse lemurs (*Microcebus murinus*).

Corresponding Author: Dr Fabien Pifferi

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

This paper examines whether Resveratrol (RSV) mimics the effects of caloric restriction on health and longevity in a nonhuman primate, the grey mouse lemur. Animals (n= 33) were assigned to either a standard diet or the diet supplemented with a medium (200 mg/kg) dose of RSV (n=18) and tested longitudinally for cognitive function (Barnes maze) and motor function (rotarod) from middle-age to death. RSV-treated animals had better cognitive and motor function and greater median lifespan than controls, but mortality was not affected. However, grey matter cerebral atrophy was greater in the RSV group than CTL group. The authors conclude that long-term RSV supplementation has health benefits in middle-age but limited effects on longevity, with potential adverse effects on brain integrity in old age.

There are many strengths in this paper, including the relatively large number of animals, the longitudinal assessments, the careful consideration of the RSV dose and the survival analysis. The presentation of the results is very clear and the paper is generally well written. My main concern is with the interpretation of the cognitive results. The conclusion that cognition was enhanced in RSV-treated lemurs is based on the performance on a single cognitive task, the Barnes maze. RSV animals were faster than CTL in the Barnes maze task, but this effect likely reflected better motor skills, as measured by the rotarod and high jump tasks. Although RSV animals also committed fewer errors, it seems that this effect could entirely be explained by the animals being faster (due to enhanced motor, not cognitive function). One way to rule this out would be to compare the RSV and CTL groups on the number of errors relative to time (e.g., errors/minute). In the absence of such a comparison or an additional cognitive task, the conclusion that RSV provided cognitive benefits is premature. As a result, the discussion should be edited to reflect this point. It would also be useful to comment on the neural substrates underlying the Barnes maze task and associated performance.

The MS would also be improved by discussing the potential functional significance of the MRI findings. How do the behavioral measures relate to the MRI findings? are there any neural correlates of better motor function in the RSV group? Do the authors have any physiological data? The addition of such data (e.g., metabolic markers, etc.) would strengthen the conclusion that RSV has health benefits.

In addition, the focus on males carries important limitations that should be clearly acknowledged. For example, the title should clarify that the study was only done in males (e.g., "in male grey mouse lemurs"), and the conclusion in the abstract should state that the effects only apply to males.

Other

Add asterisks to show statistical significance on graphs.

Wording suggestions for improved clarity

l. 10 such as non-human primates

l. 14 "with part" replace "with a subset"

l. 19 replace "situation" by "group"

l. 39 replace "indecisive" by "uncertain"

l. 47 in laboratory controlled conditions?

l. 48 sensory system

l. 57 specify the % of caloric restriction

l. 59 cognitive performance

- I. 63-66 specify if this is a standard diet for grey mouse lemurs
- I. 83 cognitive performance was
- I. 88 RSV animals had about half the number of errors and time
- I. 159-161 specify that the effects only apply to males

Reviewer #2

(Remarks to the Author)

Chronic resveratrol supplementation has health benefits during aging but does not mimic 1 the positive effects of calorie restriction on lifespan in a non-human primate
Comm Biol

This study assesses the effect of the popular polyphenol resveratrol at a dose of 200 mg/kg on cognitive and motor performance, as well as lifespan and aging-related CNS pathology in a non-human primate model – the male grey mouse lemur. At middle-age, the study found that resveratrol-treated animals had better cognitive and motor performance than controls. Median lifespan was greater in the resveratrol-treated group (7.9 years) than the control group (6.4 years). However, there was no difference in either all-cause mortality or aging-related mortality. A potentially important finding was acceleration of grey matter atrophy in the resveratrol treated group.

Despite basing the dose of resveratrol on literature searches to find what dose might be optimal, the dose seems to be based on that used in rodent models. There have been studies showing that doses of various dietary supplements used for rodent studies should not be applied to humans, and that in humans a much lower dose would be appropriate. So, I wonder if the same may apply to lemurs? Obviously, repeating the study with a range of doses would be burdensome. Instead, the authors should discuss this issue as a limitation of their study, and include suitable references.

