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1 **NEW FRONTIERS IN THE MEASUREMENT OF ENERGY METABOLISM**

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10
11 **Running Head:** Frontiers in Energy Metabolism

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31 **Abstract**

32 This perspective highlights three key areas of current and future energy metabolism research:
33 intergenerational health, climate change, and interplanetary exploration. We describe the recent
34 advances in determining estimated energy requirements for a large subset of the general
35 population using the gold standard method for free-living total daily energy expenditure
36 estimates, the doubly labeled water method. The global rise in overweight and obesity demands
37 particular attention to energy requirements in pregnancy and early life as accumulating evidence
38 contributes to our understanding of intergenerational health transmission and the potential for
39 epigenetic programming *in utero*. We also acknowledge some gaps in necessary guidelines and
40 understandings of energy requirements for underrepresented populations (i.e., individuals from
41 low and middle-income countries) or those who undergo major physiological changes in new
42 environment (e.g., astronauts). The rising prevalence of excess weight gain, together with
43 climate change, cumulate into a global syndemic exposing vulnerable populations to both
44 malnutrition and the effects of unpredictable and severe weather events, emphasizing the need
45 for varied energetic data accounting for rapid physiological and socio-economic changes.
46 Finally, we relate how specific estimated energy requirements are needed to account for the
47 energetic challenges specific to extended space travel and ensure the success of interplanetary
48 exploration.

49

50 **Introduction**

51 Body mass and composition directly depend on the dynamic balance between the amount of
52 water, protein, fat, and carbohydrate that enter the body via food and water consumption and the
53 amount of these molecules being used by the body through oxidation or metabolism. Because
54 gains and losses to body weight influence health and disease, research in energy (and substrate)
55 metabolism is critical.

56 Both energy balance and oxidative balance are involved in body weight and composition control.
57 Oxidative balance is the difference between the ingestion and oxidative rates of macronutrients
58 (lipid, carbohydrate and protein). Energy substrate oxidation can be quantified by measuring
59 changes in oxygen consumption and carbon dioxide production using indirect calorimetry along

60 with measures of urinary nitrogen output. Energy balance is the state in which energy intake is
61 equal to energy expenditure. Estimated energy requirements (EER) are used to predict the
62 average dietary energy intake needed to maintain energy balance and avoid weight gains or
63 losses. To establish accurate EER, the total number of calories burned within a given time is
64 measured using the doubly labeled water (DLW) method. The DLW method provides free-living
65 total daily energy expenditure measures over the course of multiple days, accounting for day-to-
66 day variability in energy expenditure (1, 2, 3, 4). This non-invasive method, requiring individuals
67 to drink water enriched with deuterium and oxygen-18 and collect spot urine samples, was
68 established in the early 1980s and has since become the gold-standard measure of total energy
69 expenditure under daily conditions for its reliability and ease of data collection (1).

70 Body weight control relies on accurate EER predictions that can account for energetic variation
71 between individuals and populations. In January 2023, the National Academies of Sciences,
72 Engineering, and Medicine (NASEM) published a revised report of their recommended EER for
73 the US and Canada (5). NASEM's new dietary reference intakes (DRI) for EER were derived
74 from published studies and from an international compilation of DLW data governed by the
75 International Atomic Energy Agency (IAEA) (6). They are based on sex-specific equations to
76 predict EER from birth to old age (5). Although the updated DRI report marks a turning point in
77 the definition and use of EER to maintain energy balance that optimizes health and growth, they
78 remain incomplete.

79 Global challenges such as the intergenerational transmission of health and disease, climate
80 change, and human interplanetary travel call for comprehensive approaches to energetic
81 variability in order to establish context specific EER and lay the groundwork for effective
82 precision medicine. In this perspective, we provide a brief roadmap of the advances to the field
83 of energy metabolism in the key research areas: intergenerational health, climate change and
84 their interconnecting factors, as well as human interplanetary exploration (Figure 1).

