npj | microgravity

Review

Published in cooperation with the Biodesign Institute at Arizona State University, with the support of NASA

https://doi.org/10.1038/s41526-025-00537-1

Integrative focus on the space exposome-integrome: physiological challenges and practical limits of countermeasures beyond low Earth orbit

Damian M. Bailey[1] ✉, Dieter Blottner[2,3], Hanns-Christian Gunga[4], Stefan Schneider[5], Virginia Wotring[6,7], Sarah Baatout[8,9], Marco Durante[10,11,12], Rik H. G. Olde Engberink[13,14], Nandu Goswami[15,16], Martina Heer[17,18], Anna-Maria Liphardt[19,20], Monica Monici[21], Francesco Pagnini[22], Claudia Stern[23], Jan-Bernd Stukenborg[24,25], Tobias Weber[26,27,28], Laurence Vico[29], Olivier White[30], Angelique van Ombergen[31,32] & Alexander Choukér[33] ✉

Human spaceflight is advancing toward sustainable exploration through initiatives like NASA's Artemis program, aiming for a lunar outpost and eventual Mars mission. Astronauts face hazards including altered gravity, isolation, and cosmic radiation, linked to over thirty health risks. This review, reflecting ESA community expertise, outlines how understanding the space exposome–integrome interaction can improve risk stratification, guide personalized countermeasures, and address knowledge gaps essential for safe deep-space exploration.

Adaptability and resilience are distinguishing features of *Homo sapiens*. Our large complex brains and sophisticated behavior have provided key macro-evolutionary advantages that distinguished us from other hominids, allowing our species to flourish on the African continent before eventually spreading across the entire planet[1]. However, as we aim to transition from a terrestrial to temporal extra-terrestrial species with ambitious plans to establish human research stations and habitats with rotating crew on the Moon and eventually Mars, these defining traits will be tested to unexplored extremes in unprecedented ways. Indeed, evolution is a time-consuming process that allowed humans to adapt to their changing environment. In the case of space exploration, the time continuum is minuscule, placing the challenge into a clearer context. While physiological adaptive mechanisms along with our evolved intellect have allowed humans to work routinely in microgravity and other extreme environments, how will we respond to the constellation of hazards that collectively define spaceflight beyond Earth vicinity—an enigmatic environment that simply cannot be replicated *in toto* within the boundary constraints of Earth? What countermeasures, herein defined as *solutions to prevent the undesirable physiologic and psychological outcomes associated with extreme environments*[2], need refinement or development de novo, to mitigate against these risks and better protect crew health and safety to ensure mission success?

Herein, we highlight how a better understanding of the functional interaction between the space exposome (environmental hazards) and the integrome (integrative human adaptation) can enhance risk stratification and corresponding mitigation through the development of more effective personalized countermeasures. Our primary endpoint was to identify key knowledge gaps and provide considerations and recommendations for future research priorities focused on safe, pragmatic, personalized countermeasure selection and development. The secondary endpoint was to explore potential terrestrial applications and highlight the socio-economic benefits of risk monitoring and mitigation.

Methodology

This White Paper review was developed as part of the European Space Agency's (ESA) Human Spaceflight and Exploration Directorate's[3] SciSpacE's team (now coined Exploration Science) strategic initiative to develop a wide range of White Papers on the future of the science of space exploration with a specific European view. One important topic thereof is the 'Integrative and Countermeasures Approach'—contributing to the Explore 2040 strategy under the Terrae Novae exploration programme[4] outlining Europe's long-term vision for robotic and human exploration of the Solar System. The review methodology involved a structured, multi-phase process combining systematic literature appraisal, expert consensus, and cross-disciplinary integration.

A comprehensive appraisal of peer-reviewed literature was undertaken, drawing from PubMed, Scopus, and ESA archives, focusing on publications between 1939 and 2025. Keywords included "space physiology," "integrated countermeasures," "microgravity adaptation," "radiation

A full list of affiliations appears at the end of the paper. ✉e-mail: damian.bailey@southwales.ac.uk; alexander.chouker@med.uni-muenchen.de

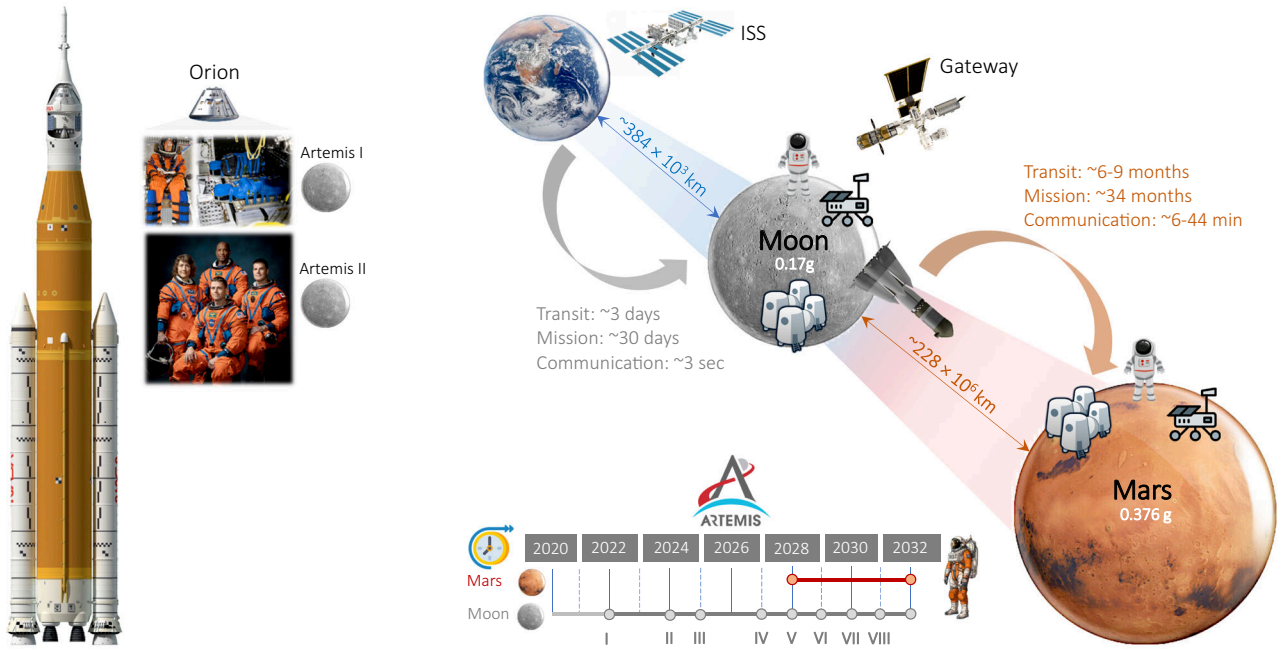


Fig. 1 | Future challenges: exploration-focused and -enabled science. In collaboration with commercial and international partners, including the European Space Agency (ESA), NASA's Artemis program will look to establish a sustainable human presence on the Moon in preparation for and de-risking of a future crewed mission to Mars (provisional flight schedules inset). Artemis I saw its first uncrewed mission fly a trio of mannequins aboard the Orion capsule (Commander Moonikin Campos at the helm, accompanied by torsos, Helga, and Zohar) fitted with sensors to measure vibration, acceleration, and cosmic radiation dose. This will be followed by NASA's Artemis II mission, the first scheduled lunar flyby, that will pave the way for a return to the Moon, crewed by NASA astronauts Mission Specialist 1, Christina Hammock Koch, Commander Reid Wiseman, Pilot Victor Glover, and Canadian Space Agency Mission Specialist 2, Jeremy Hansen. Created with BioRender.com. Note that the documented transit times reflect one-way durations, mission times reflect total mission durations, and communication delays reflect 'message-and-response' cycles. Photo credits: NASA.

risk," and "deep space human exploration." Inclusion criteria encompassed studies (preclinical, clinical, and operational) addressing physiological risks and mitigation strategies associated with long-duration spaceflight. This review builds on foundational documents encompassing the 2016 ESA SciSpacE Roadmaps and the THESEUS (Towards Human Exploration of Space: a EUropean Strategy) initiative[5], and incorporates expert 'community' contributions from over 300 specialists across 22 ESA member states. Input was gathered via structured workshops, virtual panels, and targeted thematic surveys that was strategically organized into 4 overarching research groups and 16 thematic domains. A modified Delphi process was used to identify and rank priority knowledge gaps, emerging research needs, and translational opportunities. Expert feedback was thematically analyzed to derive impact-driven recommendations focused on integrated, personalized countermeasure development. Consideration was also given to terrestrial parallels, enabling assessment of broader socio-economic and healthcare relevance. All findings were synthesized and aligned with ESA's broader exploration strategy and informed by previous ESA Science Community White Papers published in this series[6–17], capitalizing on extensive cross-disciplinary synergies.