Specific comments follow, presented line-by-line from start to finish.

Line: Comment

- 14: Change to "18 of the animals receiving resveratrol (200 mg/kg body weight) as well.
- 16, 17, 19 and throughout: I cannot see the point of using the abbreviation "CTL" for "control". It does not reduce number of words, now space. The same applies to abbreviating "resveratrol" to "RSV".
- 26: It is not true that CR is the only non-genetic intervention that increases lifespan. Intermittent fasting and restriction of particular amino acids such as aromatic amino acids and those with long branched chains also extend lifespan. I suggest changing "only" to "most effective".
- 28: Change "as" to "an"
- 29: Ref(s) needed after "human"
- 31: Change "II" to "2"
- 33: Change to "CR mimetics has increased significantly"
- 35: Resveratrol is not "abundant" in wine. I recall David Sinclair at Harvard stating that to get an effective dose of resveratrol from wine one would have to consume an amount of wine that would be lethal. And of course, because resveratrol is found in the skin of grapes, only red wines have it. Therefore, please delete "and wine". Instead, you should mention other natural sources of resveratrol.
- 37: Surely you mean "The CR mimetic action of resveratrol". Please correct.
- 39: Please replace "somehow indecisive" with "somewhat unclear".
- 42, 44, 68, 69: "–1 needs to be shown as a superscript rather than as plain text.
- 45: "the" needed before "health"
- 46: I think that you mean "median lifespan" rather than "half-life".
- 47: Change "highly relevant" to "very suitable".
- 54: insert a comma after "heterogeneous".
- 55: Change "reduced" to "lower".
- 57: Since "calorie restriction" has already been assigned an abbreviation, please change to "CR".
- 58: Change to "(by up to 13.8 years of age)".
- 59: I think that "however" can be deleted.
- 59-62: Change to "The aim of the present study is to provide the" And start a new paragraph.
- 63-71: Please move this paragraph to the Methods section. It does not belong here.
- 69: Change to "body weight, lifespan".
- 75: Please correct the grammatical error, where it should be noted that correct English requires that the word "however" must never be used as a conjunction. Instead, a new sentence must be used. Thus, change the text to "... respectively). However, the maximum ..."
- 85: Insert a comma after "... 0.03)"
- 87: Change to "after 6 years of age".
- 88: I think you mean "... animals made half as many errors and took half the time to..."
- 89: Change to "after the age of 6 years".
- 90: Change to "which is in contrast to results ..."
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- 96: Change to the singular: "performance".
- 97: Change "in" to "using" or "by".

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 144: Change to "demonstrated".
 147: Change to "the dose of RSV we tested" (and using "resveratrol" instead of "RSV").
 152: Instead of "measurable" do you mean "detectable"?
 159: Change "procures" to "results in".
 166: Change to "body weight".
 166–177: Change the position of (a), (b), (c) and (d) so that they precede rather than follow the text each refers to.
 At the bottom of the Figure, there is plenty of room for "Control" and "Resveratrol: instead of "CTL" and "RSV".
 169, 172: Thus "CTL" here can be deleted.
 170, 173: And "RSV" can be changed to "resveratrol".
 190-201: Same changes as above are required in Fig. 2 and legend to Fig. 2.
 Legends to Fig. 3 and Fig. 4 (line numbers missing): Same applies to these legends.
 320: Change "old" to "of age".
 321: Change to "and they weighed".
 327: In this context, the usual term is "fruit" not "fruits" (a common error for some whose primary language is not English).
 323: Change "given" to "provided".
 328: Change to "All of the".
 329: Change to "during the summer, i.e., when ...".
 332, 333: delete "(CTL)" and "CRSV".
 334: Change to "weight". Change "dosage" to "dose".
 335: Add "doses of" at end of line.
 338: Good to see "fruit" here.
 347-348: Do you mean "so risking head injury"?
 353: Change to "watt".
 361: Change to "was comprised of".
 373: Change "right" to "correct".
 383: Insert "which was" before "motor-driven".
 388: Insert "for". Thus text becomes "for more than one".
 391: Change to "was then used in the calculation of high".
 392: "cleant"? – seems to be a typographic error. If so, please fix.
 410: The following does not make sense to me: "1_0_c_m_ = _1_ ; _2_0_c_m_ = _2_ ; ; _1_0_0_c_m_ = _1_0_". Please address my concerns.
 414: I am confused by "See attached .rtf document". What's this about?
 424: Change "on" to "from" – text becomes "from each animal".
 433: Change to "The residuals of each model were checked for normality by".
 436: Change to "over the years of the study ..." Or something else more appropriate if necessary.
 437: Change to "the" package.
 448: I cannot understand what you mean by "what does not allow statistical analysis". Please fix.
 461-462 Table: Change "T" to "t".
 463-464 Supplementary Tables 2 and 3: Same comment: Change "T" to "t".
 465-466: Supplementary Tables 4 and 5: Same comment: Change "T" to "t".

