nature portfolio

Peer Review File

Cardiovascular Risks and Hazards Associated with Deep Space Exploration

Corresponding Author: Professor David Goukassian

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)
The authors have organized a review article focusing on spaceflight adaptations of astronauts, focusing on cardiovascular adaptations, and how different environmental factors (eg. microgravity, radiation, etc.), as it relates with different mission scenarios, in particular deep space exploration missions, may influence astronaut health.

They cover recent research and new relevant topics as well, including sleep deprivation, circadian desynchrony, isolation and confinement, and factors relevant to multi-year missions to Mars.

This is a timely and concise article, that will benefit the field and provide relevant knowledge on the topic for researchers interested in these areas.

Reviewer #2

(Remarks to the Author)
summary and overall impression of the manuscript:

This manuscript provides a review of cardiovascular risks associated with deep space exploration, with a particular focus on long-duration missions beyond low Earth orbit. The authors align their framework with NASA's Human Research Program by organizing the review around the five space flight hazards defined by NASA with the addition of nutrition and extend it to CV pathophysiology. In doing so, the authors synthesize evidence from astronaut epidemiology, in-flight physiological observations, ground-based analog studies, and mechanistic animal models to describe how space radiation, altered gravity, sleep disruption, isolation, and nutritional limitations may contribute to cardiovascular disease risk. The review places these findings within the context of future lunar and Mars missions, highlighting operational constraints, current countermeasures, and gaps in knowledge that must be addressed to ensure astronaut health during exploration-class missions.
The manuscript provides a comprehensive overview of cardiovascular risks associated with spaceflight and summarizes a broad range of relevant mechanistic findings. A major strength is its hazard-specific approach by presenting different cardiovascular disease and outcomes in relation to distinct spaceflight stressors and reviewing findings from both astronaut cohorts and experimental studies. However, the presentation would benefit from improved organizational clarity, particularly in distinguishing human epidemiologic and clinical observations from mechanistic evidence derived from animal models and experimental systems. At present, the evidence discussed are occasionally conflated, which can make the it obscure and hard to interpretate.
Additionally, while cardiovascular risks associated with short-duration and low Earth orbit (LEO) missions are discussed, there is limited differentiation between these environments and the distinct hazard profile anticipated for deep space missions. Given the manuscript's emphasis on future lunar and Mars exploration, clearer separation of LEO-derived observations from deep space–relevant risk extrapolations would improve coherence and mission relevance.
Finally, the review does not sufficiently address NASA's established methodological approach to assessing health risks in the absence of definitive epidemiologic data. In particular, it omits discussion of probabilistic risk-modeling frameworks currently used for space radiation–induced cancer risk and being explored for other health hazards. These approaches integrate terrestrial epidemiology, mechanistic and animal data, Galactic Cosmic Ray simulation studies, and explicit uncertainty quantification to inform decision-making for long-duration deep space missions. Incorporating this perspective,

with appropriate supporting literatures, is needed to strengthen the translational and operational relevance as it pertains to NASA's mission planning and Human Research current framework.
Overall, this is a timely and valuable review given NASA's preparation for future lunar and Mars missions, as well as the growing role of commercial spaceflight. Cardiovascular disease represents a recognized health risk in spaceflight, and this manuscript provides a useful overview of current knowledge. However, revisions are needed to improve clarity, strengthen organizational structure, and more explicitly address NASA's existing strategies for cardiovascular risk assessment and management under uncertainty and lack of statistical data.
Specific Comments

1. Several statements require clear referencing of the sources. For example:
• On page 6, the statement "Supporting animal studies employed acute, high-dose HZE irradiation (1 Gy at 10 cGy/min)" is presented without an accompanying reference.
• On page 8, the claim describing "~20% loss of cardiac muscle, leading to reduced cardiac function" lacks a cited source.
• A few additional instances of insufficient or unclear referencing appear in the manuscript, so they need to be properly referenced.

2. Minor comment: The manuscript is generally well written; however, several minor typographical and grammatical errors should be corrected. For example:
• Page 6: "which is differs significantly" should read "which differs significantly."
• End of page 6: "enchancing" should be corrected to "enhancing."

3. On page 6, the discussion of limitations related to dose rate and exposure duration would benefit from additional context. Similar constraints exist in space radiation cancer risk assessment, where correction factors and uncertainty modeling are routinely applied, and the data remain operationally useful. Explicitly acknowledging this parallel would provide a more balanced perspective on how cardiovascular radiation data might still inform risk assessment despite these limitations.
4. The final paragraph on page 7 may inadvertently conflate uncertainty in existing astronaut epidemiologic studies with uncertainty regarding long-duration deep space cardiovascular risk. Given that human epidemiologic data are either insufficient or lacking for long-duration lunar or Mars mission scenarios, this limitation should be explicitly discussed to avoid misinterpretation of LEO-derived findings as directly informative for deep space missions.
5. On page 8, the statement "current evidence should be interpreted as hypothesis-generating rather than conclusive, underscoring the need for large-scale, longitudinal studies using realistic spaceflight exposure models." is appropriate; however, the proposed path forward emphasizes large-scale longitudinal studies that are unlikely to be feasible for deep space missions. This framing overlooks existing probabilistic risk-modeling frameworks used by NASA to evaluate cancer risk under similar constraints. Incorporating discussion of these approaches would provide a more realistic and actionable path forward.
6. Definition of "Distance from Earth" as a Hazard: As written, the first few paragraphs of "Distance from Earth" section (beginning on page 10) primarily serves as a proxy for space radiation exposure. While the content itself is not incorrect, the framing is potentially misleading. NASA formally defines "distance from Earth" as a hazard encompassing logistical and operational challenges, including communication delays, medical autonomy, supply limitations, and so forth. Space radiation is treated as a distinct hazard and is already addressed elsewhere in the manuscript. Therefore, this section needs to be restructured to align with NASA's formal hazard definition and the space radiation content should be relocated to radiation-specific content later in the manuscript.
7. In the first paragraph on page 11 (after properly moving it to the Space Radiation section), discussion of permissible exposure limits would benefit from clarification regarding how cardiovascular risk limits are assessed differently from cancer risk limits. This distinction is already discussed in Patel et al. (2012) and would help contextualize NASA's current risk management strategy.

8. On page 12 and in the general discussion, socioeconomic risk factors are mentioned, but smoking status is not sufficiently emphasized. Given that NASA applies non-smoker (NS) corrections when estimating cancer risk to reflect astronaut health profiles, and that smoking is a major contributor to cardiovascular disease, additional discussion is warranted when comparing astronaut cardiovascular risk to that of the general population.
9. Within the Space Radiation section, the manuscript would benefit from a brief discussion of how NASA's current radiation risk framework incorporates terrestrial epidemiologic data—particularly from atomic bomb survivor studies and large occupational cohorts—to estimate excess radiation risk. Studies such as the Million Person Study are highly relevant and should be acknowledged when discussing cardiovascular radiation risk extrapolation, and how a similar strategy can be applied when assessing cardiovascular risk.

10. The discussion of radiation-associated cardiovascular risk would be strengthened by inclusion of excess relative risk modeling approaches and in particular inclusion and discussion of and the following key references are recommended:
• Little MP. Radiation and circulatory disease. Mutation Research (2016).
• Boerma M et al. Radiation-induced heart disease: mechanisms and models. Radiation Research.
• Huff et al. Cardiovascular Disease Risk Modeling for Astronauts: Making the Leap From Earth to Space. Frontiers in Cardiovascular Medicine (2022).