Human space exploration: context, constraints and challenges

To date, more than 600 space travellers have reached Earth orbit—achieving the necessary orbital velocity to remain in sustained freefall around the planet—while others have flown, or are currently flying, on suborbital tourist missions aboard commercial space vehicles. The latter exceed the Fédération Aéronautique Internationale's criterion of crossing the Kármán line[18] (100 km altitude) to qualify as spaceflight, but their trajectories do not reach orbital velocity and therefore return to Earth after brief periods of microgravity. Except for the Apollo missions, and following retirement of the Space Shuttle in 2011, the International Space Station (ISS) and more recently, the Tiangong Space Station, have been the primary foci of human spaceflight, with risk management governed almost exclusively by missions lasting from 30 days to up to a year in low Earth orbit (LEO).

However, with the decommissioning of the ISS currently planned for around 2030, the successful launch and return of the uncrewed test flight Artemis I on November 16th, 2022, laid the foundations for a revolutionary new era to support extended deep space exploration-class missions. Agencies and commercial partners are ambitiously aiming to expand humanity's reach beyond Earth vicinity, including establishing a permanent base on the Moon's surface ahead of the horizon goal, and a crewed mission to the Red Planet, Mars (Fig. 1). These endeavours involve distances spanning millions of kilometres, presenting monumental challenges unlike anything humanity has ever faced before. They will push engineering and human tolerances to, if not indeed beyond current limits, placing unprecedented and potentially unquantifiable demands on an astronaut's health, performance and medical needs[19,20].

Before humans can be sent to Mars and returned safely, critical questions must be addressed and obstacles overcome. Beyond the formidable engineering challenges of optimizing vehicles, habitats, spacesuits, and propulsion systems, one of the most pressing issues is how to effectively prioritize and safeguard crew health and safety. Space agencies carry a moral and ethical responsibility to provide astronauts with the best possible estimation of risk, ensuring they are fully informed before embarking on missions never before attempted[19]. Importantly, risk estimation is not only vital for crew preparedness but also for the agencies or other spacefaring organizations tasked with making the final "go" decision. Risk acceptance must therefore be understood and recognized as a shared responsibility among a broader community of stakeholders. Clearly, it makes intuitive sense to better phenotype the human body's integrative responses to the combined impact of multiple stressors that collectively define the space

'exposome'[21], so that biomedical risks can be more accurately characterized and contained.

Space exposome: integrative approach for personalized risk stratification

No environment is more hostile and challenging to humans than space. It is the closest known approximation to a perfect vacuum, compounded by high-energy background ionizing radiation, extremes of temperature (−270 °C in deep space when the spacecraft is in shadow and radiatively cooling toward the cosmic microwave background temperature to +120 °C in direct sunlight)[22], altered gravitational forces ranging from hypergravity during ascent/re-entry (3-6+ *g*) to transitioning through microgravity and engaging with potential surface operations under partial gravity conditions on the Moon (0.17 *g*) and Mars (0.376 *g*), particulates (micrometeoroids, cosmic dust, orbital debris and charged particles), and the highly reactive radical atomic oxygen (O) which is the most prevalent species in LEO, within the context of interplanetary missions.

These hazards exceed the physiological boundary limits set by Earth's constant gravity, geomagnetic fields, water, and breathable molecular (diatomic) oxygen (O_2) that have collectively helped shape the evolution of life on Earth[23]. While spacesuits and habitats provide some degree of protection, altered gravity, background ionizing radiation, prolonged isolation and confinement, hostile and closed environments, and ever-increasing distances from Earth, represent the core environmental stressors and hazards that space crew will ultimately face beyond Earth vicinity, as defined by the NASA Human Research Program (HRP) and outlined within the HRP Integrated Research Plan[24] (Fig. 2A). It is also important to acknowledge the role of circadian dysregulation (disruption of an astronaut's endogenous biological rhythm in a confined spacecraft or remote planetary habitat with altered sunrise/sunset cycles) underlying long-term psycho-physiological maladaptation[25].

Key focus areas have been identified in the THESEUS approach[5] a decade ago, highlighting knowledge gaps and research priorities in nutrition and metabolism[26], immunology[27], bone and musculoskeletal physiology[15,28], neurophysiology[29] and cardiopulmonary function[30]. These multi-organ systems are impacted significantly, and according to NASA's HRP[24], exploration hazards are associated with over thirty human health risks that inform research prioritization (Fig. 2B). NASA applies an evidence-based risk assessment framework to evaluate the acceptability of health and performance risks using a likelihood-consequence (L × C) matrix for a given design reference mission[19,31]. Risks classified as 'red' exceed this threshold and are considered unacceptable without validated mitigation strategies. These thresholds guide decisions on mission approval, particularly for exploration-class missions beyond low-Earth orbit, where risk tolerance is lower due to limited evacuation and resupply options.

Current red risks are broadly categorized as follows, (1) *Systemic:* radiation-induced carcinogenesis, (2) *Cerebral/Psychological/Ophthalmological:* Spaceflight-Associated Neuro-ocular Syndrome (SANS) and psychosocial maladaptation encompassing anxiety, depression, and cognitive decline, (3) *Renal:* nephrolithiasis, (4) *Musculoskeletal:* osteoporosis, (5) *Pulmonary:* celestial dust exposure, (6) *Metabolic:* complications associated with altered drug pharmacokinetics/pharmacodynamics, (7) *Nutritional:* inadequate food intake and (8) *Medical emergencies*: including extravehicular activities (EVA, Fig. 2B). However, astronauts will invariably encounter these stressors to varying degrees and never in isolation, making the physiological responses at best, challenging and at worse impossible, to accurately replicate, model or predict, emphasizing the need for multidisciplinary research and a more holistic integrative physiology approach. Our collective inability to accurately simulate multi-stressor dynamics and determine to what extent stressors exert simple linear additive or complex coupled nonlinear synergistic effects (Fig. 2A) remains a conceptual barrier.

Indeed, most stressor combinations lack empirical evidence to derive 'safe' or ethically permissible threshold limits for combined risks, further emphasizing the fundamental importance of quantitatively predicting the impact of combined stressors for optimized mitigation. Related discourse has stimulated a separate roadmap focused on space governance, outlining an ethics framework devoted to fundamental principles and practices to help guide agency's decision-making for future exploration-class missions that are inherently risky and that fail to meet existing occupational health standards: a concept that incidentally, is not unique to spaceflight[32] and requires constant evaluation[33].

Ethics and scientific considerations are not always aligned, which poses further challenges. For example, long-duration missions may require the use of experimental countermeasures (e.g., radioprotective agents or gene therapies)[34] that lack robust clinical validation. While these may be scientifically justified under extreme conditions, their application raises ethical concerns regarding autonomy, long-term safety, and the standards of informed consent—especially when terrestrial occupational or medical guidelines would prohibit their use. This illustrates how ethical and scientific priorities may diverge, presenting a unique governance challenge in space medicine. Recent attention has since turned to the space 'exposome', an emergent concept originally founded in toxicology[35], to better define personalized health risk profiles through deeper phenotyping of combined stressor impacts, including functional interactions with intrinsic modulants[21] (Fig. 2B).