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

Reviewer #2

(Remarks to the Author)

OK, I agree to sign.

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Answers to reviewers.

We would like to thank both reviewers and the editor of Communications Biology for their positive comments and fruitful remarks on our manuscript. We have tried to take them into account and believe it improves the manuscript. Please find below specific answers to your comments. For more clarity, our answers appear in [blue](#) and citations of the manuscript in *italic blue*.

Reviewers' comments:

Reviewer #1 (Remarks to the Author):

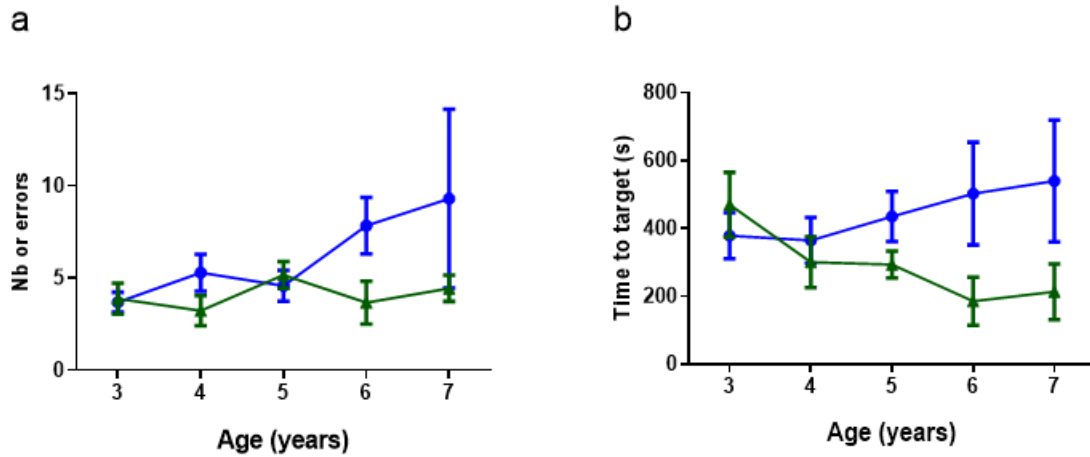
This paper examines whether Resveratrol (RSV) mimics the effects of caloric restriction on health and longevity in a nonhuman primate, the grey mouse lemur. Animals (n= 33) were assigned to either a standard diet or the diet supplemented with a medium (200 mg/kg) dose of RSV (n=18) and tested longitudinally for cognitive function (Barnes maze) and motor function (rotarod) from middle-age to death. RSV-treated animals had better cognitive and motor function and greater median lifespan than controls, but mortality was not affected. However, grey matter cerebral atrophy was greater in the RSV group than CTL group. The authors conclude that long-term RSV supplementation has health benefits in middle-age but limited effects on longevity, with potential adverse effects on brain integrity in old age.

There are many strengths in this paper, including the relatively large number of animals, the longitudinal assessments, the careful consideration of the RSV dose and the survival analysis. The presentation of the results is very clear and the paper is generally well written.

