Pre-flight exercise and bone metabolism predict unloading-induced bone loss due to spaceflight

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ABSTRACT
Objectives Bone loss remains a primary health concern for astronauts, despite in-flight exercise. We examined changes in bone microarchitecture, density and strength before and after long-duration spaceflight in relation to biochemical markers of bone turnover and exercise.

Methods Seventeen astronauts had their distal tibiae and radii imaged before and after space missions to the International Space Station using high-resolution peripheral quantitative CT. We estimated bone strength using finite element analysis and acquired blood and urine biochemical markers of bone turnover before, during and after spaceflight. Pre-flight exercise history and in-flight exercise logs were obtained. Mixed effects models examined changes in bone and biochemical variables and their relationship with mission duration and exercise.

Results At the distal tibia, median cumulative losses after spaceflight were −2.9% to −4.3% for bone strength and total volumetric bone mineral density (vBMD) and −0.8% to −2.6% for trabecular vBMD, bone volume fraction, thickness and cortical vBMD. Mission duration (range 3.5–7 months) significantly predicted bone loss and crewmembers with higher concentrations of biomarkers of bone turnover before spaceflight experienced greater losses in tibia bone strength and density. Lower body resistance training volume (repetitions per week) increased 3–6 times in-flight compared with pre-spaceflight. Increases in training volume predicted preservation of tibia bone strength and trabecular vBMD and thickness.

Conclusions Findings highlight the fundamental relationship between mission duration and bone loss. Pre-flight markers of bone turnover and exercise history may identify crewmembers at greatest risk of bone loss due to unloading and may focus preventative measures.

INTRODUCTION
Long-duration spaceflight poses a risk to astronauts’ bone health, particularly weight-bearing bones. During typical 6-month missions to the International Space Station (ISS), rate of lower limb bone loss is 0.8% (0.5%–1.0%) per month.1,2 Thus, bone loss during a 6-month spaceflight parallels that experienced by elderly men and women over a decade of ageing on Earth.3 Given longer space explorations planned in the future (eg, missions to Mars), we need to better understand how microgravity alters bone structure and affects fracture risk in order to mitigate bone atrophy.

In microgravity, unloading primarily affects weight-bearing skeletal regions accustomed to higher strains from daily living in 1g.4 Given bone tissue’s mechanosensitive nature, bone adapts its structure and strength to match the localised mechanical loading environment.4,6 Despite in-flight countermeasures including near-daily exercise aboard the ISS using a treadmill, cycle ergometer and Advanced Resistance Exercise Device (ARED), microgravity imbalances bone metabolism such that bone resorption predominates and the skeleton deteriorates.7 ARED deployed on ISS in 2008 and allows 17 resistance exercises that mimic Earth conditions. ARED use reduces astronaut bone atrophy through increased bone formation; however, the stimulus has not prevented bone loss in every astronaut.7

Spaceflight-induced bone loss has traditionally been studied using dual-energy X-ray absorptiometry (DXA), an imaging modality measuring areal bone mineral density (aBMD). DXA enhanced our understanding of gross bone loss from spaceflight; however, it cannot detect bones’ finer structures (microarchitecture) that underpin changes in bone strength.8 High-resolution peripheral quantitative CT (HR-pQCT) images trabecular and cortical bone microarchitecture in vivo at a resolution finer than a human hair (61 µm),9 allowing sensitive characterisation of how bone adapts to microgravity.2 The objectives of this study were to: (1) examine the effect of long-duration spaceflight on bone microarchitecture, density and strength at the distal tibia and radius, and (2) determine the relationships between mission duration, biochemical markers of bone turnover and pre-flight and in-flight exercise on changes in bone morphology.

METHODS
Study design
We recruited 17 astronauts from the National Aeronautics and Space Administration (NASA), Canadian Space Agency, European Space Agency (ESA) and Japan Aerospace Exploration Agency (JAXA) selected for 3.5–7 months ISS missions. Astronauts were provided 800IU vitamin D 3 supplements daily during flight.

