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3 **Daily Energy Expenditure through the Human Life Course**

4
5 Herman Pontzer^{1,2†*}, Yosuke Yamada^{3,4†}, Hiroyuki Sagayama^{5†}, Philip N. Ainslie⁶, Lene F.
6 Andersen⁷, Liam J. Anderson^{6,8}, Lenore Arab⁹, Issaad Baddou¹⁰, Kweku Bedu-Addo¹¹, Ellen E.
7 Blaak¹², Stephane Blanc^{13,14}, Alberto G. Bonomi¹⁵, Carlijn V.C. Bouten¹², Pascal Bovet¹⁶,
8 Maciej S. Buchowski¹⁷, Nancy F. Butte¹⁸, Stefan G. Camps¹², Graeme L. Close⁶, Jamie A.
9 Cooper¹³, Richard Cooper¹⁹, Sai Krupa Das²⁰, Lara R. Dugas¹⁹, Ulf Ekelund²¹, Sonja
10 Entringer^{22,23}, Terrence Forrester²⁴, Barry W. Fudge²⁵, Annelies H Goris¹², Michael Gurven²⁶,
11 Catherine Hambly²⁷, Asmaa El Hamdouchi¹⁰, Marjije B. Hoos¹², Sumei Hu²⁸, Noorjehan
12 Joonas²⁹, Annemiek M. Joosen¹², Peter Katzmarzyk³⁰, Kitty P. Kempen¹², Misaka Kimura³,
13 William E. Kraus³¹, Robert F. Kushner³², Estelle V. Lambert³³, William R. Leonard³⁴, Nader
14 Lessan³⁵, Corby Martin³⁰, Anine C. Medin^{7,36}, Erwin P. Meijer¹², James C. Morehen^{37,6}, James P.
15 Morton⁶, Marian L. Neuhouser³⁸, Theresa A. Nicklas¹⁸, Robert M. Ojiambo^{39,40}, Kirsi H.
16 Pietiläinen⁴¹, Yannis P. Pitsiladis⁴², Jacob Plange-Rhule^{43**}, Guy Plasqui⁴⁴, Ross L. Prentice³⁸,
17 Roberto A. Rabinovich⁴⁵, Susan B. Racette⁴⁶, David A. Raichlen⁴⁷, Eric Ravussin³⁰, Rebecca M.
18 Reynolds⁴⁸, Susan B. Roberts²⁰, Albertine J. Schuit⁴⁹, Anders M. Sjödin⁵⁰, Eric Stice⁵¹, Samuel
19 S. Urlacher⁵², Giulio Valenti^{12,15}, Ludo M. Van Etten¹², Edgar A. Van Mil⁵³, Jonathan C. K.
20 Wells⁵⁴, George Wilson⁶, Brian M. Wood^{55,56}, Jack Yanovski⁵⁷, Tsukasa Yoshida⁴, Xueying
21 Zhang^{27,28}, Alexia J. Murphy-Alford⁵⁸, Cornelia Loechl⁵⁸, Amy H Luke^{59†}, Jennifer Rood^{30†},
22 Dale A. Schoeller^{60†}, Klaas R. Westerterp^{61†}, William W. Wong^{18†}, John R.
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24 *co-lead corresponding author

25 †co-corresponding author

26 ** deceased

27 # see supplementary materials

28

- 29 1. Evolutionary Anthropology, Duke University, Durham NC, USA
30 2. Duke Global Health Institute, Duke University, Durham, NC, USA
31 3. Institute for Active Health, Kyoto University of Advanced Science, Kyoto, Japan.
32 4. National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health
33 and Nutrition, Tokyo, Japan.
34 5. Faculty of Health and Sport Sciences, University of Tsukuba, Ibaraki, Japan.
35 6. Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool,
36 UK.
37 7. Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, 0317 Oslo,
38 Norway.
39 8. Crewe Alexandra Football Club, Crewe, UK.
40 9. David Geffen School of Medicine, University of California, Los Angeles.