[Thanks a lot for these very positive comments!](#)

My main concern is with the interpretation of the cognitive results. The conclusion that cognition was enhanced in RSV-treated lemurs is based on the performance on a single cognitive task, the Barnes maze. RSV animals were faster than CTL in the Barnes maze task, but this effect likely reflected better motor skills, as measured by the rotarod and high jump tasks. Although RSV animals also committed fewer errors, it seems that this effect could entirely be explained by the animals being faster (due to enhanced motor, not cognitive function). One way to rule this out would be to compare the RSV and CTL groups on the number of errors relative to time (e.g., errors/minute). In the absence of such a comparison or an additional cognitive task, the conclusion that RSV provided cognitive benefits is premature. As a result, **the discussion should be edited to reflect this point**. It would also be useful to **comment on the neural substrates underlying the Barnes maze task and associated performance**.

[Your remarks are of interest. However, the latency to find the exit should not be read as an indication of the animals' speed but rather as a marker of the time spent in the apparatus and therefore as a proxy of the number of visits. Indeed, and as you can see in our results \(see below\), both parameters follow the same pattern between treatments and throughout time. This is due to the fact that when a given animal finds the correct exit after a few errors, the time spent in the apparatus is generally shorter. On the contrary, when an animal visits more holes and thus makes more errors, it consequently spends more time in the apparatus.](#)



This is consistent with the literature in rodents, such as in the paper of O'Leary in 2012 ("The effects of apparatus design and test procedure on learning and memory performance of mice on the Barnes maze"; Journal of Neuroscience Methods):

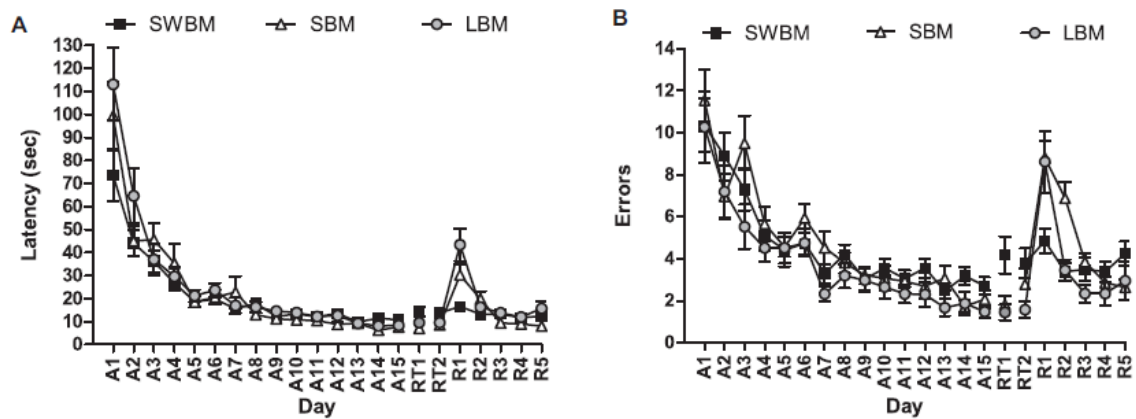
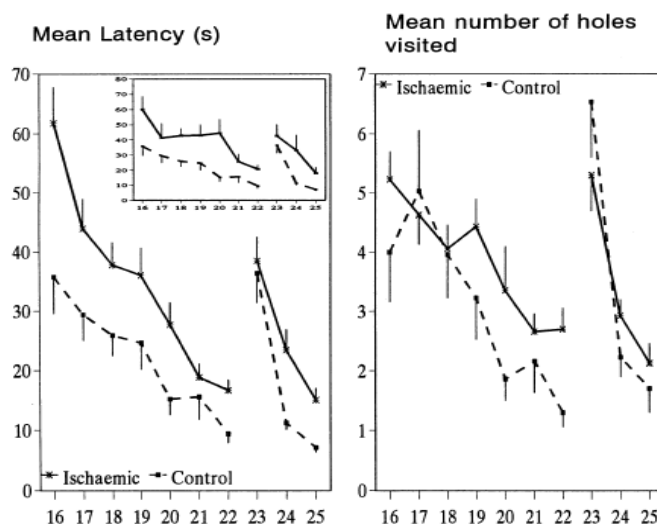


Fig. 1. Mean ($\pm$ SEM) latency (s) to enter the escape hole (A) and errors (B) made on the SWBM, SBM, and LBM, over acquisition (A1–A15) training, re-training days (RT1–RT2) following probe trials, and reversal (R1–R5) training.