85 [INSERT FIGURE 1 HERE]

86

87 **Beyond Childbirth: Intergenerational transmission of obesity**

88 In 2005, the EER for pregnancy were based upon only four studies measuring total energy
89 expenditure and six studies measuring energy deposition among pregnant women, all of whom
90 had a body mass index between 18.5 and 25 kg/m², omitting a large portion of the population (5).
91 The ongoing population shift towards a greater propensity for individuals becoming pregnant
92 whilst living with overweight or obesity requires updated considerations for pregnant individuals
93 of all body sizes (7, 8). Included in the 2023 NASEM report is a prospective study in a cohort of
94 pregnant females living with obesity (n=54) showing that to achieve the recommended weight
95 gain in pregnancy (170-270g/week) energy intake should not exceed energy expenditure (9).
96 NASEM now recommends EER for all females during pregnancy according to pre-pregnancy
97 body mass index, physical activity level, week of gestation, and pregnancy weight gain
98 recommendations (5). Indeed, there is an inverse association between the EER for pregnant
99 individuals and pre-pregnancy BMI; individuals who enter pregnancy at a higher BMI need
100 fewer additional calories in pregnancy to achieve a healthy gestational weight gain (5.0-9.0kg of
101 total weight gain) compared to lean individuals (11.5-16kg of total weight gain).

102 The intergenerational transmission of obesity and diabetes and potential for epigenetic
103 programming *in utero* and in early life promotes the need for additional succinct determinations
104 of EER across different levels of obesity before, during, and post-pregnancy including all
105 breastfeeding and partially or non-breastfeeding contexts. For the first time, the EER for
106 postpartum females consider different levels of breastfeeding instead of assuming all lactating
107 females are exclusively breastfeeding from birth to 6 and even 12 months postpartum (5). While
108 maternal obesity exposure during pregnancy and gestational weight gain increases the risk for
109 both mother and child to develop long-term obesity and type II diabetes, evidence suggests that
110 human milk feeding has a protective role against obesity for the child (10, 11, 12).

111 After evidence of an overestimation of energy expenditure and energy deposition in newborns,
112 EER was updated for children between birth and 24 months (13). The current EER for infants
113 includes groups based on age: 0 to 2.99 months and 3 to 24 months, respectively. Notably the
114 latter covers a large period of time and potentially misrepresents the variation in the effects of
115 growth and development on energy expenditure (14). The low EER of young children limits the
116 range of error which can be tolerated to avoid accelerating detrimental weight gain trajectories
117 (15). Furthermore, logistics of pregnancy and early life, such as timing of pregnancy discovery,

118 increased medical care, and behavioral shifts associated with newborn care limit opportunities
119 for longitudinal measures of energy metabolism from conception throughout postpartum.

120 Our understanding of the energetic demands of pregnancy and the postpartum period emphasizes
121 the limitations of current findings and the need for more energetic data in pregnancy, the
122 postpartum period, and prospectively in early life. In addition to examining the changes in
123 energy balance during peripartum, a better understanding of the changes in substrate oxidation is
124 needed to convey appropriate nutritional requirements during this period. Evidence shows that
125 carbohydrate oxidation decreases, and lipid utilization increases in lean individuals between
126 pregnancy and the first 6 months postpartum, especially in those lactating (16, 17). Among
127 individuals with obesity and gestational diabetes mellitus, the increase in fat oxidation between
128 early and late pregnancy is significantly greater compared to healthy individuals with obesity
129 (18). To best characterize appropriate EER across and beyond pregnancy more investigations on
130 substrate metabolism among different phenotypes and gestational weight gain variation during
131 pregnancy and postpartum are needed. The future frontiers in the measurements of energy
132 metabolism as it pertains to pregnancy will go beyond the individual and assess EER from
133 mother-infant dyads to minimize the possible detrimental health effects of parental obesity on
134 future generations (19).