Outcomes
Primary outcome variables (online supplemental document S1) were HR-pQCT (60.7 µm nominal isotropic resolution, XtremeCT II; Scanco Medical) measurements of bone microarchitecture, volumetric bone mineral density (vBMD) and strength at the bilateral distal radii and tibiae (four sites) before and after spaceflight.9,11 We manually scored motion artefact on a scale from 1 (no motion) to 5 (discontinuities in the cortical shell and significant
Reproducibility in our laboratory ranges from <3% for density and microarchitecture to <14% for Ct.Po. Failure load (F.Load; N) was estimated by finite element analysis on unregistered images at each time point (figure 1). Reproducibility in our laboratory ranges from <3% for density and microarchitecture to <14% for Ct.Po. Failure load (F.Load; N) was estimated by finite element analysis on unregistered images (FAIM, V.8.0, Numerics88 Solutions). Reproducibility in our laboratory ranges from <3% for density and microarchitecture to <14% for Ct.Po. Failure load (F.Load; N) was estimated by finite element analysis on unregistered images (FAIM, V.8.0, Numerics88 Solutions).

Results
Crewmembers included 14 men and 3 women with a mean age 46.9 years (SD 6.7), height 177.7 cm (6.0), body mass 79.1 kg (7.7) and body mass index 25.0 kg/m² (2.1). Crewmembers were on-orbit for a mean of 170 days. The current mission was the first long-duration flight (>3 months) for 14 crewmembers. We excluded three HR-pQCT radius scans with motion >3 and 1 pre-flight and post-flight tibia scan due to previous ankle fracture. Three crewmembers did not participate in a collaborative study analysing CTx; thus, biomarker maximum sample size was 17 except for CTx. No crewmembers took anti-resorptive or other bone-related medication.

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Tibia Changes in bone strength and vBMD after spaceflight were consistent between the dominant and non-dominant tibiae.

Statistical analysis
All analyses were conducted using Stata (V.16, StataCorp). Change in bone variables from pre-flight to post-flight were assessed using Wilcoxon signed rank test. Pairwise percent change data are reported in text. Mixed effects models with Kenward-Roger small sample size adjustment examined changes in bone variables and included fixed effects of time (pre/post), mission duration and the interaction between time and mission duration. A random intercept allowed individuals their own intercept for the effect of time. Changes in biochemical markers of bone turnover were also examined using mixed effects models. Bonferroni correction accounted for multiple comparisons. Relationships between biochemical markers and exercise with change in bone variables were examined by individually adding biochemical markers and exercise variables as fixed effects (along with their interactions with time) to the mixed effects bone models. Model assumptions were assessed graphically using plots of residuals and significance was set at p<0.05.

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Visualisation of trabecular bone resorption (purple) and formation (green) after spaceflight. Image is from representative male crewmember who experienced a 4% decline in trabecular vBMD and 3% decline in trabecular thickness. vBMD, volumetric bone mineral density.

Figure 1 (A) Three-dimensional image of the distal tibia depicting trabecular (dark grey) and cortical bone (light grey) prior to spaceflight. (B) Trabecular bone (dark grey) and cortical bone (light grey) prior to spaceflight. (B) Area of bone loss (purple) and bone gain (green) after spaceflight. Image is representative of a male crewmember who experienced a 4% decline in trabecular vBMD and a 3% decline in trabecular thickness. vBMD, volumetric bone mineral density.
Median post-flight change (dominant, non-dominant) was $-4.3\%$, $-3.9\%$ for bone strength (F.Load); $-3.1\%$, $-2.9\%$ for Tt.vBMD, $-1.6\%$, $-1.2\%$ for Ct.vBMD and $-2.6\%$, $-2.0\%$ for Tb.vBMD (group median values presented in table 1; figure 2). Loss per month was $0.9\%$, $0.8\%$ for F.Load, $0.6\%$, $0.5\%$ for Tt.vBMD, $0.3\%$ for Ct.vBMD and $0.4\%$ for Tb.vBMD. Post-flight changes in Tb.BV/TV ($-1.9\%$) mirrored those of Tb.vBMD, while Tb.Th was $-1.5\%$, $-0.8\%$ lower at the dominant and non-dominant tibia, respectively and Tb.N was $0.7\%$ greater at the non-dominant tibia. No other changes in bone microarchitecture were observed at landing.

Mission duration predicted change in bone variables at the tibia (figures 2 and 3), indicating progressive loss with mission duration. Bone loss was linear between 3.5 and 7 months for those of Tb.vBMD, while Tb.Th was $-1.5\%$, $-0.8\%$ lower at the dominant and non-dominant tibia, respectively and Tb.N was $0.7\%$ greater at the non-dominant tibia. No other changes in bone microarchitecture were observed at landing.