11. In the section "Insights into Risks of Multi-Year Mars Missions" (page 29), as well as in the conclusions and future directions, the manuscript should more explicitly discuss NASA's recommended strategy of probabilistic risk modeling and integration into frameworks such as REID and the broader space radiation risk architecture. The approaches outlined in Huff et al. and Patel et al. provide an appropriate foundation and should be emphasized, and risk models such as Astro-CHARM (Khera A et. al. Circulation., 2018).

12. While briefly mentioned, the manuscript will benefit in more detailed discussion of individual hazards compared to other hazards and also more discussion on the combined effect.
13. Across multiple sections, mechanistic findings are presented alongside observational data without consistently distinguishing hypothesis generation from inputs to operational risk assessment. Clarifying this distinction would improve interpretability and align the review more closely with NASA's decision-making framework.

Reviewer #3

(Remarks to the Author)
The authors present a review of cardiovascular risks associated with spaceflight, with emphasis on relevant literature for anticipated effects of long-duration exploration missions. The topic is interesting, but several deficiencies preclude publication in its current state. Specific issues that should be addressed, in the opinion of this reviewer, are identified as follows.

1. (Major) Page 5, Table 1 - An "intermediate" category should be included in the table. As is, the table implies that there are no cardiovascular risks between the end of the spaceflight and months after the career ends.
2. (Major) Throughout - While some citations are provided, there are many statements in the manuscript that must be supported with cited literature. The authors are encouraged to carefully review the manuscript and add citations as appropriate. As an example, the authors mention the Delp et al. study on page 5, but there is no citation for this study included here.
3. (Minor) Page 7 - Authors reference "large" cohort studies of astronauts. Given the relatively small number of humans who have traveled in space, the authors must clarify what is meant here.
4. (Minor) Page 7 - Authors reference "Soviet and Russian cosmonauts". The reviewer considers this to be redundant, since cosmonauts are by definition Soviet or Russian.
5. (Major) Page 10 - Item 1, "Distance from Earth", is only relevant in the context of the actual environmental exposures associated with distance from Earth. The discussion in this subsection largely addresses space radiation, which is redundant with respect to Subsection 3. The authors should consider condensing these two subsections into a single subsection on space radiation.
6. (Major) Page 10 - The authors should clarify whether the fraction of "radiation dose-equivalent" attributed to HZE particles, and specifically to iron particles, refers to the boundary condition radiation field or to the actual particles interacting with human cells. The reviewer's understanding is that virtually no iron particles reach human cells due to fragmentation with vehicular and/or astronaut body self-shielding.
7. (Major) Page 10 - The authors refer to "protocols focused on minimizing time spent around the source of IR, maximizing distance to the source, and using shielding methods" as key components of NASA's space radiation protection program. In fact, these are general principles used in terrestrial radiation protection and largely inapplicable to NASA's space radiation protection program. The stated principles are mostly useful in planned exposure situations, and NASA is compelled to address an existing exposure situation for which source-focused controls are mostly ineffective.
8. (Major) Page 12 - The authors refer to "1-3 year journeys to Mars". The Mars Design Reference Mission (DRM) consists of a 9-month journey to Mars, a 12-month surface stay, and a 9-month return journey to Earth. The authors should use more precise language in describing a Mars mission. It is highly unlikely that a journey to Mars would exceed 12 months.
9. (Minor) Page 12 - Two consecutive sentences begin with the word "Therefore". Please reword to avoid this.
10. (Major) Page 13 - The authors make the somewhat pedantic point that "Most missions within LEO remain within 90% of Earth's ground-level gravity", yet then state that there is an "absence of gravitational forces", two statements that seem to be in opposition. Indeed, weightlessness is not caused by an absence of gravitational forces but rather by the presence of those gravitational forces. It is really the weightlessness that causes human health effects and so the reviewer recommends that the authors emphasize this.
11. (Major) Page 17 - The authors claim that dysautonomia experienced by astronauts is potentially caused by radiation exposure. Given that nervous system damage is typically noted only at very high doses (> 20 Gy) of terrestrial radiation, the reviewer highly doubts that space radiation could cause such an effect. This statement must be more thoroughly justified by explanation and corresponding citation of peer-reviewed literature.
12. (Major) Page 17 - The authors state that "Primary GCRs can produce secondary particles through projection and target fragmentation, causing varied responses and degrees of DNA damage compared to IR with dense linear tracts". This sentence is confusing. The authors presumably mean "projectile" instead of "projection" and "tracks" instead of "tracts". Additionally, secondary particles resulting from primary GCR interactions typically do produce dense linear tracks, but the statement seems to indicate the opposite. Please clarify this.
13. (Major) Page 18 - The description of the origin of solar energetic protons is far too simplistic. It is not accepted that these particles are merely "emitted during solar flares". The authors are encouraged to mature this explanation. Furthermore, it is not true that "solar flares are predictable to a certain degree".
14. (Major) Page 19 - The authors do not discuss the occurrence of CV risks in the Atomic Bomb Survivor cohort or the various worker cohort studies (i.e., INWORKS or Million Person Study). These studies are likely to be far more applicable to the astronaut/cosmonaut population than are patient cohort studies.
15. (Minor) Page 22 - The authors state that astronauts "sleep only approximately 6 hours per night". The reviewer recommends that authors describe this as sleep per day rather than per night, since one day is a clearly defined time period, whereas the definition of "night" is nebulous.
16. (Major) Page 24 - The authors state that the 24.65-hour circadian clock on Mars is "not conducive to normal human rhythms." Is it really true that a difference of approximately 30 minutes is that biologically significant? If yes, then it behooves the authors to further explain this, since at first glance, this is a small difference.

17. (Major) Page 24 - The authors transition from Subsection 4 on "Sleep deprivation and circadian desynchrony" directly into a section on VO2max with no new subsection. It seems that a new subsection on this topic should start here.
18. (Major) Page 25 - Similarly, the authors begin a discussion of the effects of "absence of gravity" on the ISS, seemingly under Subsection 4. Additionally, the authors should note that statement this is in direct contradiction to the point made earlier that it is weightlessness and not necessarily absence of gravity that produces deleterious human health effects.
19. (Major) Page 26 - The authors declare that "Isolation and confinement are nonmodifiable factors..." With the increasing use of virtual reality and augmented reality approaches, the authors should reflect on whether their statement is so surely true.
20. (Major) Page 30 - Again the authors reference "the prolonged transit (~3 years)" for Mars missions. It is highly unlikely that such a mission design would be employed.
21. (Minor) Page 33 - The authors should consider whether the quote from Cernan is required for the article. The final two sentences do not seem to add to the scientific value of the manuscript.
22. (Major) Figure 2 - Several aspects of this figure can be improved. This figure seems to show the trapped radiation belts as well-defined lines, which they are not. The figure is already not to scale, so the Moon and Mars might be made larger. Finally, and most importantly, the ionizing radiation field is shown as normally incident and inexplicably shielded by the outer Van Allen belt, both of which are not accurate.

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Medicine initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Version 1:

Reviewer comments:

Reviewer #2

(Remarks to the Author)
Wanted to thank the authors for comprehensively addressing all the comments in their revision!
The authors have thoroughly addressed all the concerns and incorporated all the suggestions, which has greatly improved the clarity and organization of the manuscript and added the discussion and nuances needed for a more comprehensive review on cardiovascular risks associated with deep space exploration. Additionally in the revision NASA's and HRP strategies are also better contextualized.