41 10 Unité Mixte de Recherche en Nutrition et Alimentation, CNESTEN- Université Ibn Tofail URAC39,
42 Regional Designated Center of Nutrition Associated with AFRA/IAEA.
43 11 Department of Physiology, Kwame Nkrumah University of Science and Technology, Kumasi,
44 Ghana.
45 12 Maastricht University, Maastricht, The Netherlands.
46 13 Nutritional Sciences, University of Wisconsin, Madison, WI, USA
47 14 Institut Pluridisciplinaire Hubert Curien. CNRS Université de Strasbourg, UMR7178, France.
48 15 Phillips Research, Eindhoven, The Netherlands.
49 16 Institute of Social and Preventive Medicine, Lausanne University Hospital, Lausanne,
50 Switzerland.
51 17 Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, Vanderbilt
52 University, Nashville, Tennessee, USA
53 18 Department of Pediatrics, Baylor College of Medicine, USDA/ARS Children's Nutrition Research
54 Center, Houston, Texas, USA.
55 19 Department of Public Health Sciences, Parkinson School of Health Sciences and Public Health,
56 Loyola University, Maywood, IL, USA.
57 20 Friedman School of Nutrition Science and Policy, Tufts University, 150 Harrison Ave,
58 Boston, Massachusetts, USA
59 21 Department of Sport Medicine, Norwegian School of Sport Sciences, Oslo, Norway.
60 22 Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-
61 Universität zu Berlin, and Berlin Institute of Health (BIH), Institute of Medical Psychology, Berlin,
62 Germany.
63 23 University of California Irvine, Irvine, California, USA.
64 24 Solutions for Developing Countries, University of the West Indies, Mona, Kingston, Jamaica.
65 25 University of Glasgow, Glasgow, UK.
66 26 Department of Anthropology, University of California Santa Barbara, Santa Barbara, CA, USA.
67 27 Institute of Biological and Environmental Sciences, University of Aberdeen, Aberdeen, UK
68 28 State Key Laboratory of Molecular developmental Biology, Institute of Genetics and
69 Developmental Biology, Chinese Academy of Sciences, Beijing, China
70 29 Central Health Laboratory, Ministry of Health and Wellness, Mauritius.
71 30 Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA.
72 31 Department of Medicine, Duke University, Durham, North Carolina, USA.
73 32 Northwestern University, Chicago, IL, USA.
74 33 Health through Physical Activity, Lifestyle and Sport Research Centre (HPALS)
75 Division of Exercise Science and Sports Medicine (ESSM), FIMS International Collaborating
76 Centre of Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University
77 of Cape Town
78 34 Department of Anthropology, Northwestern University, Evanston, IL, USA.
79 35 Imperial College London Diabetes Centre, Abu Dhabi, United Arab Emirates and Imperial College
80 London, London, United Kingdom
81 36 Department of Nutrition and Public Health, Faculty of Health and Sport Sciences, University of
82 Agder, 4630 Kristiansand, Norway.
83 37 The FA Group, Burton-Upon-Trent, Staffordshire, UK.
84 38 Division of Public Health Sciences, Fred Hutchinson Cancer Research Center and School of Public
85 Health, University of Washington, Seattle, WA, USA.
86 39 Moi University, Eldoret, Kenya.
87 40 University of Global Health Equity, Rwanda.
88 41 Helsinki University Central Hospital, Helsinki, Finland.

89 42 University of Brighton, Eastbourne, UK.
90 43 Department of Physiology, Kwame Nkrumah University of Science and Technology, Kumasi,
91 Ghana
92 44 Department of Nutrition and Movement Sciences, Maastricht University, Maastricht, The
93 Netherlands.
94 45 University of Edinburgh, Edinburgh, UK.
95 46 Program in Physical Therapy and Department of Medicine, Washington University School of
96 Medicine, St. Louis, Missouri, USA.
97 47 Biological Sciences and Anthropology, University of Southern California, California, USA.
98 48 Centre for Cardiovascular Sciences, Queen's Medical Research Institute, University of Edinburgh,
99 Edinburgh, UK.
100 49 University of Wageningen, Wageningen, The Netherlands.
101 50 Department of Nutrition, Exercise and Sports, Copenhagen University, Copenhagen, Denmark.
102 51 Stanford University, Stanford CA, USA.
103 52 Department of Anthropology, Baylor University, Waco, TX, USA.
104 53 Maastricht University, Maastricht and Lifestyle Medicine Center for Children, Jeroen
105 Bosch Hospital's-Hertogenbosch, The Netherlands.
106 54 Population, Policy and Practice Research and Teaching Department, UCL Great Ormond Street
107 Institute of Child Health, London, UK.
108 55 University of California Los Angeles, Los Angeles, USA.
109 56 Max Planck Institute for Evolutionary Anthropology, Department of Human Behavior, Ecology,
110 and Culture.
111 57 Growth and Obesity, Division of Intramural Research, NIH, Bethesda, MD, USA.
112 58 Nutritional and Health Related Environmental Studies Section, Division of Human Health,
113 International Atomic Energy Agency, Vienna, Austria.
114 59 Division of Epidemiology, Department of Public Health Sciences, Loyola University School of
115 Medicine, Maywood Illinois, USA.
116 60 Biotech Center and Nutritional Sciences University of Wisconsin, Madison, Wisconsin, USA.
117 61 Department of Human Biology, University of Maastricht, Maastricht, The Netherlands.
118 62 Center for Energy Metabolism and Reproduction, Shenzhen Institutes of Advanced Technology,
119 Chinese Academy of Sciences, Shenzhen, China
120 63 CAS Center of Excellence in Animal Evolution and Genetics, Kunming, China.