Same observations were also made by Milani in 1998 ("Loss of CA1 cells following global ischemia correlates with spatial deficits in the circular platform task"; Journal of Neuroscience Methods):



This being said, you raised two very interesting points. 1) It is exact that our conclusion that cognition was enhanced in RSV group is based on the performance in a single cognitive task (i.e. Barnes Maze task); 2) Data from motor tasks show an improvement of motor performances and we thus cannot completely exclude that performances in the Barnes maze could partly be due to better motor condition.

Thus, as suggested, we edited the discussion to reflect these points and mitigate our conclusions on cognitive performance (lines 147-158):

It is highly probable that better motor performances rely more on better preservation of muscle strength than on brain modifications. Decline in muscle strength, as well as in motor coordination (assessed in the rotarod task) starts around 4 years old in mouse lemurs^{17 30}, an age at which animals are still considered young¹⁶. Interestingly, RSV was described as being able to reduce age-associated muscle loss in rodents³¹, suggesting that beneficial effects of RSV on motor performances during aging may rely more on reduced muscle loss than on brain atrophy. As a consequence, we cannot completely exclude that part of the better performance in the Barnes maze task in the RSV group relies on better motor condition. In addition, the observation of better cognitive performances under RSV supplementation is based on a single cognitive task (Barnes maze task, assessing mostly spatial reference memory and working memory). Additional tests to assess other cognitive domains may have led to other conclusions.

The MS would also be improved by discussing the **potential functional significance of the MRI findings**. How do the behavioral measures relate to the MRI findings? are there any neural correlates of better motor function in the RSV group?

Unfortunately, behavioral measurements and MRI findings were not performed in the same time window. Cognitive and motor measurements were performed until 7 years old and MRI study started at the age of 7. At this age, there was no significant differences in MRI results (grey and white matter) between the two groups, except very focal lower grey matter volume in the primary motor cortex in CTL animals (very small spot, see figure 3a,b). Such a spot cannot explain by itself the differences observed in motor and cognitive performances.

As discussed above (and now included in the manuscript) we concur with the reviewer that better motor performances rely more on muscle strength/performance than on brain modifications. Muscle strength loss starts around 4 years old in mouse lemurs, an age at which animals are considered young (Losing grip: Senescent decline in physical strength in a small-bodied primate in captivity and in the wild. Hämäläinen 2015). At this age, performance in the rotarod task (used in our study to assess motor performances) starts declining (Physical activity and balance performance as a function of age in a prosimian primate (*Microcebus murinus*), Nemoz-Bertholet, 2003). Interestingly, RSV is described as being able to reduce age-associated muscle loss in rodents (Resveratrol, a SIRT1 activator, attenuates aging-associated alterations in skeletal muscle and heart in mice (Ryusuke Hosoda, 2023). It is thus very likely that beneficial effects of RSV on motor performances rely more on reduced muscle loss than on brain/MRI correlates.

Taking your comment into account, we decided to improve the discussion by adding a few sentences about the potential functional significance of MRI findings (lines 138-158):

Differences observed on brain atrophy did not seem to be associated either with measurable cognitive impairments, nor with motor deficits. However, a caution note should be made for the interpretation of such lack of association, as behavioral and MRI measurements were not performed in the same time

window. Indeed, cognitive and motor measurements were performed until 7 years old while MRI study started at the age of 7. At that age, there was no significant difference in grey and white matter volumes between the two groups, except very focal lower grey matter volume in the primary motor cortex in CTL animals (very small spot, see figure 3a,b), which cannot explain by itself the differences observed in motor and cognitive performances between CTL and RSV animals. It is highly probable that better motor performances rely more on better preservation of muscle strength than on brain modifications. Decline in muscle strength, as well as in motor coordination (assessed in the rotarod task), starts around 4 years old in mouse lemurs^{17,30}, an age at which animals are still considered young¹⁶. Interestingly, RSV was described as being able to reduce age-associated muscle loss in rodents³¹, suggesting that beneficial effects of RSV on motor performances during aging may rely more on reduced muscle loss than on brain atrophy. As a consequence, we cannot completely exclude that part of the better performance in the Barnes maze task in the RSV group relies on better motor condition. In addition, the observation of better cognitive performances under RSV supplementation is based on a single cognitive task (Barnes maze task, assessing mostly spatial reference memory and working memory). Additional tests to assess other cognitive domains may have led to other conclusions.