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Only summary data are plotted: $x < 6 \%$ after spaceflight ($-0.5\% \text{ to } -0.9\% \text{ per month}$; online supplemental figure S1). Bone resorption markers CTx and NTx were elevated throughout flight and immediately post-flight compared with pre-flight. Markers of bone formation were elevated from midflight onwards (from FD60 for PINP and osteocalcin and FD120 for BSAP). Sclerostin was increased at FD30 and FD60. Serum phosphorus was elevated at FD30, FD120 and FD180, while urinary calcium was elevated through FD60.

Mixed effects models demonstrated negative relationships between average pre-flight bone turnover markers and changes in tibia bone strength and vBMD (online supplemental table S2; figure 5). Specifically, we observed significant negative interactions with time for pre-flight CTx ($\mu g$/day and/or $\mu g$/mmol Cr) with F.Load, Tr.vBMD and Ct.vBMD. The negative interaction with time indicated crewmembers with greater CTx before flight experienced greater loss of F.Load, Tr.vBMD and Ct.vBMD during spaceflight. A significant negative interaction with time was also observed at the dominant tibia for pre-flight NTx ($\mu g$/mmol Cr) with F.Load, OC with Tr.vBMD and PINP with Tb.vBMD, and at both tibiae for PINP with F.Load and Tr.vBMD. Pre-flight markers of bone turnover did not predict change at the radius. Greater pre-flight sclerostin predicted preservation of F.Load and Tr.vBMD at the dominant tibia. No other pre-flight biomarkers predicted changes in bone variables.

### Spaceflight and exercise

#### Aerobic exercise

On average, running frequency increased from two sessions/week (range 0–4) to four sessions/week (1–6) for a total of 86 min/week (range 0–150) to 87 min/week (24–148) from before spaceflight to in-flight, respectively. Cycling similarly increased from one session/week (0–3) to three sessions/week (1–4) and from 38 min/week (0–120) to 62 min/week (29–168), respectively. Pre-flight and in-flight running volume (min/week) were positively correlated ($r=0.589; p=0.013$), indicating those who ran most before spaceflight ran most in-flight. However, a negative relationship between pre-flight and change (in-flight–pre-flight) in running volume ($r=-0.501; p=0.040$) showed crewmembers who ran more before flight reduced running volume in-flight.

Negative interactions between pre-flight running volume and time indicated greater running volume before spaceflight predicted greater trabecular bone loss at the tibia during spaceflight (online supplemental table S3; figure 5). Neither pre-flight nor in-flight running and cycling predicted changes in F.Load, Tr.vBMD or Ct.vBMD at the dominant tibia.

#### Resistance exercise

Mean training volume (repetitions per week) for deadlifts, squats and heel raise increased from 49, 62 and 29 reps/week (range 0–180), respectively, before spaceflight to 221, 185 and 186 reps/week (range 59–456) in-flight, with change in training volume ranging from $-39$ to 356 reps/week. We observed positive interactions with time for change in deadlift training volume with F.Load at the dominant tibia ($\beta$ (95% CI): 1.6 N (0.2 to 2.9)), and change in deadlift training volume, change in heel raise volume and in-flight deadlift training volume with Tb.vBMD and Tb.Th at the non-dominant tibia (online supplemental table S1). Total body mass, lean mass and fat mass did not differ after spaceflight.
Table 2  Biochemical markers of bone turnover and bone metabolism before, during and after spaceflight