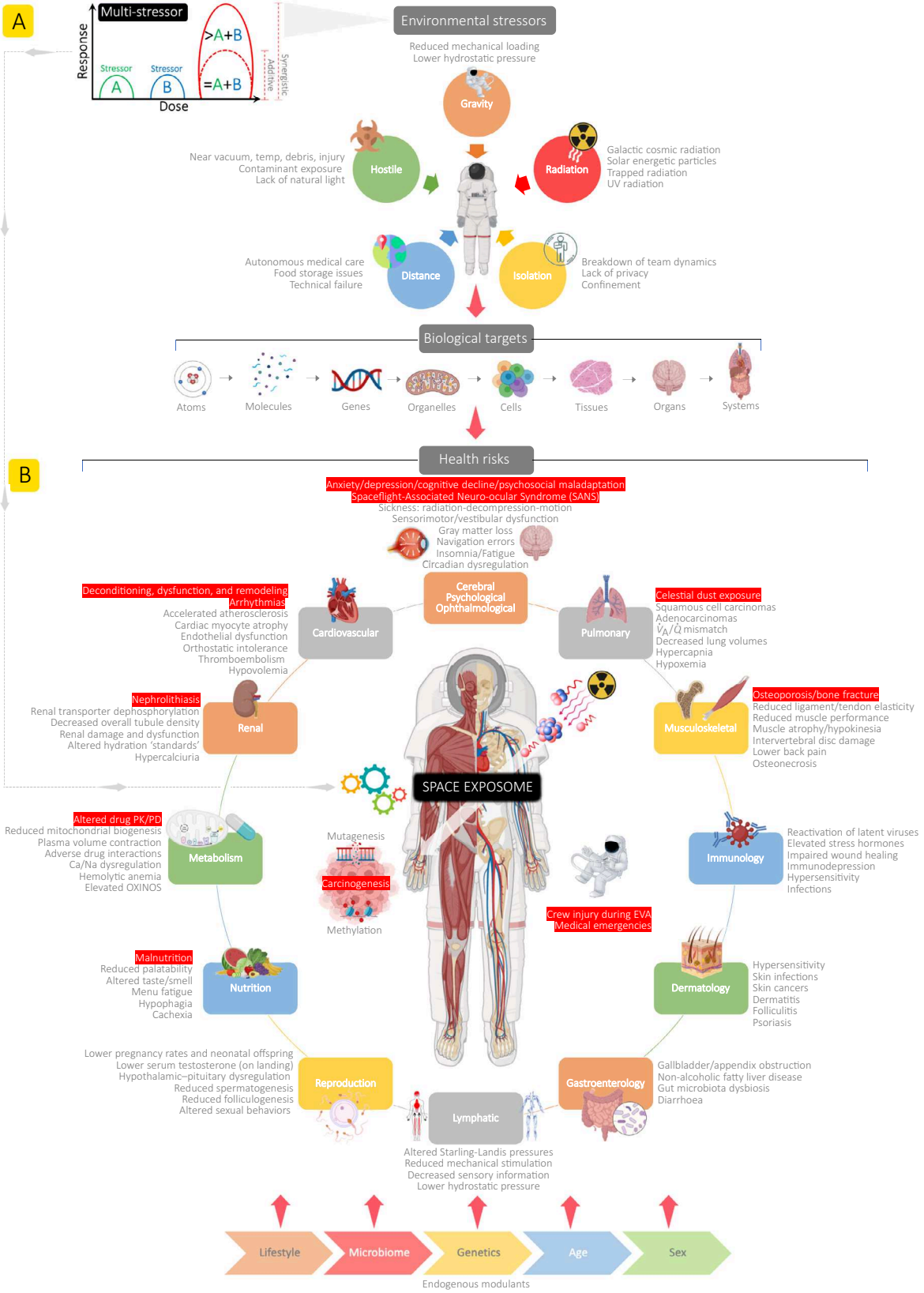
Space integrome: towards personalized countermeasure discovery

The critical role of spaceflight countermeasures—targeted interventions designed to mitigate health risks associated with the space exposome, has been acknowledged since the early 1950's[36], even before implementation of the first (exercise) countermeasures during the U.S. Gemini program. A wide variety of terrestrial spaceflight simulations and environmental analogs have been designed and tested to recreate 'select' aspects of spaceflight[2,37]. These analogs offer unique and valuable opportunities under strict laboratory-controlled high-fidelity conditions for accelerated countermeasure discovery, development, evaluation, and implementation (Fig. 3).

Primary terrestrial analogs for spaceflight include, although not exclusively confined to, immobilisation: −6° head-down tilt bed rest (HDTBR) and dry immersion (DI) to replicate microgravity-induced deconditioning; ICE (isolation, confinement, and extreme environment) facilities including Antarctic stations, caving, and undersea habitats with dedicated facilities in Moscow, Houston, Florida, Cologne, and Sardinia and terrestrial/laboratory-based facilities that induce inspiratory hypoxia to simulate the low-pressure conditions of extravehicular activity and subaquatic environments[38]. While no specific analog can perfectly recreate the totality of environmental exposures and associated multivariate physiological responses that astronauts experience, they offer practical advantages over spaceflight including wider access to comparatively larger sample sizes (to optimize statistical detection of treatment effects), reduction of confounding factors that are omnipresent in human ISS research studies, on-site specialist medical care and importantly, reduced launch costs given that payload deployment to LEO has fallen by approximately 95% from ~$65,000 USD/kg to ~$1500 USD/kg due to technological advances and commercialization[39].

To date, -6° HDTBR and DI are widely considered the most suitable physiological analogs to simulate microgravity, given their long-duration, whole body integrative focus and controlled environment that collectively afford opportunities to evaluate multiple countermeasures simultaneously[40] (Fig. 3). Recent (European) examples of countermeasure experiments include HDTBR: AGBRESA (Artificial Gravity BedRest study; commissioned by ESA and NASA together with DLR)[41], BRACE (Bed Rest with Artificial gravity and Cycling Exercise study; commissioned by ESA and CNES) and BRAVE (Bed Rest with Artificial gravity and Vibration and resistance Exercise study; commissioned by ESA) and DI: VIVALDI I-III studies[42].

The field of integrative physiology is concerned with the broader aspects of physiology focused on the interactions between molecules, cells, tissue, and organs, emphasizing the interconnectedness of physiological systems[43]. Having benefitted from recent analytical advances in



high-throughput multi-omics platforms and associated bioinformatics that underpin the systems biology approach[44], capable of analyzing upward of 100,000 molecular biomarkers[45], integrative physiology is uniquely positioned to better characterize risk profiles at low cost and unprecedented precision affording the opportunity to individualize countermeasures and allow an astronaut to perform more safely and efficiently.

Indeed, space omics and tissue responses have been described in organ-based studies on human skeletal muscle from several short and long-

Fig. 2 | Space exposome: environmental stressors and hazards, biological targets, and health risks. Primary environmental stressors of prolonged spaceflight as defined by the NASA Human Research Program (HRP) and outlined within the HRP Integrated Research Plan[24], biological targets (in ascending order of complexity including principal organ systems impacted, (**A**) and corresponding health risks (**B**). **A** Note that the systemic response is highly complex and difficult to model given the synergies between environmental stressors, multitude of organ systems affected and extraneous factors. Altered gravity fields and radiation are highly quantifiable, the other stressors less so. One of the primary research challenges is to quantify to what extent cumulative exposure to these environmental stressors exerts linear additive or complex nonlinear synergistic effects on crew health and performance (inset, upper left). The emergent concept underlying the space 'exposome' encompasses the totality of an astronaut's cumulative exposures to these hazards and functional interaction with endogenous factors that modulate risk[76]. **B** Health risks highlighted in red reflect those defined by the NASA Human Research Program (outlined within the HRP Integrated Research Plan[24]), with the highest priority based on likelihood of occurrence and severity of (adverse) consequences for crew health and performance during exploration-class missions beyond low Earth orbit (i.e., cis-lunar space, lunar surface operations, lunar outpost and Mars exploration)[31]. Note that all statements regarding key physiological systems are based on findings from human studies. SANS Spaceflight-Associated Neuro-Ocular Syndrome, OXINOS oxidative-inflammatory-nitrosative stress, $\dot{V}_A/\dot{Q}$ ventilation/perfusion, PK/PD pharmacokinetics/pharmacodynamics. Created with BioRender.com.

duration mission ISS astronauts (9 days vs. 180 days or more). Findings have highlighted expression of distinct molecular signatures (biomarkers) that are either up- or down-regulated in muscle biosamples (pre vs. postflight biopsies) following routinely performed daily onboard countermeasures[46,47]. Muscular nitrosative stress (an organ-based marker of disuse) has recently been reported as a major signature in male astronauts following long-term spaceflight[48]. Another recent study confirmed separate and distinct molecular signatures (mitochondrial damage) in human skeletal muscle from two long-duration ISS astronauts[49]. In addition to the analysis of fluid (saliva, blood, urine) and other less invasive biosamples (e.g., hairs, nails, skin flakes), the need for more organ-based and systemic studies must remain a priority.

Supporting this, the NASA Twins Study exemplifies the functionally integrative approach, establishing a methodological framework that combines physiological, telomeric, transcriptomic, epigenetic, proteomic, metabolomic, immunologic, microbiomic, cardiovascular, ophthalmologic, and cognitive metrics from both the spacefaring and Earth-bound Kelly twins[50]. It served as a precursor to the newly established Space Omics and Medical Atlas (SOMA)[51], a collaborative initiative aimed at standardizing biological measurements and sample preservation protocols—including human, microbial, and environmental specimens[52]—and promoting data sharing for spaceflight-related omics research, using longitudinal datasets from private, short-duration, civilian missions such as Inspiration4, Polaris Dawn, and Axiom, alongside terrestrial controls. This is an ambitious initiative with the potential to improve in-flight risk monitoring and mitigation, and potentially pre-mission screening and baseline risk stratification to evaluate individual susceptibility to space-related stressors before flight selection or training. European data sharing is also facilitated by the Human and Robotic Exploration Data Archive (HREDA)[53] and through European-American collaborations e.g., with NASA's GeneLab[54]. This precision health framework, best summarized by Aristotle, "*The whole is greater than the sum of its parts*", is perfectly suited to spaceflight given the small sample sizes, perpetual risk of mission failure, and unprecedented demands placed on the astronauts.