Do the authors have any **physiological data**? The addition of such data (e.g., metabolic markers, etc.) would strengthen the conclusion that RSV has health benefits.

We have recorded some physiological data during the course of the study. However, since the current article was built as a “mirror paper” of the caloric restriction article (Pifferi et al. Comm Biol 2018), we decided not to include them. Most of them were obtained during the first years of the treatments and thus do not directly or well correlate with cognition and MRI data. These data will be published in a more appropriate way in an article with direct comparison with caloric restriction data.

In addition, the focus on **males** carry important limitations that should be clearly acknowledged. For example, the **title** should clarify that the study was only done in males (e.g., “in male grey mouse lemurs”), **and the conclusion in the abstract** should state that the effects only apply to males.

This is exact and we now indicate it accordingly. Please also note that the following sentence is included at the end of the discussion section (lines 175-178):

Finally, it must be noted that the present study focused on males, and we cannot rule out the possibility of a differential effect on health or longevity outcomes between males and females as observed with RSV³³ or CR³⁴ in humans.

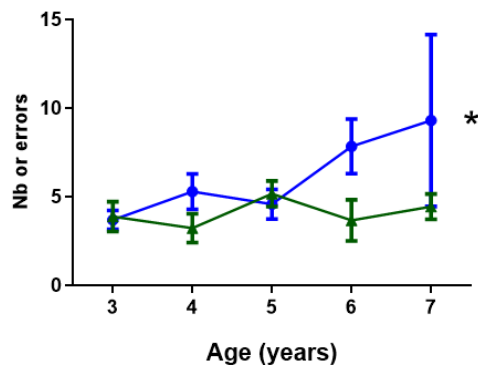
Other

Add asterisks to show statistical significance on graphs.

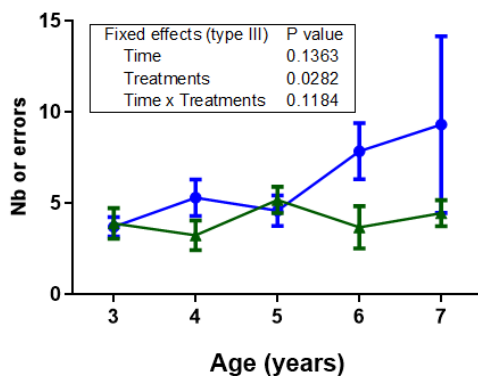
Statistical analyses were performed on the basis of mixed-effects analysis, to describe the general effects of time, treatments and time x treatments. Post-hoc tests could not be performed since the number of animals within each group over the duration of the experiment was too low to reach sufficient statistical power (more specifically the last two years of follow-up). Thus, if showing asterisks, they would only show significance of fixed effects (Treatment and Time – option 1 below), without really discriminating between those. Another option would be to add a table describing the effects observed (Option 2 below), but we are not very favorable for that as the reading of the figures would somehow be quite a bit complexified. In addition, the statistics are included in the result section and the legends of the figures. We thus propose not to modify the figures, but will

follow the opinion of the editor about the relevance of changing them or not (please specify which option best meets the criteria).