135

136 **Beyond Borders: Underrepresented populations and the global malnutrition syndemic**

137 The rapidly changing environments, be it extreme temperatures due to climate change or the
138 growing rates of obesogenic environments in predominantly low- and middle-income countries,
139 create a global syndemic, i.e., the association of malnutrition (undernutrition and obesity) and
140 climate change, requiring rapid physiological adjustments (20, 21). By increasing food and water
141 insecurity, climate change along with rapid and continuous modifications in land use,
142 agriculture, and food enhance the risk of malnutrition among vulnerable populations (22). Policy
143 inertia, economic burdens, and the exclusion of obesity from global concerns worsen the
144 malnutrition syndemic, especially among disadvantaged groups such as low-income and non-
145 white individuals (21). Given the increased risk of becoming overweight later in life related to
146 undernutrition of fetuses and infants, obesity and overweight prevalence is likely to rise quickly
147 in these populations. (21). The interdependence of physiological and socioeconomic factors that

148 contribute to malnutrition and energy imbalance emphasizes the need for a holistic and
149 comprehensive approach to EER and precision medicine, more broadly. The rapid global shift
150 towards industrialization promotes an increase in obesogenic environments in turn contributing
151 to weight gain, especially among African Americans and Native populations (23, 24). Extreme
152 weather events (both heat and cold exposure) due to climate change, will continue to drive
153 human migration towards urban centers exposing many to thermogenic stressors in addition to
154 novel obesogenic environments compounding adjustments in energy requirements (25, 26, 27).
155 The speed of shifts in the global socio-economic landscape coupled with the rapid increase in
156 novel environmental extremes limit the existing data on their effects on human energy
157 expenditure and substrate utilization. The systematic underrepresentation of non-White
158 populations in energetic studies further exacerbates the lack of understanding of the variation in
159 physiological adaptations to these rapid changes. Controlled DLW and substrate utilization data,
160 of which currently very little or none exist, are needed among populations facing urbanization
161 along with nutrition and physical activity transitions to determine the etiology of obesity and
162 support future EER in accounting for and addressing the global syndemic. Given their relative
163 ease of use, the DLW method and indirect calorimetry represent safe and non-invasive ways to
164 bridge the gap in our understanding of the interaction between the physical activity and nutrition
165 in populations undergoing these transitions (28, 29).

166

167 **Beyond Earth: Human interplanetary exploration**

168 The current use of the DLW equations may, however, fall short for individuals with specific
169 requirements (e.g., astronauts). Spaceflight is characterized by systematic body mass loss and
170 large inter-individual variability in EI and EE (30, 31, 32). Chronic energy deficit can lead to a
171 cascade of health issues and exacerbate those already triggered by microgravity including
172 cardiovascular deconditioning, loss of bone and muscle mass, and changes to intermediate
173 metabolism (33, 34). Using the DLW method to measure EE during the 16-day LMS mission, an
174 energy deficit of up to 5.7 ± 0.3 MJ/day was reported in four male astronauts (35). The
175 systematic body mass changes that were once acceptable for shorter-duration spaceflight
176 represent a serious health risk (e.g., reductions in crew performance, increased risk of illness,
177 severe dehydration, etc.) (36) and are incompatible with a mission to Mars, where weight losses

178 of 15% or more are projected (33). Thus, the space agencies' roadmaps have assigned inflight
179 energy balance control a high priority for both operational and medical reasons (37).

180 The energy cost of exercise, the cornerstone of the countermeasure program developed to
181 mitigate the microgravity-induced body alterations, was considered for the first time in a study
182 measuring EER among 11 male astronauts during 6-month missions onboard the International
183 Space Station (ISS) (38). It established that inflight body composition regulation is influenced by
184 inflight activity energy expenditure, which is connected to both non-exercise and exercise
185 physical activities. Astronauts with stable total energy expenditure (n=6) maintained their fat-
186 free mass while losing fat mass. Those who were unable to maintain the preflight energy
187 expenditure (n=5) lost fat-free mass but gained fat mass. The changes in fat mass resulted from
188 energy intake adaptations uncoupled with inflight energy expenditures.