As illustrated in Fig. 3, functional integration of these 'big data' sets from multimodal terrestrial/flight-based platforms will help build a more holistic picture of the dynamic interplay between genotype and space exposome phenotype. This integrated whole, or space 'integrome', uniquely reflecting combinatorial events that may aggregate to alter risk profiles, is concerned not only with amalgamating complex orthogonal datasets, but more importantly, exposing unanticipated interactions underlying the exposome phenotype. What distinguishes the integrome from the exposome concept, is how the former moves beyond boundary constraints imposed when focusing on how a single system or gene responds to the space exposome to a deeper phenotyping of the multivariate integrated responses. Accelerated discovery and improved validation of biomarkers (e.g., via targeted and untargeted multiplex mass spectrometry-based proteomics[55]) can reveal novel pathways and mechanisms, generate new hypotheses, and ultimately shorten times for novel countermeasure discovery and development[56].

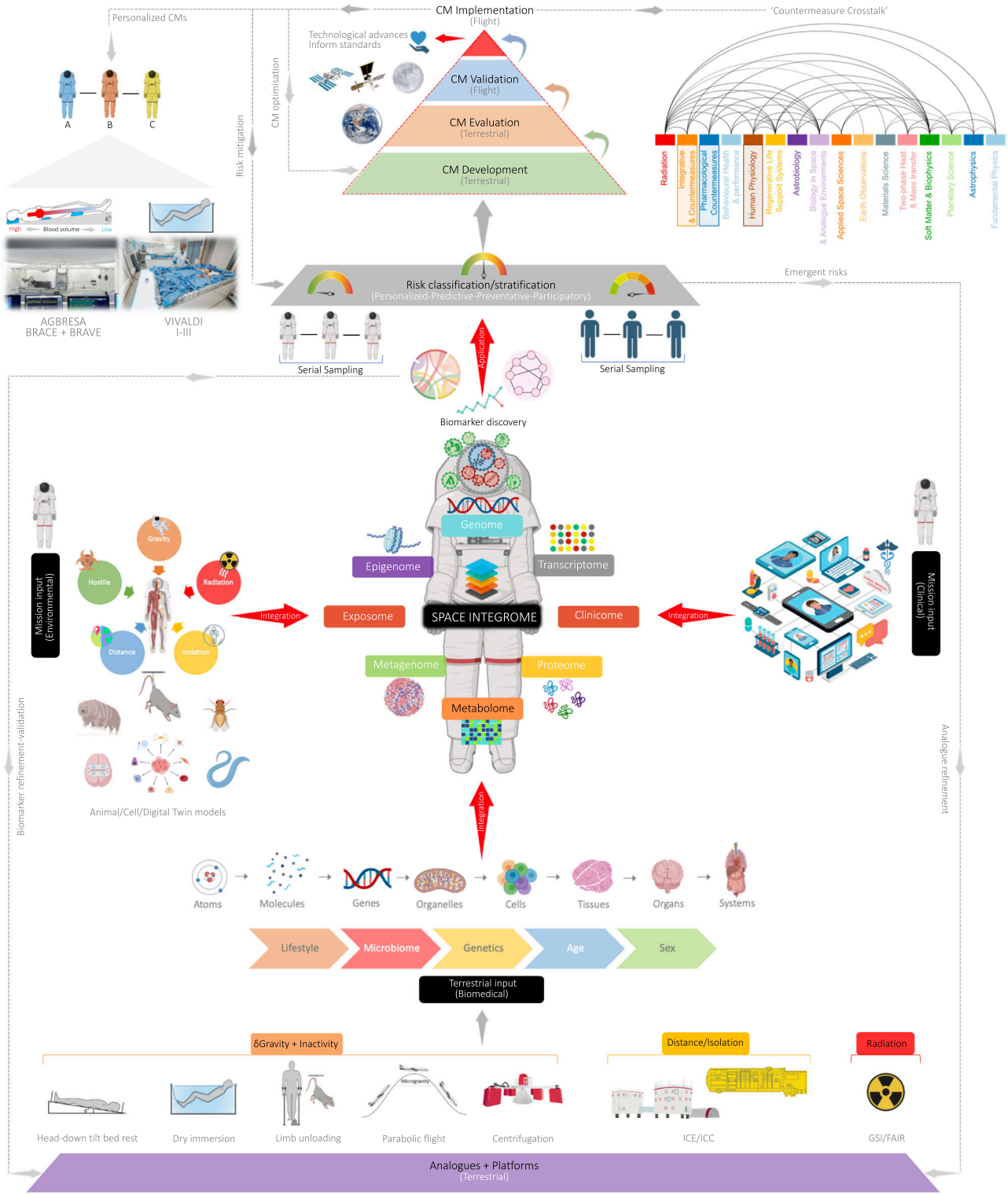
Key knowledge gaps, research priorities and recommendations for risk mitigation

Given the complex scientific and practical challenges associated with space exploration, determining how agencies/commercial partners should prioritize research to accelerate the optimization of existing and development of new countermeasures to improve personalized risk mitigation is crucial. Within ESA-HRE, 'Exploration Enabled Science' (traditional 'bottom-up' science led by the scientific community) is complemented by 'Exploration Focused Science' (top-down, driven by the needs of the exploration programme), with the latter involving closer collaboration with ESA Medical Operations/Support (ESA MedOps) to define the priorities based on operational needs and challenges. Strengthening global collaborations with NASA MedOps and other international partners is also essential. As highlighted, the prevailing consensus among the ESA exploration scientific community emphasizes the need for more basic integrative research focused on deeper phenotyping of the space exposome-integrome concept. This involves understanding how individual and combined environmental stressors impact integrated aspects of crew health and performance, through the identification and validation of precision biomarkers.

Deep space radiation exposure represents one such focused risk that is especially challenging to mitigate and further complicated by location-dependent differences. On the LEO-based ISS, astronauts remain partially protected by the Earth's magnetosphere. In contrast, the Moon and Mars offer minimal to no magnetic shielding, leading to greater exposure to galactic cosmic rays and solar particle events. Mars lacks a protective magnetosphere and has only a thin atmosphere, offering minimal shielding that is insufficient to mitigate deep-space radiation risks.

It is predicted that a 1000-day mission to Mars could increase cancer mortality rates from a predicted background probability of 15 percent (%) to approximately 20% for an average body mass, non-smoking astronaut[57]. To put this into a clearer clinical perspective, this elevation in cancer risk probability—representing a 33% increase in lifetime mortality risk—is comparable to that of an individual who is overweight, consumes alcohol, follows an average diet, and leads a less active lifestyle than a typical astronaut[57]. However, there is considerable uncertainty associated with these calculations due to differences in radiation quality in space compared to that experienced terrestrially. This means that the 5% increase in lifetime cancer risk can range between 1 and 20% when taking into account the (95%) confidence interval[58]. Current research is ongoing to further reduce this uncertainty, an essential step in the design and validation of appropriate countermeasures.

Although a lower albeit emergent current priority, research is exploring the induction of torpor—an intrinsically regulated hypometabolic state analogous to hibernation—as a potentially transformative countermeasure to mitigate the risks associated with the space exposome in future astronauts[59]. Fine-tuning metabolic rate in humans, similar to that observed in torpid animals[60], but different from the protective effects incurred through external induction of therapeutic hypothermia[61–63], would mean the ability to significantly slow down energy consumption. This unique countermeasure could reduce the need for water, O_2, and food



intake by up to 75%, significantly reduce the spacecraft's payload, and improve biochemical resilience, shifting glycolysis to lipolysis and ketone utilization, while inducing myriad physiological adaptations[59]. The collective responses would protect against disuse-induced organ degeneration, enhance resistance to radiation damage[64] and confer neuroprotection[65], a potential 'game-changing' countermeasure for crewed exploration.

While the precise mechanisms underpinning the space integrome remain the topic of ongoing investigation[66], as of now, addressing the hazards and providing countermeasure solutions will require a combination of more immediate human health/performance and engineering solutions requiring a delicate balance between 'acceptable' risks and mission parameters. In terms of bespoke countermeasure strategies, Fig. 4 provides a schematic overview of those currently employed and prioritized for future consideration with the collective aim of de-risking deep space transit and habitation. These range from precision (Fig. 4A), systemic

Fig. 3 | Space integrome: programmatics underlying precision-based countermeasure design. The bedrock of fundamental research incorporates multiple ground-based analogs designed to simulate 'select' aspects of theenvironmental stressors/hazards of spaceflight (base of the pyramid). Functional integration of terrestrial and mission-specific inputthrough the combined application of multivariate high-throughput technologies (e.g., extensive multi-omics profiling supported bybig-data computational approaches incorporating Artificial Intelligence, Network Physiology, Monte Carlo Simulation bioinformaticapproaches, and extended reality and digital twin biological models collectively encompassed within 'Space digital health') canprovide unique insights to better inform an astronaut's personalized space 'integrome'[45]. Personalized biomarker discovery anddevelopment, combining genomic information complimented by longitudinal molecular analyses of samples aligned to physiologicalstates incorporating serial sampling to define underlying kinetics, will help reveal unique heteroallelic changes to the spaceexposome and better inform spaceflight risk stratification to develop more effective, personalized countermeasures that move beyondthe traditional non-specific 'one-size-fits-all' approach (inset, upper left). However, despite vast quantities of complex datasets becoming available, scientific applications remain in their infancy requiring improved standardization and communication[77]. Countermeasure discovery and development is an iterative process, requiring constant evaluation/optimization andvalidation/standardization (bottom-up/top-down) prior to subsequent implementation to mitigate flight risks that are highlyindividual and mission-specific (tip of the pyramid). Emergent risks/biomarkers and associated knowledge gaps reflect dynamicfeedback loops that accelerate experimental activities during refinement phases. Note the countermeasure 'crosstalk' and organicmulti-disciplinary synergies that exist between human physiology and countermeasure discovery (inset, upper right). CMcountermeasure; ICE Isolated, confined, and extreme; ICC isolated, confined, and controlled; GSI/FAIR Facility for Antiproton andIon Research, ISS International Space Station, AGBRESA Artificial Gravity BedRest study, BRACE Bed Rest with Artificial gravityand Cycling Exercise study, BRAVE Bed Rest with Artificial gravity and Vibration and resistance Exercise study. Photo: ©ESA.Created with BioRender.com.