Option 1:



Option 2:



Wording suggestions for improved clarity

All the suggestions below have been approved and modified consequently

- l. 10 such as non-human primates
- l. 14 "with part" replace "with a subset"
- l. 19 replace "situation" by "group"
- l. 39 replace "indecisive" by "uncertain"
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Reviewer #2 (Remarks to the Author):

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Despite basing the dose of resveratrol on literature searches to find what **dose** might be optimal, the dose seems to be based on that used in rodent models. There have been studies showing that doses of various dietary supplements used for rodent studies should not be applied to humans, and that in humans a much lower dose would be appropriate. So, I wonder if the same may apply to lemurs? Obviously, repeating the study with a range of doses would be burdensome. Instead, the authors should **discuss this issue as a limitation of their study, and include suitable references.**

As mentioned, it was impossible for us to test a range of doses, given the limited number of animals we were able to treat at the same time. Concerning the dose selection (bases on rodent models), one should remember that the study was designed in 2005, a time at which very little was known about RSV and more specifically about its adverse effects or correct dose. Thus, the dose we selected was considered appropriate, based on rodents' studies, at the beginning of our experiment (in 2006). Studies about dosage in humans were issued much later the start of our life-long experiment. However, this is a limitation of our study and we have tried to discuss it better in the revised version of the manuscript and have updated the related references:

Recent observations in humans suggest that RSV might be efficient at much lower doses (between 500mg and 1g/day for an adult, what would mean a dose between 7.15 and 14.3 mg/kg.day⁻¹ if we consider a 70 kg human adult³¹). Such a low dose, compared to high doses commonly applied in rodents¹² and the current study, could limit the potential adverse effects of RSV^{14,32}.

Specific comments follow, presented line-by-line from start to finish.

Line: Comment

14: Change to "18 of the animals receiving resveratrol (200 mg/kg body weight) as well.

Done

16, 17, 19 and throughout: I cannot see the point of using the abbreviation "CTL" for "control". It does not reduce number of words, now space. The same applies to abbreviating "resveratrol" to "RSV".

We decided to use abbreviations for both control and resveratrol to reduce space and also to be consistent with our previous publications using same groups/interventions¹⁻⁶. Thus, if the reviewers

and editor do consider this is mandatory, we will use the full words. If not mandatory we preferably would like to keep using the abbreviation for both words.

26: It is not true that CR is the only non-genetic intervention that increases lifespan. Intermittent fasting and restriction of particular amino acids such as aromatic amino acids and those with long branched chains also extend lifespan. I suggest changing “only” to “most effective”.

Done

28: Change “as” to “an” Done

29: Ref(s) needed after “human”

The reference [Front Nutr. 2024 Jun 12;11:1408651. 2024.Multidimensional biological activities of resveratrol and its prospects and challenges in the health field Xi Yu 1 , Yuanqiang Jia 1 , Feiyue Ren 1] has been added.

31: Change “II” to “2” Done

33: Change to “CR mimetics has increased significantly” Done

35: Resveratrol is not “abundant” in wine. I recall David Sinclair at Harvard stating that to get an effective dose of resveratrol from wine one would have to consume an amount of wine that would be lethal. And of course, because resveratrol is found in the skin of grapes, only red wines have it. Therefore, please delete “and wine”. Instead, you should **mention other natural sources of resveratrol**.

Thank you for your remark, we deleted wine and now mention peanuts, berries and grapes

37: Surely you mean “The CR mimetic action of resveratrol”. Please correct. Done

39: Please replace “somehow indecisive” with “somewhat unclear”. Done

42, 44, 68, 69: “–1 needs to be shown as a superscript rather than as plain text. Done

45: “the” needed before “health” Done

46: I think that you mean “median lifespan” rather than “half-life”.

Yes, we meant “median lifespan” and changed it accordingly

47: Change “highly relevant” to “very suitable”. Done

54: insert a comma after “heterogeneous”. Done

55: Change “reduced” to “lower”. Done

57: Since “calorie restriction” has already been assigned an abbreviation, please change to “CR”. Done

58: Change to “(by up to 13.8 years of age)”. Done

59: I think that “however” can be deleted. Done

59-62: Change to “The aim of the present study is to provide the” And start a new paragraph. Done

63-71: Please move this paragraph to the Methods section. It does not belong here.

Since all the information contained in this paragraph is already present in the methods section, we decided to remove it here.