|                  | Pre-flight | FD15 | FD30 | FD60 | FD120 | FD180 | R+0 |
|------------------|------------|------|------|------|-------|-------|-----|
| **n†**           | 17         | 14   | 13   | 14   | 13    | 15    | 17  |
| **Bone resorption** |           |      |      |      |       |       |     |
| CTx (μg/d)       | 1513 (1068, 1935) | 2845 (2047, 4126)** | 3009 (2587, 3427)** | 3669 (3083, 4708)** | 3231 (2609, 4065)** | 2768 (2335, 4108)** | 2834 (2108, 3909)** |
| CTx (μg/mmol Cr) | 91 (63, 135) | 139 (123, 178)** | 165 (131, 225)** | 191 (161, 226)** | 186 (137, 217)** | 163 (120, 240)** | 145 (112, 207)** |
| NTx (mmol/d)     | 390 (323, 439) | 606 (461, 954)** | 589 (488, 702)** | 713 (531, 874)** | 600 (449, 905)** | 619 (479, 782)** | 651 (519, 740)** |
| NTx (mmol/mmol Cr) | 23 (20, 28) | 33 (22, 44)** | 32 (24, 40)** | 34 (28, 53)** | 31 (28, 41)** | 34 (27, 48)** | 38 (29, 45)** |
| **Bone formation** |           |      |      |      |       |       |     |
| BSAP (U/L)       | 21.2 (18, 22.5) | 20.9 (19.2, 21.9) | 19.8 (18.1, 22.8) | 23.7 (20.5, 26.3) | 25.2 (22.6, 27.2)** | 26.9 (22.4, 31.2)** | 27 (23.6, 32.5)** |
| OC (ng/mL)       | 20.9 (18.3, 23.6) | 20.3 (17.9, 26.4) | 22.6 (18.2, 27.2) | 24.6 (22.6, 28.9) ** | 29.9 (28.1, 36.1)** | 32.1 (29.4, 39.8)** | 32.6 (19.2, 28.7)** |
| P1NP (μg/L)      | 48.8 (42.3, 57.1) | 46.3 (35.4, 58.4) | 51.2 (48.9, 58.8) | 75.1 (68.8, 82.1) ** | 99.5 (77.4, 109.6)** | 94.4 (74.8, 112.6)** | 83.0 (72.0, 100.5)** |
| **Osteocyte activity** |           |      |      |      |       |       |     |
| Sclerostin (pmol/L) | 26.2 (21.3, 31.3) | 31.0 (25.9, 35.6) | 29.7 (26.3, 36.9)** | 30.4 (25.7, 37.1)* | 31.5 (24.3, 35.1) | 26.9 (22.6, 33.5) | 28.7 (21.1, 31.9) |
| **Regulators of bone metabolism** |           |      |      |      |       |       |     |
| Urinary calcium (mmol/d) | 4.86 (4.20, 6.14) | 7.43 (5.20, 9.10)** | 5.63 (4.51, 6.50)* | 6.77 (6.08, 8.00)** | 6.64 (4.40, 7.39) | 5.06 (3.32, 6.21) | 6.56 (5.15, 7.73) |
| Serum calcium (mmol/L) | 2.30 (2.28, 2.35) | 2.38 (2.35, 2.45) | 2.40 (2.37, 2.42) | 2.35 (2.32, 2.40) | 2.35 (2.31, 2.41) | 2.35 (2.30, 2.45) | 2.27 (2.25, 2.40) |
| PTH (pg/mL)      | 25.2 (22.1, 31.5) | 22.6 (18.0, 27.7) | 27.8 (21.3, 30.0) | 25.1 (17.0, 32.0) | 25.5 (19.0, 32.0) | 28.5 (22.0, 36.0) | 28.8 (25.5, 35.3) |
| 1,25(OH)2D (pmol/L) | 145 (128, 187) | 118 (102, 167) | 116 (96, 132)** | 133 (102, 160) | 130 (101, 162) | 137 (121, 171) | 185 (169, 232) |
| 25OHD (nmol/L)   | 86 (76, 96) | 82 (65, 86) | 77 (72, 87) | 81 (72, 86) | 79 (74, 85) | 80 (77, 84) | 77 (74, 81) |
| Phosphorus (mg/dL) | 3.8 (3.4, 4.0) | 4.0 (3.9, 4.1) | 4.3 (4.0, 4.7)* | 4.0 (3.7, 4.3) | 4.5 (3.8, 5.1)** | 4.2 (3.8, 4.6)* | 3.5 (3.2, 3.8) |
| OPG (pmol/L)     | 4.7 (3.7, 5.2) | 4.5 (4.0, 4.9) | 4.5 (4.1, 5.3) | 4.7 (4.1, 5.2) | 4.8 (4.4, 5.1) | 4.5 (4.1, 5.3) | 4.7 (4.1, 5.6) |
| RANKL (pmol/L)   | 361 (274, 462) | 196 (110, 304) | 222 (167, 318) | 171 (134, 273) | 183 (123, 296) | 207 (144, 317) | 140 (114, 287) |
| RANKL/OPG      | 46 (31, 68) | 47 (39, 63) | 45 (37, 71) | 40 (30, 57) | 37 (29, 60) | 48 (28, 81) | 29 (20, 67) |
| **Chemistry** |           |      |      |      |       |       |     |
| 24 hours urine volume (mL) | 1741 (1475, 2062) | 1408 (1020, 1845) | 1302 (1156, 1775) | 1472 (1221, 2241) | 1291 (1130, 1922) | 1358 (1123, 2025) | 1921 (1602, 2549) |
| Urinary creatinine (mmol/d) | 17 (16, 18) | 20 (18, 21) | 20 (18, 23) | 20 (18, 21) | 19 (16, 21) | 20 (17, 24) | 18 (17, 19) |
| Serum creatinine (mg/dL) | 1.00 (0.90, 1.00) | 1.00 (0.90, 1.00) | 1.00 (0.90, 1.00) | 0.97 (0.87, 1.00) | 0.99 (0.90, 1.10) | 1.00 (0.88, 1.10) | 0.90 (0.78, 0.90) |