(Fig. 4B) and organ-specific (Fig. 4C) countermeasures to those requiring further refinement or de novo development (Fig. 4D).

Furthermore, future selection of more space 'exposome-resilient' astronauts also warrants consideration. This extends, for example, to all-female crews that are potentially smaller in stature, thereby conferring operational advantages given constrained space habitats and lower bioenergetic demands requiring less food and water[67]. It may also involve selecting for gene variants that collectively confer enhanced physiological resilience to many if not most of these exposomes, and/or intervention-induced targeted gene expression (e.g., via exercise/hypoxia/hypercapnia pre-conditioning or polypharmacological manipulation). There are approximately 79 variants already identified that could prove potentially advantageous for deep spaceflight[68], given functional augmentation in: [1] exercise responsiveness and vascular oxygen transport, [2] pain tolerance, [3] bone density and myogenic signalling, [4] radiation resistance, [5] drug tolerance and [6] geroprotection characterized by suppression of oxidative-inflammatory-nitrosative stress (OXINOS), tissue rejuvenation, and structural improvements in the central nervous system and systemic vasculature subsequent to resetting of circadian programs[69,70]. Ethical and safety issues remain a topic of ongoing debate for emergent gene editing technologies, including the recently established CRISPR-Cas9[71]. However, despite these promising biological capabilities, it is more practical—and consistent with historical precedent—to focus on improving Environmental Control and Life Support Systems (ECLSS) and food systems, rather than simply selecting crews based on reduced water or food requirements. Furthermore, all agencies—including ESA—have tended to adopt a 'select out' rather than a 'select in' strategy; in practice, this means prioritizing technical and behavioral competence while excluding individuals with medical risk factors. For the present and foreseeable future, crew survival and well-being in space will likely depend far more on these selection criteria than on any potentially protective genotype.

Ultimately and as highlighted, the collective objective of countermeasures should be to functionally suppress the psychophysiological burden imposed by the exposome dose and establish a personalized state of 'adaptive homeostasis' for the integrome—the 'Goldilocks Zone' refers to the optimal dose—*not too little, not too much*—required to confer optimized physiological adaptation and resilience (Fig. 4D). However, before this can be achieved, there is an urgent need by our group of specialists to better understand and optimize outstanding challenges associated with countermeasures, continued engagement of crew and MedOps across all international partners, selection and monitoring and establishment/modulation of controlled environments.

Knowledge translation and terrestrial benefits

A more concerted focus on communicating and translating the scientific challenges to relevant stakeholders, including aerospace and biotechnology industries, national space agencies, health and regulatory bodies, international funding councils, policymakers, philanthropic organizations, academic institutions, and the wider public, is recommended to maximize impact. This integrative approach should seek to provide novel insight into the pathophysiology, prevention, treatment, and management of terrestrial human diseases. It should further reinforce the unique fundamental scientific and biomedical importance of space biomedical research to raise its funding profile with research councils and to encourage the next generation of researchers to engage with and advance this specialist field.

Since the early days of space exploration, starting with Project Mercury (1958-1963)[72] and its telemetric monitoring innovations, aerospace research has contributed to the development of medical technologies. These advancements have not only benefitted space missions but have also translated into significant improvements in the understanding and management of human terrestrial healthcare[73], including the potential future translational application of implementable solutions during pandemics[74]. In addition to facilitating healthcare delivery on Earth, examples include improved LASIK® eye surgery precision, engineering advances for Martian sample collection that led to biocompatible surgical suture materials, and an endoscopic robotic surgery arm inspired by robotic repair arms on the ISS[75]. Future technological solutions will be required, given humanity's aspirations to explore deep space beyond Earth vicinity including precision medicine-based telemetrics that demand more astronaut autonomy in the early and accurate detection, diagnosis, monitoring, and treatment of remote health conditions.

Future perspectives and summary

Human spaceflight has always posed significant risks, pushing the ethical boundaries of acceptable (occupational) health and safety standards for astronauts. With ambitious plans for crewed orbital missions to Mars likely extending beyond 1000 days, exploration-class deep space missions will push these boundaries to new and unchartered extremes, exposing crews to complex and poorly characterized risks, which could be uncertain, unforeseen, and challenging to manage.

This White Paper review reflects a consensus statement endorsed by multidisciplinary specialists convened by ESA to highlight existing knowledge gaps and priorities aligned to the 'Integrative and Countermeasures Approach' in support of the ESA exploration research programme. While distinctly European in character, there was a broad consensus on the need for greater international collaboration to promote knowledge exchange across agencies and commercial partners, given the sheer complexity of the challenges and the mission timelines ahead. It was agreed that more fundamental research is warranted with a dedicated focus on deeper phenotyping of the space exposome-integrome conundrum, to better understand how multiple environmental stressors individually and in combination, impact integrated aspects of crew health and performance.

Closer integration of precision-based biomarkers, taking full advantage of recent advances in high-throughput multi-omics platforms and