69: Change to “body weight, lifespan”. [Done](#)

75: Please correct the grammatical error, where it should be noted that correct English requires that the word “however” must never be used as a conjunction. Instead, a new sentence must be used. Thus, change the text to “... respectively). However, the maximum ...” [Done](#)

85: Insert a comma after “... 0.03)” [Done](#)

87: Change to “after 6 years of age”. [Done](#)

88: I think you mean “... animals made half as many errors and took half the time to...” [Done](#)

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142-143: Change to “groups, with the RSV-treated group displaying ...” [Done](#)

144: Change to “demonstrated”. [Done](#)

147: Change to “the dose of RSV we tested” (and using “resveratrol” instead of “RSV”). [Done](#), but as suggested after your second comment, we prefer to keep using the abbreviation for RSV.

152: Instead of “measurable” do you mean “detectable”?

Yes. “measurable” was thus changed to “detectable”.

159: Change “procures” to “results in”. [Done](#)

166: Change to “body weight”. [Done](#)

166–177: Change the position of (a), (b), (c) and (d) so that they precede rather than follow the text each refers to. [Done](#)

At the bottom of the Figure, there is plenty of room for “Control” and “Resveratrol: instead of “CTL” and “RSV”. [See our answer to your second remark concerning abbreviations use.](#)

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170, 173: And “RSV” can be changed to “resveratrol”. [See our answer to your second remark concerning abbreviations use.](#)

190-201: Same changes as above are required in Fig. 2 and legend to Fig. 2. [Done](#)

Legends to Fig. 3 and Fig. 4 (line numbers missing): Same applies to these legends. [Done](#)

320: Change “old” to “of age” [Done](#)
321: Change to “and they weighed” [Done](#)
327: In this context, the usual term is “fruit” not “fruits” (a common error for some whose primary language is not English). [Thanks for the help with English improvement!](#)
323: Change “given” to “provided”. [Done](#)
328: Change to “All of the”. [Done](#)
329: Change to “during the summer, i.e., when ...” [Done](#)
332, 333: delete “(CTL)” and “CRSV)” [Done](#)
334: Change to “weight”. Change “dosage” to “dose”. [Done](#)
335: Add “doses of” at end of line. [Done](#)
338: Good to see “fruit” here. [Thanks!](#)
347-348: Do you mean “so risking head injury”?

[No, the black plywood box was placed beneath the non-target holes to prevent exiting the apparatus through a non-target exit. We changed this sentence for clarification:](#)

[A small black plywood box was placed beneath the other \(non-target\) holes to prevent lemurs exiting the apparatus through a non-target exit.](#)

353: Change to “watt”. [Done](#)
361: Change to “was comprised of”. [Done](#)
373: Change “right” to “correct”. [Done](#)
383: Insert “which was” before “motor-driven”. [Done](#)
388: Insert “for”. Thus text becomes “for more than one” [Done](#)
391: Change to “was then used in the calculation of high”. [Done](#)
392: “cleant”? – seems to be a typographic error. If so, please fix. [Done](#)
410: The following does not make sense to me: “1_0_c_m_=_1_ ;_2_0_c_m_=_2_ ;_... _ ;_1_0_0_c_m_=_1_0_.”. Please address my concerns. [Done](#)
414: I am confused by “See attached .rtf document”. What’s this about?

[The attached .rtf document was corresponding to MRI material and methods and could not be included due to a formula that did not fit the word format. It is now changed and included in the material and methods section \(lines 432-518\).](#)

424: Change “on” to “from” – text becomes “from each animal”. [Done](#)
433: Change to “The residuals of each model were checked for normality by” [Done](#)
436: Change to “over the years of the study ...” Or something else more appropriate if necessary. [Done](#)
437: Change to “the” package. [Done](#)
448: I cannot understand what you mean by “what does not allow statistical analysis”. Please fix.

[Since one survival curve translates into one value of median lifespan, then it is not possible to statistically compare the median lifespan of the two groups. The information of median lifespan is here purely descriptive. To clarify this point we decided to remove this sentence that led to misunderstanding.](#)

461-462 Table: Change “T” to “t”. [Done](#)
463-464 Supplementary Tables 2 and 3: Same comment: Change “T” to “t”. [Done](#)
465-466: Supplementary Tables 4 and 5: Same comment: Change “T” to “t”. [Done](#)