Data are median (IQR). *p<0.05; **p<0.01 compared with pre-flight (mean of L-180 and L-45) based on linear mixed effects model with small sample adjustment and Benferroni correction. OC, 25OHD, RANKL, and RANKL/OPG were log-transformed for analysis. Maximal sample size for data collection period. Three participants did not have CTx analysed at any timepoint. BSAP: bone-specific alkaline phosphatase; CTx: type I collagen C-terminal cross-linked telopeptide; NTx: type I collagen N-terminal cross-linked telopeptide; OC: osteocalcin; 25OHD: 25-hydroxyvitamin D; 1,25(OH)2D, 1,25 di-hydroxyvitamin D; OPG, osteoprotegerin; P1NP, procollagen type 1 amino-terminal propeptide; PTH, intact parathyroid hormone.
S3 and figure S3). Pre-flight heel raise volume predicted loss of Tb.Th at the non-dominant tibia.

**DISCUSSION**

We observed substantial bone loss at the weight-bearing distal tibia over 3.5–7 months space missions. Astronauts’ bone quality was similar to terrestrial populations before spaceflight: mean 46th percentile for tibia total vBMD (range 0.4–9.5; based on age and sex-specific normative data). The five percentile decline in tibia vBMD after spaceflight (mean 41st percentile) parallels bone loss observed over two decades (from age 40 to 60) in men, while rate of bone loss was six times faster during spaceflight than during menopause. Loss of bone strength and vBMD at the radius. In contrast to our findings, EDOS did not observe trabecular thinning. However, EDOS employed an earlier generation HR-pQCT; whereas second-generation HR-pQCT directly captures and can better detect changes in trabecular microarchitecture.

**Bone microarchitecture, density and strength**

The Early Detection of Osteoporosis in Space (EDOS) study previously explored bone loss and recovery in 13 cosmonauts using HR-pQCT. As in our study, tibia vBMD declined by 1%–3% over 6 months of spaceflight while no changes in vBMD were observed at the radius. In contrast to our findings, EDOS did not observe trabecular thinning. However, EDOS employed an earlier generation HR-pQCT scanner with a lower image resolution (82 µm voxel size) unable to directly measure trabecular microarchitecture, whereas second-generation HR-pQCT directly captures and can better detect changes in trabecular microarchitecture.

Trabecular bone is located at the epiphyses of long bones and in vertebral bodies, where its 3D lattice microarchitecture enables load transfer and energy absorption. Given trabecular bone’s large surface area and proximity to bone marrow, it is designed for metabolic activities associated with bone turnover. Loss of trabecular bone connectivity may irreversibly damage bone structure, as there is no adaptive mechanism to reconnect dissociated trabeculae. The profound deterioration of trabecular vBMD and BV/TV we observed for tibial vBMD and strength would stabilise on longer missions or would continue to deteriorate. Thus, future studies of missions longer than 6-month spaceflights are required to examine temporality of bone loss and define the risks of proposed future missions outside Low-Earth orbit.