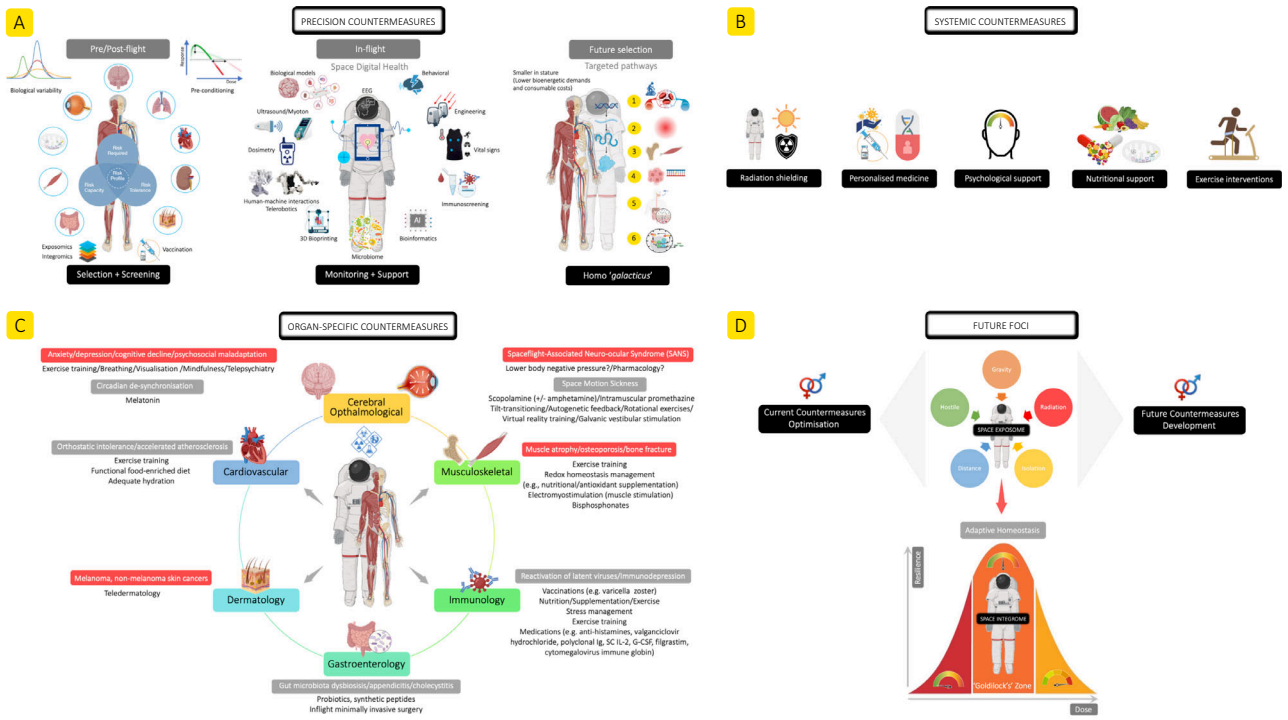


Fig. 4 | Current and future countermeasures to de-risk deep space transit and habitation. A Precision countermeasures collectively encompass Earth-based (preflight) selection, rigorous medical screening/certification and mission-specific pre-conditioning involving individual/combinatorial exposure to exposome stressors to accelerate hormetic adaptation. Health screening typically involves age/sex/ethnicity-specific integrative assessments of all major organ systems including cardiopulmonary fitness testing, vaccinations, and potential multi-omics profiling to better inform an astronaut's individual risk profile. Longitudinal assessments (e.g., over 6–12 months) are encouraged to determine the 'critical difference' for any given integrative diagnostic to account for analytical imprecision and biological variation to establish an astronaut's individual 'physiological corridor' to better interpret 'clinically important' space-mediated deviations[78,79] (inset, upper left). Inflight measurements also involve longitudinal monitoring of integrative multi-metric parameters taking advantage of disruptive medical technologies to inform the personalized space integrome, with 'space digital health' and 'precision physiology' placing the astronaut at the 'point-of-care'. This would provide astronauts with more autonomy to remotely record, access and analyze biomedical data informing them of their vital signs, predict if any medical conditions are likely to arise (i.e., deviations from normative baselines), deploy timely targeted countermeasures, including treatment(s), and contribute to the shared decision-making processes that inform their care given unavoidable communication latencies. This mirrors the 'P4'vision of medical care, a vision that is predictive, preventive, personalized, and participatory[80]. Future selection of more space 'exposome-resilient' astronauts also warrants consideration (see Key knowledge gaps, research priorities, and recommendations for risk mitigation). **B** Systemic countermeasures reflect those that are currently operational and arguably the most commonly deployed (ground and/or flight) with documented evidence of benefit. In terms of exercise countermeasures, it is worth highlighting that NASA's Advanced Resistive Exercise Device (ARED) which has been crucial for mitigating muscle and bone loss on the ISS since 2009, will not be available for future missions—highlighting the need to develop alternative, practically-implementable devices that optimize the systemic (i.e., multi-organ) responses[66,81]. **C** Organ-specific countermeasures reflect those interventions also known to confer physiological benefit(s), sometimes used in combination with systemic countermeasures. **D** Deeper integrated phenotyping of the space exposome-integrome will help inform optimization of existing countermeasures and future development of new countermeasures. For example, combinatorial approaches that integrate multiple interventions—biomedical, behavioral, physical, environmental, and technological—to mitigate the complex, interacting risks associated with the space exposome. These strategies are designed to be more effective than individual measures by targeting multiple systems simultaneously, acknowledging the interconnected physiology of the human body in space. The collective objective of countermeasures should be to functionally suppress the physiological burden imposed by the exposome dose and establish a personalized state of 'adaptive homeostasis' for the integrome. The 'Goldilock's' Zone highlights the 'just right' dose required to confer optimized adaptation/resilience. Created with BioRender.com.

associated bioinformatics will better inform and guide risk stratification, reveal unexplored pathways and mechanisms, and shorten times for personalized countermeasure discovery and development, which will ultimately allow an astronaut to function more safely and at the very highest level. This continuous endeavour shall include diverse and frequent input following solicitation from stakeholders outside of the immediate space science community.

These consultations will further help shape the priorities, that are not all equal, to enable safe and successful deep space exploration beyond Earth vicinity, including future mitigation of unexpected, imponderable non-terrestrial diseases through optimized and personalized countermeasures, which will likely become a feature of the next generation of space travellers engaging in prolonged planetary crewed missions. Space agencies and companies should strive to make their data more accessible to the wider scientific community; equally, investigators have a responsibility to engage proactively with these agencies and broaden their searches beyond mainstream peer-reviewed literature. Since agencies are operational rather than academic in nature, some of the most relevant information resides in gray literature, including technical reports and mission documents. Finally, from new materials and medical breakthroughs to improved environmental/telemetric health monitoring and resource management, the knowledge gained through exploration science has the potential to address global challenges here on Earth.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Received: 18 September 2024; Accepted: 2 October 2025;
Published online: 20 November 2025

References

1. Roberts, P. et al. Isotopic evidence for initial coastal colonization and subsequent diversification in the human occupation of Wallacea. *Nat. Commun.* **11**, 2068 (2020).
2. Ploutz-Snyder, L. Evaluating countermeasures in spaceflight analogs. *J. Appl. Physiol.* **120**, 915–921 (2016).
3. ESA. The SciSpacE White Papers, https://www.esa.int/Science_Exploration/Human_and_Robotic_Exploration/Research/The_SciSpacE_White_Papers (2021).
4. ESA. Terrae Novae 2030+ Strategy Roadmap. 1-25 (2022).
5. Vernikos, J., Walter, N., Worms, J. C. & Blanc, S. THESEUS: The European research priorities for human exploration of space. *NPJ Microgravity* **2**, 16034, (2016).
6. Pittia, P., Blanc, S. & Heer, M. Unraveling the intricate connection between dietary factors and the success in long-term space missions. *NPJ Microgravity* **9**, 89 (2023).
7. Zuccarelli, L. et al. Effects of whole-body vibration or resistive-vibration exercise on blood clotting and related biomarkers: a systematic review. *NPJ Microgravity* **9**, 87 (2023).
8. Stahn, A. C. et al. Paving the way to better understand the effects of prolonged spaceflight on operational performance and its neural bases. *NPJ Microgravity* **9**, 59 (2023).
9. Stern, C., Yucel, Y. H., Zu Eulenburg, P., Pavy-Le Traon, A. & Petersen, L. G. Eye-brain axis in microgravity and its implications for Spaceflight Associated Neuro-ocular Syndrome. *NPJ Microgravity* **9**, 56 (2023).
10. Jacob, P. et al. Next generation of astronauts or ESA astronaut 2.0 concept and spotlight on immunity. *NPJ Microgravity* **9**, 51 (2023).
11. Olde Engberink, R. H. G. et al. The kidney, volume homeostasis and osmoregulation in space: current perspective and knowledge gaps. *NPJ Microgravity* **9**, 29 (2023).
12. Pagnini, F. et al. Human behavior and performance in deep space exploration: next challenges and research gaps. *NPJ Microgravity* **9**, 27 (2023).
13. Jain, V. et al. Human development and reproduction in space-a European perspective. *NPJ Microgravity* **9**, 24 (2023).
14. Harris, K. M. et al. Pathophysiology, risk, diagnosis, and management of venous thrombosis in space: where are we now?. *NPJ Microgravity* **9**, 17 (2023).
15. Liphardt, A. M., Fernandez-Gonzalo, R., Albracht, K., Rittweger, J. & Vico, L. Musculoskeletal research in human space flight - unmet needs for the success of crewed deep space exploration. *NPJ Microgravity* **9**, 9 (2023).
16. Ahmed, S. S. et al. Systematic review of the effectiveness of standalone passive countermeasures on microgravity-induced physiologic deconditioning. *NPJ Microgravity* **10**, 48 (2024).
17. Davis, T. et al. How are cell and tissue structure and function influenced by gravity and what are the gravity perception mechanisms?. *NPJ Microgravity* **10**, 16 (2024).
18. Wikipedia. http://en.wikipedia.org/wiki/List_of_space_travelers_by_name (2024).
19. Antonsen, E. L. et al. Updates to the NASA human system risk management process for space exploration. *NPJ Microgravity* **9**, 72 (2023).
20. Goswami, N. et al. Human physiology adaptation to altered gravity environments. *Acta Astronautica* **189**, 216–221 (2021).
21. Patel, Z. S. et al. Red risks for a journey to the red planet: The highest priority human health risks for a mission to Mars. *NPJ Microgravity* **6**, 33 (2020).
22. Neukart, F. Towards sustainable horizons: A comprehensive blueprint for Mars colonization. *Heliyon* **10**, e26180. https://doi.org/10.1016/j.heliyon.2024.e26180 (2024).
23. Bailey, D. M. Oxygen, evolution and redox signalling in the human brain; quantum in the quotidian. *J. Physiol.* **597**, 15–28 (2019).
24. NASA. Human Research Program Integrated Research Plan. 1-53 (Lyndon B. Johnson Space Center, Houston, Texas, 2023).
25. Malhan, D., Schoenrock, B., Yalcin, M., Blottner, D. & Relogio, A. Circadian regulation in aging: Implications for spaceflight and life on earth. *Aging Cell* **22**, e13935 (2023).
26. Bergouignan, A. et al. Towards human exploration of space: The THESEUS review series on nutrition and metabolism research priorities. *NPJ Microgravity* **2**, 16029 (2016).
27. Frippiat, J. P. et al. Towards human exploration of space: The THESEUS review series on immunology research priorities. *NPJ Microgravity* **2**, 16040 (2016).
28. Lang, T. et al. Towards human exploration of space: the THESEUS review series on muscle and bone research priorities. *NPJ Microgravity* **3**, 8 (2017).
29. White, O. et al. Towards human exploration of space: the THESEUS review series on neurophysiology research priorities. *NPJ Microgravity* **2**, 16023 (2016).
30. Sandal, P. H. et al. Effectiveness of nutritional countermeasures in microgravity and its ground-based analogues to ameliorate musculoskeletal and cardiopulmonary deconditioning-A Systematic Review. *PloS one* **15**, e0234412 (2020).
31. Romero, E. & Francisco, D. The NASA human system risk mitigation process for space exploration. *Acta Astronaut* **175**, 606–615 (2020).
32. Health Standards for Long Duration and Exploration Spaceflight: *Ethics Principles, Responsibilities, and Decision Framework*. (National Academies Press (USA), 2014).
33. Rajput, S. et al. Medical ethics of long-duration spaceflight. *NPJ Microgravity* **9**, 85 (2023).
34. Greenberger, J. Gene therapy for radiation protection. *Gene Ther.* **6**, 1495–1496 (1999).
35. Bliss, C. The toxicity of poisons applied jointly. *Ann. Appl. Biol.* **26**, 585–615 (1939).
36. Von Braun, W. & Ryan, C. Can we get to Mars?. *Collier's* **30**, 22–29 (1954).
37. Afshinnekoo, E. et al. Fundamental Biological Features of Spaceflight: Advancing the Field to Enable Deep-Space Exploration. *Cell* **183**, 1162–1184 (2020).
38. Cromwell, R. L., Huff, J. L., Simonsen, L. C. & Patel, Z. S. Earth-Based Research Analogs to Investigate Space-Based Health Risks. *N. Space* **9**, 204–216 (2021).
39. Roberts, T. G. (2022, September 1). Space launch to low earth orbit: how much does it cost? Aerospace Security, a project of the Center for Strategic and International Studies. Accessed October 3, 2024. https://aerospace.csis.org/data/space-launch-to-low-earth-orbit-how-much-does-it-cost/.
40. Fernandez-Gonzalo, R., Deane, C. S. & Bailey, D. M. Experimental bed rest as a model to investigate mechanisms of, and countermeasures against, microgravity and disease-free inactivity. *Exp. Physiol.* https://doi.org/10.1113/EP091795 (2024).
41. Clément, G. et al. Assessing the effects of artificial gravity in an analog of long-duration spaceflight: The protocol and implementation of the AGBRESA bed rest study. *Front. Physiol.* **13**, 976926. https://doi.org/10.3389/fphys.2022.976926 (2022).
42. Robin, A. et al. Comprehensive assessment of physiological responses in women during the ESA dry immersion VIVALDI microgravity simulation. *Nat. Commun.* **14**, 6311 (2023).
43. Lemoine, M. & Pradeu, T. Dissecting the Meanings of "Physiology" to Assess the Vitality of the Discipline. *Physiol. (Bethesda)* **33**, 236–245 (2018).
44. Kohl, P., Crampin, E. J., Quinn, T. A. & Noble, D. Systems biology: an approach. *Clin. Pharm. Ther.* **88**, 25–33 (2010).
45. Chen, R. et al. Personal omics profiling reveals dynamic molecular and medical phenotypes. *Cell* **148**, 1293–1307 (2012).
46. Blottner, D. et al. Space Omics and Tissue Response in Astronaut Skeletal Muscle after Short and Long Duration Missions. *Int. J. Mol. Sci.* **24**, https://doi.org/10.3390/ijms24044095 (2023).