189 Given the significant inter-astronaut heterogeneity in energy balance and other underlying issues
190 impacting astronauts' energy balance, EER for space travel cannot be determined using general
191 population equations. Monitoring in-flight changes in body composition, calorie intake, and
192 energy expenditure is essential for guaranteeing astronaut performance and the success of future
193 exploratory missions. The next stages should be to identify the DRI for both male and female
194 astronauts of various age groups for prolonged space missions and assess the energy cost and
195 impact on the energy balance of the countermeasure, such as exercise, in the astronauts' deep
196 space trip program. The ideal exercise parameters and other possible countermeasures, and the
197 tolerable body mass, fat mass and fat-free mass loss thresholds will need to be defined. As a
198 variety of factors, such as limited food availability, contribute to the loss of body mass (39), it is
199 essential to investigate the nutritional value of the food produced in space and how well it is
200 assimilated if we want to consider the potential of human existence on another planet.
201 Ultimately, EER for humans living on planets with lower gravity (e.g., 0.38 on Mars and 0.17 on
202 the Moon) will need to be established.

203 Research is also required on the mechanisms underlying inflight energy imbalance, including
204 regulation of energy expenditures, feeding behavior and appetite, mechanical and metabolic
205 efficiencies, and substrate use. Human ground-based studies repeatedly reported alterations in
206 substrate oxidation during simulated microgravity, with a shift toward carbohydrate use as fuel
207 and to the detriment of fat oxidation (40, 41, 42). Recently, we observed such a fuel shift in

208 astronauts while onboard the ISS. Although muscle remodeling, transcriptional and molecular
209 adaptations of peripheral tissues are likely involved, we unexpectedly found that dietary changes
210 during spaceflight widely contribute to this shift in fuel selection (unpublished data,
211 Bergouignan). Further investigations are needed to better understand the factors regulating
212 energy and substrate metabolism in low or zero gravity.

213

214 **Future Frontiers of Energy Metabolism**

215 NASEM's new EER guidelines acknowledge and incorporate the changing metabolic landscapes
216 of the US and Canada. Their advances also shed light on the limitations of current energy
217 metabolism measures and their applicability. These include the use of physical activity level for
218 late pregnancy and postpartum EER determination or the lack of energetic data in humans
219 experiencing environmental and social stressor such as climate change and prolonged
220 microgravity.

221 Future scientific pursuits will need to evaluate how the NASEM EER translates to low- and
222 middle-income countries and across population subgroups and provide accurate EER for people
223 worldwide. Although the IAEA dataset allows for a broad overview of different DLW measures
224 across ages, ethnicities, geographies, and socio-economic contexts, many socio-ecological
225 contexts remain understudied (e.g., early life, deep space, or extreme temperatures) and need to
226 be included in future data collections to best represent the dynamic and intersecting
227 environmental, social and physiological characteristics contributing to energetic requirements.
228 Research on energy metabolism is entering an exciting era as it ought to tackle the biggest and
229 novel challenges in energy metabolism facing humankind; obesity, climate change, and human
230 deep space exploration.

231

232 **Author Contributions**

233 A.N. and P.S. drafted manuscript; A.N. prepared figure; A.N., P.S., L.R., and A.B. edited and
234 revised manuscript; A.N., P.S., L.R., and A.B. approved final version of manuscript.