As such recommend for acceptance of the manuscript for publication.

Reviewer #3

(Remarks to the Author)
The reviewer appreciates the substantial edits made to the manuscript by the authors, which have made the submission much stronger. Although the authors have done a good job of addressing reviewer comments, there remain some conceptual and presentation issues that preclude acceptance for publication.

1. (Major) Page 20 - The authors statement on ALARA implies that NASA does not incorporate the two other principles of radiation protection, Justification and Limitation, in its radiation health program. The exposures are arguably a priori justified by the existence of the human spaceflight program. However, radiation exposure limits have undergone substantial changes in recent years and these are important to highlight. Limits exist for both tissue reactions and stochastic effects.
2. (Major) Page 20 - NASA no longer uses 3% REID at the upper-95% confidence limit as the career radiation limit for astronauts. Instead, NASA now employs a 600 mSv career effective dose limit, calculated using NASA-defined quality factors and tissue weighting factors. The reviewer understands that this corresponds to the 3% point estimate for a young (35-year-old) female astronaut using existing cancer risk models.
3. (Major) Page 27 - The atomic bomb survivors were exposed to a mixed field of photons and neutrons. Weighted absorbed doses, calculated as photon dose plus ten times neutron dose, were used in the dosimetry system for corresponding epidemiological analyses. The text currently implies that LSS exposures involved only "acute, high-dose-rate gamma exposure".
4. (Major) Table 3 - ISS exposures definitely involve GCR as a primary source. Both LEO and deep space involve mixed field exposures of both high and low LET. RBE is defined for specific biological outcomes; generically stating "Lower RBE" and "High RBE" is not sufficiently precise.
5. (Minor) Throughout - The entire manuscript needs to undergo a careful reading as there remain noticeable spelling and grammatical errors.

Co-reviewer notes:

- The authors appear to have made a mistake in their correction for reviewer 2, comment 1. In both their rebuttal and the original paper they report an LV mass loss of "12 +/- 6.9%", but in the paper (both revised and merged) they say "12-16%".
- In table 2 for epidemiologic evidence, the authors list LSS and radiotherapy, but in the paper they stress the use of

occupational studies. Including occupational studies in the table would make it more complete.

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Medicine initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Version 2:

Reviewer comments:

Reviewer #3

(Remarks to the Author)
The reviewer appreciates and acknowledges the efforts of the authors to render the manuscript nearly suitable for publication. There are only a few minor issues that should be addressed before publication.

1. Page 18. "In Low Earth Orbit (LEO), the Earth's geomagnetic field provides substantial protection, with radiation primarily consisting of trapped protons and secondary neutrons." This statement should be reconciled with the table edit that clearly indicates that GCR are a concern in LEO. Trapped protons are only a concern in LEO in the South Atlantic Anomaly; everywhere else, GCR dominates.

2. Page 19. "Consequently, cardiovascular risk models must account for this quality factor (Q), ..." The concept of the quality factor has not been introduced at this point in the manuscript. Additionally, I think that RBE-weighted dose is a more relevant dosimetric quantity than dose equivalent for cardiovascular effects, which are presently classified as tissue reactions.

3. The authors use the term "thresholds" where the term "limits" should instead be used throughout the manuscript. An example is on page 20, where the 600 mSv limit is referred to as a threshold. This is an important distinction; the term "threshold" implies there is no effect below the value. Please carefully review and revise where appropriate.

4. Page 28. "...which differs fundamentally from the chronic, low-dose-rate exposure to high-LET GCR and SP) encountered during transit to Mars." Should this be SPE instead of SP)?

The co-reviewer has no additional comments.

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Medicine initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Version 3:

Reviewer comments:

Reviewer #3

(Remarks to the Author)
I have no additional concerns and recommend that the manuscript be accepted for publication.

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Medicine initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Reviewer #2, (Remarks to the Author):

T**he presentation would benefit from improved organizational clarity, particularly in distinguishing human epidemiologic and clinical observations from mechanistic evidence derived from animal models and experimental systems. At present, the evidence discussed is occasionally conflated, which can make it obscure and hard to interpret.**

We acknowledge the reviewer's concern regarding the potential conflation of human and experimental evidence. To improve clarity and interpretability and to further eliminate any ambiguity between clinical facts and experimental hypotheses, we have included ***Table 2.*** *This table serves as an organizational anchor for the paper, explicitly categorizing findings by their source (Human vs. Animal) and their specific role in NASA's Risk Assessment framework. This allows the reader to clearly distinguish between established epidemiologic data and the mechanistic evidence derived from the murine simulated GCR studies.* ***Table 2*** *is a summary which refers to the NASA Human Research Program's specific goal (Gap CVD 101 and CVD 102) to "determine the cardiovascular disease risk from space radiation." Pages 10-11.*

Additionally, while cardiovascular risks associated with short-duration and low Earth orbit (LEO) missions are discussed, there is limited differentiation between these environments and the distinct hazard profile anticipated for deep space missions. Given the manuscript's emphasis on future lunar and Mars exploration, clearer separation of LEO-derived observations from deep space–relevant risk extrapolations would improve coherence and mission relevance.

*We appreciate the reviewer's request for a more nuanced differentiation between orbital environments. We agree that the shielding provided by the Earth's magnetosphere in Low Earth Orbit (LEO) results in a cardiovascular risk profile that is fundamentally different from the high-LET (Linear Energy Transfer) environment of deep space. In the revised manuscript, we have implemented the following changes to ensure mission relevance – a) we have added a comparative table (****Table 3****) that explicitly contrasts the radiation environment of the International Space Station (ISS/LEO) with the deep space environment (Lunar/Mars). This table highlights differences in dose rates, particle composition (GCR vs. trapped protons), and shielding effectiveness; b) we have added a sentence to emphasize that while LEO missions have shown minimal acute cardiovascular impact, the distinct hazard profile of deep space - specifically the chronic, high-LET exposure - requires the predictive biomarkers to be validated in simulated GCR environments; c) we also discuss why LEO-derived data may underestimate the late-onset cardiovascular effects of the heavy ions (HZE particles) encountered in deep space. Moreover, we would like to point out that the information in* ***Table 3*** *substantiates the necessity of ground-based studies using simulated GCR environment (high-LET HZE ions) rather than LEO-like conditions. This may ensure that the cardiovascular pathologies observed in these studies (e.g., accelerated atherosclerosis and transcriptomic shifts) are directly applicable to the deep space hazard profile identified by the Reviewer. Pages 19-20.*

Finally, the review does not sufficiently address NASA's established methodological approach to assessing health risks in the absence of definitive epidemiologic data. In particular, it omits discussion of probabilistic risk-modeling frameworks currently used for

space radiation–induced cancer risk and being explored for other health hazards. These approaches integrate terrestrial epidemiology, mechanistic and animal data, Galactic Cosmic Ray simulation studies, and explicit uncertainty quantification to inform decision-making for long-duration deep space missions. Incorporating this perspective, with appropriate supporting literatures, is needed to strengthen the translational and operational relevance as it pertains to NASA's mission planning and Human Research current framework.