**Biomarkers of bone turnover**

In-flight serum and urine samples allowed us to examine how bone metabolism changes during flight. Whereas HR-pQCT bone measures reflect localised adaptation to the mechanical environment, biomarkers of bone turnover indicate systemic changes in bone mass balance that reflect the dynamics of bone remodelling and precede visible changes in mineralised bone mass. Variability probabilities for each biomarker are indicated in open circles next to a boxplot (median change, IQR) and overlaid by a lowess smoothing curve. CTX, type I collagen C-terminal cross-linked telopeptide; NTx, type I collagen N-terminal cross-linked telopeptide; P1NP, procollagen type 1 amino-terminal propeptide; BSAP, bone-specific alkaline phosphatase; OC, osteocalcin. Trajectories for remaining biomarkers can be found in online supplemental figure S2.
Rapid and sustained increases in markers of bone resorption were followed by slow increases in bone formation, such that crewmembers with elevated markers of bone resorption prior to spaceflight experienced greater losses in vBMD and strength. Although bone remodelling is integral for maintaining the skeleton’s mechanical competence by replacing old and damaged bone with new bone, excessive turnover may impair mechanical competence.11,31 We suspect bone in an elevated state of breakdown and repair prior to spaceflight may be primed for losing more bone in microgravity due to increased resorption and reduced formation. For example, when steady state remodelling is perturbed by microgravity, excavation of bone may be exacerbated by bone multicellular units (BMU) in a resorptive phase while deposition or mineralisation of new bone matrix may be reduced by BMUs in formation phase, resulting in net bone loss.

Exercise
Substantial bone loss occurred despite near-daily exercise on-orbit. Change in training volume from pre-flight may be essential for designing effective in-flight exercise regimes; thus, detailed pre-flight exercise histories should be obtained. Space agency’s Astronaut Strength, Conditioning and Rehabilitation (ASCR) specialists must balance exercise countermeasure time between preventing deconditioning of multiple body systems and avoiding overtraining injuries. In-flight resistance training volume increased 3–6 times on average compared with pre-flight volume, which may be sufficient for some astronauts to maintain bone structure and strength in microgravity. However, crewmembers with high strength training volumes prior to flight did not increase their training volume in-flight and experienced greater bone loss. It is challenging to provide the skeleton with adaptive strains in microgravity, particularly for crewmembers with high strength training volumes prior to flight. Exercise regimes with an approach that alternates training load and volume throughout the week35 may enhance osteogenic stimuli within the allotted time. Aerobic capacity and muscle strength likely recover after post-flight reconditioning36; however, microgravity-induced deterioration of bone structure may be irreversible. Thus, recognising high pre-flight running in markers of bone turnover is due to many factors, including genetics, age, sex, diet and exercise.30 We observed unbalancing of the normal bone remodelling process during spaceflight,18 31 where more bone was resorbed than formed, as also seen during menopause.32

What are the findings?

- Bone loss progresses with mission duration and does not stabilise on missions up to 7 months duration.
- Individuals with heightened pre-flight bone turnover may be more sensitive to the negative effects of unloading in microgravity.
- Crewmembers who increased their resistance training volume in-flight compared with pre-flight were more likely to preserve bone strength and trabecular bone at the tibia.
- Current in-flight exercise regimes may be insufficient to maintain bone structure and strength at the tibia in crewmembers with high pre-flight exercise training.

How might it impact on clinical practice in the future?

- Pre-flight bone turnover markers are an indicator of flight-induced bone loss, and as such could be used for prescribing exercise or other countermeasures.
- Crewmembers who run and/or strength train frequently prior to spaceflight may require different and/or additional preventative measures to mitigate bone loss.
- Findings are relevant for understanding how exercise affects bone loss in terrestrial populations where bone loss occurs due to reduced mechanical loading (eg, injury, disuse or disease).
and resistance training volumes as harbingers of spaceflight-induced bone loss may help flight surgeons and ASCR’s tailor in-flight exercise and other countermeasures. This study has several limitations. Our sample size was small; however, this is an inherent limitation of space-related research. Given sample size constraints, we were unable to examine differences between women and men. Second, in-flight exercise was automatically logged; however, crewmembers may have engaged in additional ARED workouts that were not logged. Further, pre-flight exercise was ascertained by self-report, which should be complemented by an objective measure (eg, accelerometer) in the future. Device-measured instead of self-reported physical activity may clarify relationships between habitual exercise and biomarkers of bone turnover, as we did not observe correlations between exercise and biomarkers (data not shown).

In summary, bone’s response to microgravity is site-specific and heterogeneous between individuals. We highlight the effect of mission duration for bone deterioration and the need for data from longer missions to confirm trajectories of (or plateaus in) bone loss. Microgravity-induced bone loss is complex and influenced by several factors; however, magnitude of change in the mechanical loading environment (ie, microgravity and exercise) is paramount for bone adaptation, particularly in the context of elevated pre-flight biomarkers of bone turnover. Thus, three key considerations include: (1) mission duration; (2) pre-flight markers of bone turnover and (3) pre-flight exercise training.

Correction notice This article has been corrected since it published Online First. The last author’s name has been amended.

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