235

236 **References**

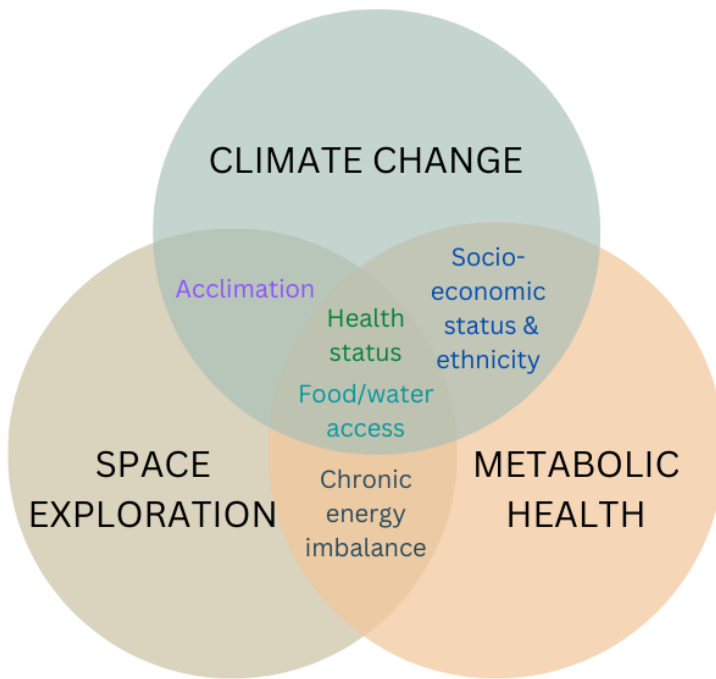
- 237 1. **Schoeller DA, & Van Santen E.** Measurement of energy expenditure in humans by doubly
238 labeled water method. *J Appl Phys* 53: C955-959, 1982.
239
- 240 2. **Schoeller DA, Ravussin E, Schutz Y, Acheson KJ, Baertschi P, & Jequier E.** Energy
241 expenditure by doubly labeled water: validation in humans and proposed calculation. *A J*
242 *Phys-Reg, Int Comp Phys* 250: R82, 1986
243
- 244 3. **Westerterp KR, Brouns F, Saris WH & ten Hoor F.** Comparison of doubly labeled water
245 with respirometry at low-and high-activity levels. *J App Phys*, 65: 53-56, 1988.
246
- 247 4. **Ainslie PN, Reilly T & Westerterp KR.** Estimating human energy expenditure: a review of
248 techniques with particular reference to doubly labelled water. *Sports Med*, 33: 683-698, 2003.
249
- 250 5. **National Academies of Sciences, Engineering, and Medicine.** *Dietary Reference Intakes for*
251 *Energy*, 2023.
252
- 253 6. **Speakman JR, Pontzer H, Rood J, Sagayama H, Schoeller DA, Westerterp KR, Wong**
254 **WW, Yamada Y, Loechl C. & Murphy-Alford AJ.** The international atomic energy agency
255 international doubly labelled water database: aims, scope and procedures. *Ann Nutr*
256 *Metab*, 75: 114-118. 2019.
257
- 258 7. **Statistics Canada.** Health fact sheets: Overweight and obese adults, 2018. 2019.
259 <https://www150.statcan.gc.ca/n1/pub/82-625-x/2019001/article/00005-eng.htm> [accessed
260 September 30, 2022].
261
- 262 8. **Fryar CD, Carroll MD, & Ogden CL.** Prevalence of overweight, obesity, and severe obesity
263 among children and adolescents aged 2–19 years: United States, 1963–1965 through 2017–
264 2018. *NCHS Health E-Stats*, 2020.
265
- 266 9. **Most J, St Amant M, Hsia DS, Altazan AD, Thomas DM, Gilmore LA, Vallo PM, Beyl**
267 **RA, Ravussin E, & Redman LM.** Evidence-based recommendations for energy intake in
268 pregnant women with obesity. *J Clin Investig*, 129: 4682-4690, 2019
269
- 270 10. **Pettitt DJ, & Jovanovic L.** Birth weight as a predictor of type 2 diabetes mellitus: the U-
271 shaped curve. *Curr Diabetes Rep*, 1: 78-81, 2001.
272
- 273 11. **Mamun AA, Kinarivala M, O’Callaghan MJ, Williams GM, Najman JM, & Callaway**
274 **LK.** Associations of excess weight gain during pregnancy with long-term maternal
275 overweight and obesity: evidence from 21 y postpartum follow-up. *Am J Clin Nutr*, 91: 1336-
276 1341, 2010.
277
- 278 12. **Yan J, Liu L, Zhu Y, Huang G. & Wang PP.** The association between breastfeeding and
279 childhood obesity: a meta-analysis. *BMC Public Health*, 14: 1-11, 2014.
280
- 281 13. **Butte NF.** Energy requirements of infants. *Public Health Nutr*, 8(7a): 953-967, 2005.
282