We thank the reviewer for this insightful recommendation. We agree that the manuscript would be significantly strengthened by explicitly discussing the probabilistic risk-modeling frameworks that NASA utilizes to translate mechanistic and surrogate data into operational risk assessments. In the revised version of the manuscript, we have added a dedicated paragraph subtitled "Risk Modeling and Operational Mission Planning." In this paragraph, we address the following: a) Integration of multi-scale data – we now describe how NASA utilizes probabilistic models to bridge the gap between terrestrial X- and γ-ray epidemiology and the complex, high-LET radiation environment of deep space; this include integration of terrestrial epidemiology (e.g., atomic bomb survivors, medical exposures) with mechanistic insights, animal models (including simulated Galactic Cosmic Ray [GCR] studies), and physics-based transport codes; b) Probabilistic risk assessment - we highlight the role of uncertainty quantification in these models - specifically how the simple extrapolation of risk are replaced by probability distributions to better inform mechanistic data that is used to inform the risk of exposure-induced death (REID) metric to augment the decision-making for long-duration deep space missions; c) Application to non-cancer hazards - while these models are most mature for carcinogenesis, we have included a discussion on how similar methodologies are being explored and adapted for cardiovascular and degenerative tissue risks, referencing the current Human Research Program (HRP) Integrated Path to Risk Reduction (iPRR) illustrating how the cardiovascular risks identified in murine models are being mapped onto the operational requirements for future Artemis and Mars missions. We believe these additions provide the necessary translational context, aligning our review manuscript with NASA's current operational framework and its mission-planning requirements for Artemis and beyond. Pages 27-28.

However, revisions are needed to improve clarity, strengthen organizational structure, and more explicitly address NASA's existing strategies for cardiovascular risk assessment and management under uncertainty and lack of statistical data.

We have revised the manuscript to better reflect NASA's strategic framework. Specifically, we added a full paragraph, "Translational Cardiovascular Risk Management", which associates the reviewed material to the NASA HRP Gaps CV-102 and CV-102. To address the reviewer's concern regarding statistical uncertainty, we have clarified how high-resolution ground-based analogs data (e.g., murine, rat etc.,) serves as a critical surrogate for sparse human clinical data, providing the probabilistic evidence needed to refine the integrated medical model (IMM) and mission-specific permissible outcome limits (PELs). Pages 26-27.

Specific Comments

1. Several statements require clear referencing of the sources. For example:

• On page 6, the statement "Supporting animal studies employed acute, high-dose HZE irradiation (1 Gy at 10 cGy/min)" is presented without an accompanying reference.
• On page 8, the claim describing "~20% loss of cardiac muscle, leading to reduced cardiac function" lacks a cited source.
• A few additional instances of insufficient or unclear referencing appear in the manuscript, so they need to be properly referenced.

We thank the reviewer for this comment. The corresponding references are now added on pages 6 and 8. Moreover, we also corrected the text on page 8 to reflect the exact findings -, i.e., "including up to 12±6.9% loss LV mass, leading to reduced cardiac function". We have also corrected the insufficient or unclear references elsewhere in the text.

3. On page 6, the discussion of limitations related to dose rate and exposure duration would benefit from additional context. Similar constraints exist in space radiation cancer risk assessment, where correction factors and uncertainty modeling are routinely applied, and the data remain operationally useful. Explicitly acknowledging this parallel would provide a more balanced perspective on how cardiovascular radiation data might still inform risk assessment despite these limitations.

We agree with the Reviewers suggestion and added explicit acknowledgment of the balanced perspective on correction factors and uncertainty modeling on page 6.

4. The final paragraph on page 7 may inadvertently conflate uncertainty in existing astronaut epidemiologic studies with uncertainty regarding long-duration deep space cardiovascular risk. Given that human epidemiologic data are either insufficient or lacking for long-duration lunar or Mars mission scenarios, this limitation should be explicitly discussed to avoid misinterpretation of LEO-derived findings as directly informative for deep space missions.

We agree with the Reviewers suggestion and these limitations are now discussed on page 8.

5. On page 8, the statement "current evidence should be interpreted as hypothesis-generating rather than conclusive, underscoring the need for large-scale, longitudinal studies using realistic spaceflight exposure models." is appropriate; however, the proposed path forward emphasizes large-scale longitudinal studies that are unlikely to be feasible for deep space missions. This framing overlooks existing probabilistic risk-modeling frameworks used by NASA to evaluate cancer risk under similar constraints. Incorporating discussion of these approaches would provide a more realistic and actionable path forward.

We agree with the Reviewers suggestions and now incorporated a brief discussion on probabilistic risk-modeling frameworks on page 9.

6. Definition of "Distance from Earth" as a Hazard: As written, the first few paragraphs of "Distance from Earth" section (beginning on page 10) primarily serves as a proxy for space radiation exposure. While the content itself is not incorrect, the framing is potentially misleading. NASA formally defines "distance from Earth" as a hazard encompassing

logistical and operational challenges, including communication delays, medical autonomy, supply limitations, and so forth. Space radiation is treated as a distinct hazard and is already addressed elsewhere in the manuscript. Therefore, this section needs to be restructured to align with NASA's formal hazard definition and the space radiation content should be relocated to radiation-specific content later in the manuscript.

We agree with the Reviewer comments and section had been restructured to reflect possible difference in extraterrestrial environment including isolation and confinement. Moreover, the section for the space radiation had been moved to the specific section for "Space Radiation" on pages 20-21.

7. In the first paragraph on page 11 (after properly moving it to the Space Radiation section), discussion of permissible exposure limits would benefit from clarification regarding how cardiovascular risk limits are assessed differently from cancer risk limits. This distinction is already discussed in Patel et al. (2012) and would help contextualize NASA's current risk management strategy.

We agree with the Reviewer comment and added updated reference of Patel Z., et al., 2016 to the new paragraph on page 21 to help contextualize NASA's current risk management strategies for cancer and CVD.

8. On page 12 and in the general discussion, socioeconomic risk factors are mentioned, but smoking status is not sufficiently emphasized. Given that NASA applies non-smoker (NS) corrections when estimating cancer risk to reflect astronaut health profiles, and that smoking is a major contributor to cardiovascular disease, additional discussion is warranted when comparing astronaut cardiovascular risk to that of the general population.

We agree with the reviewer that smoking status is a critical, independent variable that warrants explicit emphasis alongside socioeconomic factors. In the revised manuscript, we have expanded the discussion to highlight that the "Healthy Worker Effect" in the astronaut corps is significantly driven by their non-smoking status. We now explicitly discuss NASA's application of non-smoker (NS) corrections within its risk-modeling frameworks (e.g., the NSCR model). We note that because smoking is a primary driver of endothelial dysfunction and systemic inflammation, the use of NS correction is essential to prevent an exaggeration of the "astronaut advantage." By adjusting the baseline to a non-smoking cohort, we can more accurately isolate the cardiovascular stressors unique to the space environment, such as galactic cosmic radiation (GCR) and microgravity, from the confounding noise of tobacco-induced pathology. pages 12-13.

9. Within the Space Radiation section, the manuscript would benefit from a brief discussion of how NASA's current radiation risk framework incorporates terrestrial epidemiologic data—particularly from atomic bomb survivor studies and large occupational cohorts—to estimate excess radiation risk. Studies such as the Million Person Study are highly relevant and should be acknowledged when discussing cardiovascular radiation risk extrapolation, and how a similar strategy can be applied when assessing cardiovascular risk.