47. Rittweger, J. et al. Sarcolab pilot study into skeletal muscle's adaptation to long-term spaceflight. *NPJ Microgravity* **4**, 18 (2018).
48. Blottner, D. et al. Nitrosative stress in astronaut skeletal muscle in spaceflight. *Antioxid. (Basel)* **13**, 432 (2024).
49. Murgia, M. et al. Spaceflight on the ISS changed the skeletal muscle proteome of two astronauts. *NPJ Microgravity* **10**, 60 (2024).
50. Garrett-Bakelman, F. E. et al. The NASA Twins Study: A multidimensional analysis of a year-long human spaceflight. *Science* **364**, https://doi.org/10.1126/science.aau8650 (2019).
51. Overbey, E. G. et al. The Space Omics and Medical Atlas (SOMA) and international astronaut biobank. *Nature* **632**, 1145–1154 (2024).
52. Overbey, E. G. et al. Collection of biospecimens from the inspiration4 mission establishes the standards for the space omics and medical atlas (SOMA). *Nat. Commun.* **15**, 4964 (2024).
53. ESA. HREDA - Human and *Robotic Exploration Data Archive*, https://hreda.esac.esa.int/hreda/#/pages/home (2024).
54. NASA. GeneLab, https://www.nasa.gov/osdr-genelab-about/ (2025).
55. Sobsey, C. A. et al. Targeted and Untargeted Proteomics Approaches in Biomarker Development. *Proteomics* **20**, e1900029 (2020).
56. Schmidt, M. A. & Goodwin, T. J. Personalized medicine in human space flight: using Omics based analyses to develop individualized countermeasures that enhance astronaut safety and performance. *Metabolomics* **9**, 1134–1156 (2013).
57. NASA. Human Health and Performance: Keeping Astronauts Safe & Productive On a Mission to Mars. 1-4 (2023).
58. Durante, M. & Cucinotta, F. A. Heavy ion carcinogenesis and human space exploration. *Nat. Rev. Cancer* **8**, 465–472 (2008).
59. Chouker, A. et al. European space agency's hibernation (torpor) strategy for deep space missions: Linking biology to engineering. *Neurosci. Biobehav. Rev.* **131**, 618–626 (2021).
60. Chouker, A., Bereiter-Hahn, J., Singer, D. & Heldmaier, G. Hibernating astronauts-science or fiction?. *Pflug. Arch. Eur. J. Physiol.* **471**, 819–828 (2019).
61. Cockett, T. K. & Beehler, C. C. Protective effects of hypothermia in exploration of space. *JAMA* **182**, 977–979 (1962).
62. Nordeen, C. A. & Martin, S. L. Engineering Human Stasis for Long-Duration Spaceflight. *Physiol. (Bethesda)* **34**, 101–111 (2019).
63. Cerri, M., Hitrec, T., Luppi, M. & Amici, R. Be cool to be far: Exploiting hibernation for space exploration. *Neurosci. Biobehav. Rev.* **128**, 218–232 (2021).
64. Cerri, M. et al. Hibernation for space travel: Impact on radioprotection. *Life Sci. Space Res (Amst.)* **11**, 1–9 (2016).
65. Bailey, D. M. Oxygen and brain death; back from the brink. *Exp. Physiol.* **104**, 1769–1779 (2019).
66. Bailey, D. M. Decoding the space integrome: Personalized countermeasures for a mission to Mars. *Exp. Physiol.* https://doi.org/10.1113/EP092629 (2025).
67. Scott, J. P. R., Green, D. A., Weerts, G. & Cheuvront, S. N. Effects of body size and countermeasure exercise on estimates of life support resources during all-female crewed exploration missions. *Sci. Rep.* **13**, 5950 (2023).
68. Rutter, L. A. et al. Protective alleles and precision healthcare in crewed spaceflight. *Nat. Commun.* **15**, 6158 (2024).
69. Sun, S. et al. A single-cell transcriptomic atlas of exercise-induced anti-inflammatory and geroprotective effects across the body. *Innov. (Camb.)* **4**, 100380 (2023).
70. Pillon, N. J. et al. Transcriptomic profiling of skeletal muscle adaptations to exercise and inactivity. *Nat. Commun.* **11**, 470 (2020).
71. Lander, E. S. et al. Adopt a moratorium on heritable genome editing. *Nature* **567**, 165–168 (2019).
72. Link, M. M. Space medicine in project mercury. (Washington, DC, USA, 1965).
73. Shirah, B., Bukhari, H., Pandya, S. & Ezmeirlly, H. A. Benefits of space medicine research for healthcare on Earth. *Cureus* **15**, e39174 (2023).
74. Cinelli, I. & Russomano, T. Advances in Space Medicine Applied to Pandemics on Earth. Space: *Sci. Technol.* **2021**, 1–3 (2021).
75. Scarpa, J., Parazynski, S. & Strangman, G. Space exploration as a catalyst for medical innovations. *Front Med (Lausanne)* **10**, 1226531 (2023).
76. Price, E. J. et al. Merging the exposome into an integrated framework for "omics" sciences. *iScience* **25**, 103976 (2022).
77. Rutter, L. et al. A New Era for Space Life Science: International Standards for Space Omics Processing. *Patterns (N. Y)* **1**, 100148 (2020).
78. Fraser, C. G. & Fogarty, Y. Interpreting laboratory results. *Br. Med. J.* **298**, 1659–1660 (1989).
79. Rose, G. A. et al. The cardiopulmonary exercise test grey zone; optimising fitness stratification by application of critical difference. *Br. J. Anaesth.* **120**, 1187–1194 (2018).
80. Hood, L. & Friend, S. H. Predictive, personalized, preventive, participatory (P4) cancer medicine. *Nat. Rev. Clin. Oncol.* **8**, 184–187 (2011).
81. Fernandez-Gonzalo, R., Schneider, S., Heer, M. & Liphardt, A. M. The search for the ultimate exercise countermeasure to preserve crew health and ensure mission success in long-duration spaceflight. *Exp. Physiol.* https://doi.org/10.1113/EP091737 (2025).