- 283 14. **Pontzer H, Yamada Y, Sagayama H, Ainslie PN, Andersen LF, Anderson LJ, ... &**
284 **IAEA DLW Database Consortium.** Daily energy expenditure through the human life
285 course. *Science*, 373(6556): 808-812. 2021.
286
- 287 15. **Altazan AD, Gilmore LA, Guo J, Rosenberg DM, Toupo D, Gowins A, ... & Redman**
288 **LM.** Unintentional error in formula preparation and its simulated impact on infant weight
289 and adiposity. *Pediatric Obesity*, 14(12): e12564. 2019.
290
- 291 16. **Butte N F, Hopkinson JM, Mehta N, Moon JK, & Smith EOB.** Adjustments in energy
292 expenditure and substrate utilization during late pregnancy and lactation. *Am J Clin*
293 *Nutr*, 69(2): 299-307. 1999.
294
- 295 17. **Butte NF.** Carbohydrate and lipid metabolism in pregnancy: normal compared with
296 gestational diabetes mellitus. *Am J Clin Nutr*, 71(5): 1256S-1261S. 2000.
297
298
- 299 18. **Okereke NC, Huston-Presley L, Amini SB, Kalhan S, & Catalano PM.** Longitudinal
300 changes in energy expenditure and body composition in obese women with normal and
301 impaired glucose tolerance. *Am J Physiol Endo Metab*, 287(3): E472-E479. 2009.
302
- 303 19. **Thompson AL.** Intergenerational impact of maternal obesity and postnatal feeding practices
304 on pediatric obesity. *Nutr Rev*, 71(suppl_1): S55-S61. 2013.
305
- 306 20. **Singer M.** *Introduction to syndemics: a critical systems approach to public and community*
307 *health.* New York: Wiley, 2009.
308
- 309 21. **Swinburn BA, Kraak VI, Allender S, Atkins VJ, Baker PI, Bogard JR, Brinsden H,**
310 **Calvillo A, De Schutter O, Devarajan R & Ezzati M, 2019.** The global syndemic of
311 obesity, undernutrition, and climate change: the Lancet Commission report. *Lancet*, 393:
312 791-846, 2019.
313
- 314 22. **Thompson AL, Nicholas KM, Watson E, Terán E, & Bentley ME.** Water, food, and the
315 dual burden of disease in Galápagos, Ecuador. *Am J Hum Bio*, 32: e23344, 2020.
316
- 317 23. **Guo F, Bostean G, Berardi V, Velasquez AJ. & Robinette JW.** Obesogenic environments
318 and cardiovascular disease: a path analysis using US nationally representative data. *BMC*
319 *Public Health*, 22(1): 1-12. 2022.
320
- 321 24. **Lake A, & Townshend T.** Obesogenic environments: exploring the built and food
322 environments. *J R Soc Promot Health*, 126(6): 262-267. 2006.
323
- 324 25. **Delavari M, Sønderlund AL, Swinburn B, Mellor D, & Renzaho A.** Acculturation and
325 obesity among migrant populations in high income countries—a systematic review. *BMC*
326 *Public Health*, 13: 1-11. 2013.
327
- 328 26. **Minos D, Butzlaff I, Demmler KM, & Rischke R.** Economic growth, climate change, and
329 obesity. *Curr Obes Rep*, 5: 441-448. 2016.