The authors appreciate this suggestion. We have added a new paragraph within the Space Radiation section. In this paragraph, we discuss how NASA's framework translates terrestrial data - historically from the Life Span Study (LSS) of atomic bomb survivors - to the space environment. In addition, have added a discussion of the Million Person Study (MPS) of U.S. radiation workers and veterans, including the most recent (2025) corresponding references to the MPS studies We emphasize that the MPS is uniquely relevant to cardiovascular risk assessment because it examines chronic, low-dose-rate exposures in a "healthy worker" cohort, which is more closely mirroring the astronaut profile than acute high-dose data. This addition clarifies how terrestrial findings on stochastic cardiovascular effects at low doses (0.1 Gy) are being used to refine the Risk of Exposure-Induced Death (REID) for deep-space missions, pages 28-29.

10. The discussion of radiation-associated cardiovascular risk would be strengthened by inclusion of excess relative risk modeling approaches and in particular inclusion and discussion of and the following key references are recommended:
• Little MP. Radiation and circulatory disease. Mutation Research (2016).
• Boerma M et al. Radiation-induced heart disease: mechanisms and models. Radiation Research.
• Huff et al. Cardiovascular Disease Risk Modeling for Astronauts: Making the Leap From Earth to Space. Frontiers in Cardiovascular Medicine (2022).

We thank the reviewer for highlighting these important studies. We have integrated the Excess Relative Risk (ERR) modeling approach into our discussion, citing Little (2016) to address the epidemiological evidence for circulatory disease at low doses. We have also expanded the mechanistic and translational sections using Boerma et al. and Huff et al. (2022). These additions clarify how terrestrial "Earth-based" cardiovascular data is extrapolated to the "Space" environment, specifically addressing the shift from deterministic to stochastic risk models, page 29.

11. In the section "Insights into Risks of Multi-Year Mars Missions" (page 29), as well as in the conclusions and future directions, the manuscript should more explicitly discuss NASA's recommended strategy of probabilistic risk modeling and integration into frameworks such as REID and the broader space radiation risk architecture. The approaches outlined in Huff et al. and Patel et al. provide an appropriate foundation and should be emphasized, and risk models such as Astro-CHARM (Khera A et. al. Circulation., 2018).

We thank the reviewer for this guidance. We have significantly expanded the "Insights into Risks of Multi-Year Mars Missions" section (Page 39) to explicitly address NASA's probabilistic risk modeling strategy. Following the foundations laid by Huff et al. and Patel et al., we now describe how cardiovascular risk is integrated into the Risk of Exposure-Induced Death (REID) framework. Specifically, we have introduced the Astro-CHARM (Cardiovascular Health and Risk Monitoring) tool as a primary example of how terrestrial clinical data can be adapted to the astronaut population to provide a more individualized, integrated risk profile.

12. While briefly mentioned, the manuscript will benefit in more detailed discussion of individual hazards compared to other hazards and also more discussion on the combined effect.

We thank the reviewer for this critical observation. We have expanded the "Conclusion and Future Direction" section to include a comparative analysis of the primary stressors. In the revised text (Page 41-42), we now explicitly discuss the hierarchy of these hazards regarding cardiovascular risk - noting that while GCR provides the primary stochastic risk (REID), microgravity-induced fluid shifts and deconditioning provide the most immediate deterministic challenges. Furthermore, we have added a subsection on synergistic effects, discussing how the combination of radiation and weightlessness may accelerate vascular aging more rapidly than the sum of their individual parts.

13. Across multiple sections, mechanistic findings are presented alongside observational data without consistently distinguishing hypothesis generation from inputs to operational risk assessment. Clarifying this distinction would improve interpretability and align the review more closely with NASA's decision-making framework.

We acknowledge that the original manuscript did not sufficiently distinguish between mechanistic exploration and operational inputs. Throughout the manuscript we revised and added several paragraphs/sections to apply a more rigorous categorization (pages 6, 8-10, 13-14, 20, 22, 25, 27-30, 39-40). We now explicitly define mechanistic data as hypothesis-generating, aimed at identifying potential biomarkers and countermeasures. Conversely, we categorize epidemiologic and clinical data (e.g., the Million Person Study, Astro-CHARM) as operational inputs used to define established risk thresholds. This distinction clarifies that while mechanistic findings provide the why behind vascular aging, the operational frameworks provide the what and how much regarding mission safety limits.

2. Minor comment: The manuscript is generally well written; however, several minor typographical and grammatical errors should be corrected. For example:
• Page 6: "which is differs significantly" should read "which differs significantly."
• End of page 6: "enchancing" should be corrected to "enhancing."

The minor typographical errors are now corrected on page 7.

Reviewer #3, (Remarks to the Author):

1. (Major) Page 5, Table 1 - An "intermediate" category should be included in the table. As is, the table implies that there are no cardiovascular risks between the end of the spaceflight and months after the career ends.

We thank the Reviewer for this suggestion. ***Table 1*** *has been revised to describe short- and long-term in-flight health risks, as well as short- and long-term post-flight health risks. We also updated the text referring to* ***Table 1****, pages 4-5.*

2. (Major) Throughout - While some citations are provided, there are many statements in the manuscript that must be supported with cited literature. The authors are encouraged to carefully review the manuscript and add citations as appropriate. As an example, the authors mention the Delp et al. study on page 5, but there is no citation for this study included here.

We thank the Reviewer for these valuable comments. We reviewed the manuscript carefully and added appropriate references throughout, including the Delp et al. citation noted by the reviewer. Overall, 49 additional references were incorporated.

5. (Major) Page 10 - Item 1, "Distance from Earth", is only relevant in the context of the actual environmental exposures associated with distance from Earth. The discussion in this subsection largely addresses space radiation, which is redundant with respect to Subsection

We agree with the reviewer's suggestion and have revised the section accordingly. As this issue was also raised by Reviewer 2, we implemented the requested changes; please see our response to Reviewer 2, question 6.

3. The authors should consider condensing these two subsections into a single subsection on space radiation.

We thank the reviewer for this valuable suggestion. However, we decided to revise the manuscript structure to distinguish between health issues associated with distance from Earth and those related specifically to radiation exposure. Accordingly, the latter is now discussed in a separate section entitled "Space Radiation."

6. (Major) Page 10 - The authors should clarify whether the fraction of "radiation dose-equivalent" attributed to HZE particles, and specifically to iron particles, refers to the boundary condition radiation field or to the actual particles interacting with human cells. The reviewer's understanding is that virtually no iron particles reach human cells due to fragmentation with vehicular and/or astronaut body self-shielding.

We thank the reviewer for this important observation. We agree that the previously cited fraction of radiation dose-equivalent attributable to HZE particles, and specifically to iron, should not be interpreted as the fraction of primary iron ions directly reaching human cells. In the revised manuscript, we now clarify that these estimates refer to the external/free-space GCR field. After

passage through spacecraft shielding and body tissues, primary Fe and other high-Z ions are strongly attenuated and fragmented, such that the transported field at organ and cellular level contains a much larger contribution from secondary protons, helium ions, light fragments, and neutrons. Accordingly, the contribution of primary iron ions at the tissue level is substantially reduced, even though residual heavy-ion tracks and their fragments remain biologically relevant. The text has been revised accordingly, page 20.

7. (Major) Page 10 - The authors refer to "protocols focused on minimizing time spent around the source of IR, maximizing distance to the source, and using shielding methods" as key components of NASA's space radiation protection program. In fact, these are general principles used in terrestrial radiation protection and largely inapplicable to NASA's space radiation protection program. The stated principles are mostly useful in planned exposure situations, and NASA is compelled to address an existing exposure situation for which source-focused controls are mostly ineffective.