Acknowledgements

The authors acknowledge stimulating discussions and specialist input provided by Drs Kirsten MacDonell, Nicole Buckley, Christiane Hahn, Nicol Caplin, and Christopher Puhl of the European Space Agency (ESA) and Dr James Pawelczyk of Penn State University, USA. We also extend our sincere appreciation to the broader Exploration Science Team of ESA's Human Spaceflight and Exploration Directorate for initiating the ESA exploration science community White Papers concept. This paper is dedicated to the enduring memories of M. Bailey and Professor Dr. Med. Jörn Rittweger (1962–2025). D.M.B. is supported by ESA (ESA-HRE-RS-LE-0504), SpaceX (#grant number N/A) and a Royal Society Wolfson Research Fellowship (#WM170007). A.C. (#50WB2222), A.M.L. (#50WB2021), D.B. (#50WB2329), M.H. (50WB2137), and S.S. (#50WB2214 and #50WB2020) are supported by the German Ministry of Economic Affairs and Climate Action funds. D.B. is also supported by the German Federal Department of Education (BMBF) and German Aerospace Agency (DLR e.V.), Grant# 50WB2029/-2329. S.B. is supported by ESA/BELSPO/PRODEX IMPULSE2 contract CO-90-11-2801-04/PEA 4000140806. L.V. is supported by CNES (Centre National d'Études Spatiales) and ESA (DAR/OAR/TSR-2023.0003353 and 4000133329/20/NL/CLR). M.D. is supported by ESA contract 4000102355 (IBPER). F.P. is supported by the Italian Space Agency through the RelaxPro (DC-VUM-2020-007) and MINDFUL-ICE II (DC-DSR-UVS-2022-212), and ICEBLUE (A.N. 2025-14-HH.0) projects, ESA, the French Polar Institute Paul-Émile Victor, and the Programma Nazionale di Ricerche in Antartide. M.M. is supported by ESA-WHISPER (Contract Number 4000130928/20/NL/PG/pt) and EXPOSOME SIGNATURE (ESA-AO-2019-ISS-SDM, ESA-AO-2019-!SS-PP), and the Italian Space Agency EXPOSOME SIGNATURE, NUT (A.N. 2023-63-HH.0) and ICEBLUE (A.N. 2025-14-HH.0) projects.

Author contributions

D.M.B., D.B., H.C.G., S.S., V.W., S.B., M.D., R.H.G.O.E., N.G., M.H., A.M.L., M.M., F.P., C.S., J.B.S., T.W., L.V., O.W., A.V.O., and A.C. served as select working group members to the ESA White Paper #15 (Integrative and Countermeasures Approach). D.M.B. wrote the first draft of the manuscript, including figures, with input from A.V.O. and A.C. D.M.B., D.B., H.C.G., S.S., V.W., S.B., M.D., R.H.G.O.E., N.G., M.H., A.M.L., M.M., F.P., C.S., J.B.S., T.W., L.V., O.W., A.V.O., and A.C. edited and revised the manuscript. D.M.B., D.B., H.C.G., S.S., V.W., S.B., M.D., R.H.G.O.E., N.G., M.H., A.M.L., M.M., F.P., C.S., J.B.S., T.W., L.V., O.W., A.V.O., and A.C. approved the final version submitted for publication.

Competing interests

D.M.B. is Editor-in-Chief of Experimental Physiology and outgoing Chair of the Life Sciences Working Group and outgoing member of the Human Spaceflight and Exploration Science Advisory Committee to ESA. D.M.B. is a current member of the ESA-HRE-Biology Panel and Space Exploration Advisory Committees to the UK and Swedish National Space Agencies, and consultant to Bexorg, Inc. (USA) focused on the technological development of novel biomarkers of cerebral bioenergetic function in humans. A.V.O. is ESA's Chief Exploration Scientist, Directorate of Human and Robotic Exploration to ESA and Associate Editor of NPJ Microgravity. A.C. is Associate Editor of NPJ Microgravity, outgoing Chair of the Life and Physical Sciences Panel of the European Space Science Committee (ESSC) at the European Science Foundation (ESF), and Chair of the German Space Agency (DLR) Advisory Board 'Research and Exploration', and consultant to ESA. D.B. is Associate Editor of Frontiers in Physiology, Environmental, Aviation and Space Physiology, and Life Sciences in Space Research. C.S. is consultant to ESA and a member of the International Space Station SANS sub-working group. M.H. is consultant to ESA. M.M. is a consultant to ESA-FST for the development of the 3D bioprinter and 3D cell cultures system integrated research facility for the ISS.

Additional information

Correspondence and requests for materials should be addressed to Damian M. Bailey or Alexander Choukér.

[1]Neurovascular Research Laboratory, Faculty of Life Sciences and Education, University of South Wales, Glamorgan, UK. [2]Institute of Integrative Neuroanatomy, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany. [3]Center of Space Medicine and Extreme Environments, Charité-Universitätsmedizin Berlin, Berlin, Germany. [4]Department of Physiology, Center of Space Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany. [5]Institute of Movement and Neurosciences, Center for Health and Integrative Physiology in Space (CHIPS), German Sport University Cologne, Cologne, Germany. [6]International Space University, Strasbourg, France. [7]Center for Space Medicine, Baylor College of Medicine, Houston, TX, USA. [8]Institute of Nuclear Medical Applications, Belgian Nuclear Research Centre (SCK CEN), Mol, Belgium. [9]Gent University, Gent, Belgium. [10]Biophysics Department, GSI Helmholtzzentrum für Schwerionenforschung GmbH, Darmstadt, Germany. [11]Technische Universität Darmstadt, Institut für Physik Kondensierter Materie, Darmstadt, Germany. [12]Universita' Federico II, Dipartimento di Fisica "Ettore Pancini", Naples, Italy. [13]Department of Internal Medicine, Section of Nephrology, Amsterdam UMC Location University of Amsterdam, Amsterdam, Netherlands. [14]Amsterdam Cardiovascular Sciences, Microcirculation, Amsterdam, Netherlands. [15]Gravitational Physiology and Medicine Research Unit, Division of Physiology, Otto Löwi Research Center of Vascular Biology, Inflammation, and Immunity, Medical University of Graz, Graz, Austria. [16]College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates. [17]IU International University of Applied Sciences, Erfurt, Germany. [18]Institute of Nutritional and Food Sciences, University of Bonn, Bonn, Germany. [19]Department of Internal Medicine 3 – Rheumatology & Immunology, Universitätsklinikum Erlangen & Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany. [20]Deutsches Zentrum Immuntherapie (DZI), Universitätsklinikum Erlangen & Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany. [21]ASAcampus Joint Laboratory, ASA Res. Div., DSBSC-University of Florence, Florence, Italy. [22]Department of Psychology, Università Cattolica del Sacro Cuore, Milan, Italy. [23]German Aerospace Center, Institute of Aerospace Medicine, Cologne, Germany. [24]NORDFERTIL Research Lab Stockholm, Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet, and Karolinska University Hospital, Solna, Sweden. [25]NORDFERTIL Research Lab Uppsala, Department of Organismal Biology, University of Uppsala, Uppsala, Sweden. [26]ESA, EAC European Astronaut Centre, Spaceship and Facilities Team, Cologne, Germany. [27]KBR GmbH, Cologne, Germany. [28]Aerospace Medicine & Rehabilitation Laboratory, Department of Sport, Exercise & Rehabilitation, Northumbria University, Newcastle upon Tyne, UK. [29]U1059, INSERM, University Jean Monnet, Mines Saint-Etienne, France. [30]Cognition action and sensorimotor plasticity (INSERM U1093 CAPS), Université Bourgogne Europe, UFR des Sciences du sport, Dijon, France. [31]Directorate of Human and Robotic Exploration Programmes, European Space Agency, Cologne, Germany. [32]Translational Neurosciences, University of Antwerp, Antwerp, Belgium. [33]Laboratory of Translational Research "Stress and Immunity", Department of Anaesthesiology, LMU University Hospital, LMU Munich, Germany. ✉e-mail: damian.bailey@southwales.ac.uk; alexander.chouker@med.uni-muenchen.de