- 330
331 27. **Ocobock C.** Human cold adaptation: An unfinished agenda v2. 0. *Am J Hum Bio*, e23937.
332 2023.
- 333 28. **Popkin BM.** Global nutrition dynamics: the world is shifting rapidly toward a diet linked
334 with noncommunicable diseases. *Am J Clin Nutr*, 84(2): 289-298. 2006.
- 335 29. **Bourdier P, Duboz P, Macia E, Ka A, Nazare JA, Cohen E, Boetsch G, Blanc S, Simon**
336 **C, Bergouignan A.** How interdisciplinary research at the crossroad between socio-cultural
337 anthropology and nutritional physiology can help addressing the obesity epidemic. *Cahiers*
338 *de Nutrition et Diététique*, 56(1): 51-58.
- 339 30. **Wade CE, Miller MM, Baer LA, Moran MM, Steele MK, & Stein TP.** Body mass,
340 energy intake, and water consumption of rats and humans during space flight, *Nutr J*, 18(10),
341 C829–836, 2002. doi:10.1016/S0899-9007(02)00914-0.
- 342
343 31. **Matsumoto A, Storch KJ, Stolfi A, Mohler SR, Frey MA & Stein TP.** Weight Loss in
344 Humans in Space, *ASEM*, 82(6), C615–621, 2011. doi.10.3357/ASEM.2792.2011.
- 345
346 32. **Laurens C, Simon C, Vernikos J, Gauquelin-Koch G, Blanc S, & Bergouignan A.**
347 Revisiting the role of exercise countermeasure on the regulation of energy balance during
348 space flight. *Front Physiol*, 10, 321, 2019. doi:10.3389/fphys.2019.00321.
- 349
350 33. **Mulavara AP, Peters BT, Miller CA, Kofman IS, Reschke MF, Taylor LC, Lawrence**
351 **EL, Wood SJ, Laurie SS, Lee SMC, Buxton RE, May-Philipps TR, Stenger MB, Ploutz-**
352 **Snyder, LL, Ryder JW, Feiveson AH & Bloomberg, JJ.** Physiological and functional
353 alterations after spaceflight and bed rest. *Med Sci Sports Exerc*, 50(9), 1961., 2018.
354 doi:10.1249/MSS.0000000000001615.
- 355
356 34. **Lang T, Van Loon, JJ, Bloomfield S, Vico L, Chopard A, Rittweger J, Kyparos A,**
357 **Blottner D, Vuori I, Gerzer R & Cavanagh, PR.** Towards human exploration of space: the
358 THESEUS review series on muscle and bone research priorities. *npj Microgravity*, 3(1), 8,
359 2017.
- 360
361 35. **Stein, T. P., Leskiw, M. J., Schluter, M. D., Hoyt, R. W., Lane, H. W., Gretebeck, R. E.,**
362 **& LeBlanc, A. D.** Energy expenditure and balance during spaceflight on the space shuttle.
363 *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*,
364 276(6), R1739-R1748. 1999. doi:10.1152/ajpregu.1999.276.6.R1739.
- 365
366 36. **Douglas GL, Cooper M, Bermudez-Aguirre D, & Sirmons T.** *Risk of performance*
367 *decrement and crew illness due to an inadequate food system.* No. JSC-CN-37577. 2016.
- 368
369 37. **Bergouignan A, Stein TP, Hibold C, Coxam V, O’gorman D, & Blanc S.** Towards
370 human exploration of space: The THESEUS review series on nutrition and metabolism
371 research priorities. *npj Microgravity*, 2(1), 1-8, 2016.
- 372

- 373 38. **Bourdier C, Zahariev A, Schoeller DA, Chery I, Le Roux E, Thevenot C, Maillet A,**
374 **Garnotel M, Gauquelin-Koch G, Bergouignan A, Blanc S & Simon C.** Effect of Exercise
375 on Energy Expenditure and Body Composition in Astronauts Onboard the International
376 Space Station: Considerations for Interplanetary Travel, *Sports Med*, 52(12), C3039–3053,
377 2022. doi:10.1007/s40279-022-01728-6.
378
- 379 39. **Douglas GL, Zwart SR, & Smith SM.** Space food for thought: challenges and
380 considerations for food and nutrition on exploration missions. *J Nutr*, 150(9), 2242-2244,
381 2020.
382
- 383 40. **Blanc S, Normand S, Pachiaudi C, Fortrat JO, Laville M, & Gharib C.** Fuel homeostasis
384 during physical inactivity induced by bed rest. *J Clin Endo Metab*, 85(6): 2223-2233. 2000.
385
- 386 41. **Bergouignan, A., Trudel, G., Simon, C., Chopard, A., Schoeller, D. A., Momken, I., ... &**
387 **Blanc, S.** Physical inactivity differentially alters dietary oleate and palmitate trafficking.
388 *Diabetes*, 58(2), 367-376, 2009.
389
- 390 42. **Le Roux, E., De Jong, N. P., Blanc, S., Simon, C., Bessesen, D. H., & Bergouignan, A.**
391 **Physiology of physical inactivity, sedentary behaviours and non- exercise activity: insights**
392 **from the space bedrest model. *The Journal of Physiology*, 600(5), 1037-1051, 2022.**
393
394
395

396 **Figure legend**



397
398

399 Figure 1. Future frontiers in the measurement of energy metabolism and the underlying
400 connecting factors contributing to variations in energetic requirements between and within
401 populations.

402

403