We thank the reviewer for this important comment. We agree that our previous wording was imprecise and that the "time, distance, and shielding" framework does not accurately describe NASA's space radiation protection program. We have revised the text accordingly to state that NASA manages astronaut ionizing-radiation risk through ALARA principles. We also removed the implication that source-focused controls are the primary basis of radiation protection in spaceflight, page 21.

8. (Major) Page 12 - The authors refer to "1-3 year journeys to Mars". The Mars Design Reference Mission (DRM) consists of a 9-month journey to Mars, a 12-month surface stay, and a 9-month return journey to Earth. The authors should use more precise language in describing a Mars mission. It is highly unlikely that a journey to Mars would exceed 12 months.

We thank the Reviewer for this helpful comment. We agree that the mentioned phrase was imprecise. We now distinguish between transit time and total mission duration, noting that travel to Mars is generally expected to require approximately 6-9 months, whereas the full mission, including surface operations and return transit, may extend to approximately 2-3 years, page 14.

10. (Major) Page 13 - The authors make the somewhat pedantic point that "Most missions within LEO remain within 90% of Earth's ground-level gravity", yet then state that there is an "absence of gravitational forces", two statements that seem to be in opposition. Indeed, weightlessness is not caused by an absence of gravitational forces but rather by the presence of those gravitational forces. It is really the weightlessness that causes human health effects and so the reviewer recommends that the authors emphasize this.

We thank the Reviewer for this valuable observation. We revised the text to explicitly indicate that the relevant physiological effects are driven by microgravity/weightlessness, rather than by an absence of gravitational forces, page 15.

11. (Major) Page 17 - The authors claim that dysautonomia experienced by astronauts is potentially caused by radiation exposure. Given that nervous system damage is typically

noted only at very high doses (> 20 Gy) of terrestrial radiation, the reviewer highly doubts that space radiation could cause such an effect. This statement must be more thoroughly justified by explanation and corresponding citation of peer-reviewed literature.

We thank the reviewer for this important comment. We agree that our original wording may have implied that space radiation causes direct injury to specific peripheral autonomic structures, such as the carotid body and vagus nerve. However, we believe it remains appropriate to note a potential neural contribution of space radiation, as animal studies using charged-particle exposures relevant to the space environment have shown persistent nervous system effects even at low to moderate doses, including changes in cognition, motor coordination, oxidative stress, neuroinflammation, synaptic plasticity, and neuronal excitability. These findings suggest that space radiation may influence neural tissues as one component of the multifactorial physiological stress associated with long-duration spaceflight. We have revised the text to clarify this point, page 19.

12. (Major) Page 17 - The authors state that "Primary GCRs can produce secondary particles through projection and target fragmentation, causing varied responses and degrees of DNA damage compared to IR with dense linear tracts". This sentence is confusing. The authors presumably mean "projectile" instead of "projection" and "tracks" instead of "tracts". Additionally, secondary particles resulting from primary GCR interactions typically do produce dense linear tracks, but the statement seems to indicate the opposite. Please clarify this.

We thank the reviewer for this comment. We have revised the text to replace "projection" with "projectile" and "tracts" with "tracks," and to clarify that fragmentation of primary GCRs generates a mixed radiation field composed of both high-LET and lower-LET secondary components, which results in DNA damage patterns distinct from those induced by predominantly low-LET ionizing radiation, page 22.

13. (Major) Page 18 - The description of the origin of solar energetic protons is far too simplistic. It is not accepted that these particles are merely "emitted during solar flares". The authors are encouraged to mature this explanation. Furthermore, it is not true that "solar flares are predictable to a certain degree".

We thank the reviewer for this comment. We revised the text to clarify that solar energetic proton events are associated with solar eruptive activity. We also revised the statement on predictability of IR producing events, page 22.

14. (Major) Page 19 - The authors do not discuss the occurrence of CV risks in the Atomic Bomb Survivor cohort or the various worker cohort studies (i.e., INWORKS or Million Person Study). These studies are likely to be far more applicable to the astronaut/cosmonaut population than are patient cohort studies.

We agree with the reviewer's comment and have revised the manuscript accordingly. As this issue was also raised by Reviewer 2, we implemented the requested changes; please see our response to Reviewer 2, question 9.

16. (Major) Page 24 - The authors state that the 24.65-hour circadian clock on Mars is "not conducive to normal human rhythms." Is it really true that a difference of approximately 30 minutes is that biologically significant? If yes, then it behooves the authors to further explain this, since at first glance, this is a small difference.

We thank the reviewer for this important comment. A Martian sol is approximately 24.6 hours, which is close to the terrestrial day, however, the approximately 39-minute difference from Earth's 24-hour cycle can still be biologically meaningful because, if entrainment is not maintained, that phase difference accumulates across consecutive sols. Experimental work has shown that the 24.65-hour Martian sol lies outside the natural entrainment range of the human circadian pacemaker under lighting intensities typically encountered by astronauts, although appropriately timed light exposure can enable adaptation. Accordingly, we have revised the text to clarify that the Martian sol should be described not as "not conducive to normal human rhythms" but as a schedule that can challenge circadian entrainment and therefore requires active countermeasures, page 32.

17. (Major) Page 24 - The authors transition from Subsection 4 on "Sleep deprivation and circadian desynchrony" directly into a section on VO2max with no new subsection. It seems that a new subsection on this topic should start here.

We agree with the Reviewer's comment that this topic should be discussed under new subsection. Therefore we separated this topic into a separate section 5, pages 32-35.

18. (Major) Page 25 - Similarly, the authors begin a discussion of the effects of "absence of gravity" on the ISS, seemingly under Subsection 4. Additionally, the authors should note that statement this is in direct contradiction to the point made earlier that it is weightlessness and not necessarily absence of gravity that produces deleterious human health effects.

We acknowledge the discrepancy in terminology and apologize for inconsistency. We agree that while the term 'absence of gravity' is occasionally used colloquially, it is technically inaccurate in the context of the International Space Station (ISS). We have revised the text to consistently use 'microgravity' or 'weightlessness' to describe the orbital environment. This ensures alignment with our earlier assertion that the deleterious health effects are primarily driven by the lack of mechanical loading and fluid shifts associated with weightlessness, rather than a true zero-G environment, page 33-35

19. (Major) Page 26 - The authors declare that "Isolation and confinement are nonmodifiable factors..." With the increasing use of virtual reality and augmented reality approaches, the authors should reflect on whether their statement is so surely true.

We thank the reviewer for this important comment. We agree that the term "nonmodifiable" was too absolute. We have therefore revised the manuscript to clarify that these factors are not strictly nonmodifiable, but rather mission-inherent stressors whose effects may be partially

mitigated through evolving countermeasure strategies, including virtual reality and related digital tools, page 35.

20. (Major) Page 30 - Again the authors reference "the prolonged transit (~3 years)" for Mars missions. It is highly unlikely that such a mission design would be employed.

We agree with the reviewer and corrected the wording to distinguish between full mission and transit durations. Page 14.

22. (Major) Figure 2 - Several aspects of this figure can be improved. This figure seems to show the trapped radiation belts as well-defined lines, which they are not. The figure is already not to scale, so the Moon and Mars might be made larger. Finally, and most importantly, the ionizing radiation field is shown as normally incident and inexplicably shielded by the outer Van Allen belt, both of which are not accurate.

We thank the reviewer for the helpful suggestions to improve the scientific accuracy and clarity of ***Figure 2****. The figure has been revised accordingly. In response, the Van Allen radiation belts are no longer depicted as sharply defined lines. In the revised version, they are illustrated as diffuse regions with gradual color gradients to better represent the dynamic and spatially variable distribution of trapped particles within the belts rather than discrete boundaries. The relative sizes of the Moon and Mars have been increased to improve visibility and visual balance within the diagram. In addition, the figure legend has been revised to explicitly indicate that ` Finally, the representation of the ionizing radiation field has also been corrected. In the previous version, radiation was illustrated as directional arrows that could give the impression of an incident radiation and suggested that the outer Van Allen belt acts as a shielding barrier. In the revised figure, this directional depiction has been removed and replaced with a diffuse radiation field surrounding the Earth system to better represent the multidirectional nature of galactic cosmic radiation. This also removes any visual implication that the outer Van Allen belt blocks incoming radiation. We hope these revisions improve both the scientific accuracy and the readability of the schematic representation of the near-Earth radiation environment.*

3. (Minor) Page 7 - Authors reference "large" cohort studies of astronauts. Given the relatively small number of humans who have traveled in space, the authors must clarify what is meant here.

We now clarified that the referenced study was the data from Longitudinal Study of Astronaut Health that included 310 NASA astronauts and 981 non-astronaut NASA employees where non-astronauts were matched to the astronauts on age, sex, and body mass index.

4. (Minor) Page 7 - Authors reference "Soviet and Russian cosmonauts". The reviewer considers this to be redundant, since cosmonauts are by definition Soviet or Russian.

We agree, the reference to Soviet and Russian are deleted, to keep only cosmonauts.

9. (Minor) Page 12 - Two consecutive sentences begin with the word "Therefore". Please reword to avoid this.

The second sentence was changes to "Thus".

15. (Minor) Page 22 - The authors state that astronauts "sleep only approximately 6 hours per night". The reviewer recommends that authors describe this as sleep per day rather than per night, since one day is a clearly defined time period, whereas the definition of "night" is nebulous.

We agree with this comment, the night is now changed to "per day".

21. (Minor) Page 33 - The authors should consider whether the quote from Cernan is required for the article. The final two sentences do not seem to add to the scientific value of the manuscript.

We understand the reviewer suggestion that these two sentences may not be adding scientific value, however we kindly ask reviewers to allow this concluding forward looking statement remain in the text.

Reviewer #2 (Remarks to the Author):
Wanted to thank the authors for comprehensively addressing all the comments in their revision! The authors have thoroughly addressed all the concerns and incorporated all the suggestions, which has greatly improved the clarity and organization of the manuscript and added the discussion and nuances needed for a more comprehensive review on cardiovascular risks associated with deep space exploration. Additionally in the revision NASA's and HRP strategies are also better contextualized. As such recommend for acceptance of the manuscript for publication.

The authors would like to sincerely thank the reviewer for their time, expertise, and the thoughtful feedback provided throughout this review process. We are very pleased that our revisions, particularly regarding the nuances of NASA's radiation protection principles, the transition to the 600 mSv career limit, and the complexities of RBE, successfully addressed your concerns and strengthened the manuscript. Reviewer's insights were instrumental in ensuring this review provides a technically accurate and comprehensive resource for the space radiation community. We are honored by the recommendation for acceptance.

Reviewer #3 (Remarks to the Author):
The reviewer appreciates the substantial edits made to the manuscript by the authors, which have made the submission much stronger. Although the authors have done a good job of addressing reviewer comments, there remain some conceptual and presentation issues that preclude acceptance for publication.

The authors thank the Reviewer for their continued engagement and for the positive feedback regarding the strengthened nature of our revised manuscript. We are encouraged that the substantial edits made thus far have moved the submission closer to publication. We acknowledge that the reviewer still identifies certain conceptual and presentation issues. We are fully committed to refining the manuscript to meet the jounral's high standards and appreciate more specific guidance on the areas requiring further clarification or reorganization.

1. (Major) Page 20 - The authors statement on ALARA implies that NASA does not incorporate the two other principles of radiation protection, Justification and Limitation, in its radiation health program. The exposures are arguably a priori justified by the existence of the human spaceflight program. However, radiation exposure limits have undergone substantial changes in recent years, and these are important to highlight. Limits exist for both tissue reactions and stochastic effects.

We appreciate the reviewer's insightful clarification regarding the three pillars of radiation protection. It was not our intent to imply that NASA ignores Justification and Limitation; however, we recognize that focusing solely on ALARA in the text creates an incomplete picture of the agency's safety framework. We have revised the manuscript on page 20 to explicitly address these components: (i) We now clarify that mission-related exposures are justified by the high-priority scientific and exploratory objectives of the human spaceflight program, as determined by federal and agency-level stakeholders; (2) We have added a section discussing the recent evolution of NASA's dose limits. This includes a transition toward a unified age- and sex-invariant 600 mSv career limit (based on the National Academies' recommendations) aimed at balancing stochastic

risks (cancer) with the need to prevent tissue reactions (such as cataracts or cardiovascular effects); (iii) We have contextualized ALARA as the operational mechanism used to keep exposures as far below these established limits as mission success allows.

2. (Major) Page 20 – NASA no longer uses 3% REID at the upper-95% confidence limit as the career radiation limit for astronauts. Instead, NASA now employs a 600 mSv career effective dose limit, calculated using NASA-defined quality factors and tissue weighting factors. The reviewer understands that this corresponds to the 3%-point estimate for a young (35-year-old) female astronaut using existing cancer risk models.

We appreciate the reviewer's precision regarding the current NASA radiation protection standards. We acknowledge that NASA has moved away from the 95% confidence level (CL) approach to a risk-informed, point-estimate approach. We have updated the manuscript to reflect that the current career limit is a uniform 600 mSv (page 20). Furthermore, we have added a clarifying statement acknowledging that this 600 mSv value was derived to harmonize protection across the astronaut corps, representing the 3% REID point estimate for a 35-year-old female - the demographic previously identified as having the highest risk-to-dose ratio (page 21).

3. (Major) Page 27 - The atomic bomb survivors were exposed to a mixed field of photons and neutrons. Weighted absorbed doses, calculated as photon dose plus ten times neutron dose, were used in the dosimetry system for corresponding epidemiological analyses. The text currently implies that LSS exposures involved only "acute, high-dose-rate gamma exposure".

We appreciate this correction regarding the LSS cohort dosimetry. We acknowledge that while the primary component of the atomic bomb radiation was gamma rays, the dosimetry system (DS02) explicitly accounts for the mixed-field nature of the exposure by utilizing weighted absorbed doses (i.e., incorporating a neutron weighting factor of 10). We have revised the text on page 27 to accurately reflect that the LSS findings are based on these weighted doses rather than purely gamma exposure, while maintaining the distinction that these remain acute, high-dose-rate events compared to the protracted, low-dose-rate environment of deep space.

4. (Major) Table 3 – ISS exposures definitely involve GCR as a primary source. Both LEO and deep space involve mixed field exposures of both high and low LET. RBE is defined for specific biological outcomes; generically stating "Lower RBE" and "High RBE" is not sufficiently precise.

We agree with the reviewer's assessment. We have revised Table 3 and the accompanying text to clarify that GCR is a primary component of the radiation environment in low Earth orbit (LEO), although the Earth's geomagnetic field modulates it. We have also replaced the generic high/low RBE' descriptors with more precise terminology. We added a new, separate Table 4 to the text to specify the radiation quality in terms of LET components and acknowledge that RBE is an endpoint-dependent value. Specifically, we now refer to 'increased biological effectiveness for late-term effects (such as carcinogenesis or cardiovascular degeneration) rather than using RBE as a static descriptor. To address the reviewer's concern regarding the precision of RBE, we have added a footnote to Table 4. This footnote explicitly defines RBE as an endpoint-dependent variable and

clarifies that our comparisons of biological effectiveness specifically refer to late-term stochastic and tissue-specific (cardiovascular) outcomes induced by high-LET HZE ions.

5. (Minor) Throughout - The entire manuscript needs to undergo careful reading as there remain noticeable spelling and grammatical errors.

The authors appreciate the reviewer's attention to detail. We apologize for the oversight regarding the remaining typographical and grammatical errors. The manuscript has since undergone a comprehensive, line-by-line review by all co-authors to ensure linguistic precision, technical consistency, and clarity. We have corrected the errors identified and believe the presentation now matches the scientific quality of the work.

Co-reviewer notes:
The authors appear to have made a mistake in their correction for reviewer 2, comment 1. In both their rebuttal and the original paper, they report an LV mass loss of "12 +/- 6.9%", but in the paper (both revised and merged) they say "12-16%".

We sincerely thank the Co-Reviewer for identifying this numerical inconsistency. We apologize for the oversight and any confusion this may have caused. The correct value for the left ventricular (LV) mass loss observed in our study is 12±6.9. We have performed a thorough audit of the manuscript and have updated the text to ensure that the reported values are consistent with our primary data analysis. The previous range of 12 - 16% was an artifact from a preliminary analysis of a subset of the data; we have now standardized the reporting to the final mean and standard deviation throughout the entire document and the rebuttal letter.

In table 2 for epidemiological evidence, the authors list LSS and radiotherapy, but in the paper, they stress the use of occupational studies. Including occupational studies in the table would make it more complete.

*We appreciate this suggestion to align **Table 2** with the narrative of the manuscript. We agree that occupational studies represent a critical bridge between the acute high-dose-rate exposures of the LSS and the chronic low-dose-rate exposures relevant to spaceflight. We have kept Table 2 intact (now designated as Table 2.1) and added **Table 2.2** to include key occupational cohorts and highlight their contributions to our understanding of cardiovascular risks following protracted, low-dose-rate ionizing radiation exposure.*

Reviewer #4 (Remarks to the Author):
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Medicine initiative to facilitate peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

The authors would like to specifically acknowledge the contribution of the Early Career Researcher (ECR) who co-reviewed this manuscript as part of the Communications Medicine initiative. We highly value the perspective and technical rigor provided through this collaborative review process.

RESPONSE TO CTRITIQUES

Reviewer 3

1. Page 18. "In Low Earth Orbit (LEO), the Earth's geomagnetic field provides substantial protection, with radiation primarily consisting of trapped protons and secondary neutrons." This statement should be reconciled with the table edit that clearly indicates that GCR are a concern in LEO. Trapped protons are only a concern in LEO in the South Atlantic Anomaly; everywhere else, GCR dominates.

We agree with the Reviewer's comment and have clarified this in the text on page 18. While the geomagnetic field provides substantial protection against low-energy particles, its effectiveness is not uniform. Galactic Cosmic Rays (GCRs) are a persistent, penetrating background concern, especially outside the concentrated hotspots of trapped radiation. The radiation environment in LEO is characterized by two distinct regimes – 1) The South Atlantic Anomaly (SAA) in this specific region, the inner radiation belt dips toward the Earth due to the offset of the magnetic field. Trapped protons here can account for as much as 91% of the peak particle flux in certain low-inclination orbits. For the International Space Station (ISS), although it spends only about 5% of its mission time in the SAA, astronauts can receive more than 50% of their total absorbed dose during these short passes; 2) Outside the SAA, trapped proton flux drops significantly. In these regions, GCRs consist of high-energy protons (87%), helium ions (12%), and heavy (HZE) ions (1%) but they become the primary source of background radiation. Therefore, the geomagnetic field acts as a filter rather than a complete block. Its shielding effectiveness is defined by the geomagnetic cutoff rigidity, which varies by latitude. Near the geomagnetic equator, the field is strongest, and only GCRs with extremely high energies can penetrate. Near the polar regions, the field lines are nearly vertical, allowing lower-energy GCRs to enter LEO. As spacecraft orbits reach higher latitudes, GCR exposure increases accordingly.

2. Page 19. "Consequently, cardiovascular risk models must account for this quality factor (Q), ..." The concept of the quality factor has not been introduced at this point in the manuscript. Additionally, I think that RBE-weighted dose is a more relevant dosimetric quantity than dose equivalent for cardiovascular effects, which are presently classified as tissue reactions.

To address Reviewer's point about quality factor (Q) versus Relative Biological Effectiveness (RBE), we added a small paragraph to clarify the regulatory and biological distinctions between these terms (Pages 19). Quality Factor (Q) is a parameter specifically defined for radiation protection purposes to account for the stochastic risk (primarily cancer and heritable effects) of low-dose, low-LET radiation. This is intended for regulatory monitoring rather than precise biological risk prediction. Q is a one-size-fits-all function of LET. In contrast, RBE can be tailored to the specific tissue (e.g., myocardium vs. coronary arteries) and the specific ion species (e.g., ^{56}Fe vs. protons). Cardiovascular effects, such as ischemic heart disease and stroke, are now classified by the International Commission on Radiological (ICRP) as tissue reactions. For these effects, the ICRP and NASA recommend using RBE an experimentally derived ratio rather than the generalized Q function. Therefore, for cardiovascular risks, using the RBE-weighted dose is scientifically superior because cardiovascular damage often involves inflammatory pathways and

endothelial dysfunction that follows a threshold-like tissue reaction pattern rather than the linear-no-threshold (LNT) model used for cancer.

3. The authors use the term "thresholds" where the term "limits" should instead be used throughout the manuscript. An example is on page 20, where the 600 mSv limit is referred to as a threshold. This is an important distinction; the term "threshold" implies there is no effect below the value. Please carefully review and revise where appropriate.

We agree with the reviewer that the terms "threshold" and "limit" were used interchangeably in error. We have performed a comprehensive review of the manuscript to ensure these terms are applied correctly based on their regulatory and biological definitions. The following clarifications were made in the revision: 1) the 600 mSv value (and similar career exposure caps) is now strictly referred to as a limit. We acknowledge that this is a policy-based administrative constraint designed to keep the Risk of Exposure-Induced Death (REID) below a specific percentage, and it does not imply that doses below this level are safe or devoid of biological effect; 2) The term threshold is now reserved exclusively for tissue reactions (deterministic effects). For example, we refer to the 0.5 Gy threshold for cardiovascular disease as defined by ICRP, which represents the estimated dose below which the specific biological effect is not clinically observed.

4. Page 28. "...which differs fundamentally from the chronic, low-dose-rate exposure to high-LET GCR and SP) encountered during transit to Mars." Should this be SPE instead of SP)?

We apologize for the omission, yes, it should be SPE, corrected, page 29.

Reviewer 4.
We thank you this reviewer for their time and effort.