121 **Abstract:** Total daily energy expenditure (“total expenditure”, MJ/d) reflects daily energy needs
122 and is a critical variable in human health and physiology, yet it is unclear how daily expenditure
123 changes over the life course. Here, we analyze a large, globally diverse database of total
124 expenditure measured by the doubly labeled water method for males and females aged 8 days to
125 95 yr. We show that total expenditure is strongly related to fat free mass in a power-law manner
126 and identify four distinct metabolic life stages. Fat free mass-adjusted daily expenditure
127 accelerates rapidly in neonates (0-1yr) to ~46% above adult values at ~1 yr, declines slowly
128 throughout childhood and adolescence (1-20 yr) to adult levels at ~20 yr, remains stable in
129 adulthood (20-60 yr) even during pregnancy, and declines in older adults (60+ yr). These
130 changes in total expenditure shed new light on human development and aging and should help
131 shape nutrition and health strategies across the lifespan.

132

133 **One Sentence Summary:** Expenditure varies as we age, with four distinct metabolic life stages
134 reflecting changes in behavior, anatomy, and tissue metabolism.

135

136 **Main Text:** All of life’s essential tasks, from development and reproduction to maintenance and
137 movement, require energy. Total expenditure is thus fundamental to understanding both daily
138 nutritional requirements and the body’s investment among activities. Yet we know surprisingly
139 little about the determinants of total expenditure in humans or how it changes over the lifespan.
140 Most large ($n > 1,000$) analyses of human energy expenditure have been limited to basal
141 expenditure, the metabolic rate at rest (I), which accounts for only a portion (usually ~50-70%)
142 of total expenditure, or have estimated total expenditure from basal expenditure and daily
143 physical activity (2-5). Measurements of total expenditure in humans during daily life, outside of

144 the laboratory, became possible in the 1980's with the advancement of the doubly labeled water
145 method , but doubly labeled water studies to date have been limited in sample size (n < 600),
146 geographic and socioeconomic representation, and/or age (6-9).

147 Body composition, size, and physical activity change over the life course, often in
148 concert, making it difficult to parse the determinants of energy expenditure. Total expenditure
149 increases with age as children grow (10), but the relative effects of increasing physical activity
150 (11-13) and age-related changes in tissue-specific metabolic rates, as have been reported for the
151 brain (14), are unclear. Total and basal expenditure increase from childhood through puberty, but
152 much of this increase is attributable to increased fat free mass, and the role of endocrine or other
153 effects is uncertain (15). The decline in total expenditure beginning in the sixth decade of life
154 corresponds with a decline in fat free mass (9) and “physical activity level”, PAL (the ratio of
155 total/basal expenditure), but may also reflect age-related reductions in organ metabolism.

156 We investigated the effects of age, body composition, and sex on total expenditure and its
157 components, using a large (n = 6,421; 64% female), geographically and economical diverse (n =
158 29 countries) database of doubly labeled water measurements for subjects aged eight days to 95
159 years (16), calculating total expenditure from isotopic measurements using a single, validated
160 equation for all subjects (17). Basal expenditure, measured *via* indirect calorimetry, was
161 available for a n = 2,008 subjects, and we augmented the dataset with additional published
162 measures of basal expenditure in neonates and doubly labeled water-measured total expenditure in
163 pregnant and post-partum women (Methods; Table S1).

164 We found that both total and basal expenditure increased with fat free mass in a power-
165 law manner ($TEE = 0.677FFM^{0.708}$, $r^2 = 0.83$ Figures 1, S1, S2, Table S1). Thus, body size,
166 particularly fat free mass, accounted for most (83%) of the variation in daily expenditure,

167 requiring us to adjust for body size in subsequent analyses of expenditure across subjects and
168 cohorts to isolate potential effects of age, sex, and other factors. Notably, analyses indicated an
169 exponent <1 , meaning that the ratio of energy expenditure/mass does not adequately control for
170 body size because the ratio inherently trends lower for larger individuals (Figure S1 (18)).
171 Instead, we used regression analysis to control for body size (18). A general linear model with
172 *ln*-transformed values of energy expenditure (total or basal), fat free mass, and fat mass in adults
173 20 – 60 y (Table S2) was used to calculate residual energy expenditures for each subject. We
174 converted these residuals to “adjusted” expenditures for clarity in discussing age-related
175 changes: 100% indicates an expenditure that matches the expected value given the subject’s fat
176 free mass and fat mass, 120% indicates an expenditure 20% above expected, *etc.* (Methods).
177 Using this approach, we also calculated the portion of adjusted total expenditure attributed to
178 basal expenditure (Figure 2D; Methods). Segmented regression analysis of (Methods) revealed
179 four distinct phases of adjusted (or residual) total and basal expenditure over the lifespan.

180 Neonates (0 to 1 y): Neonates in the first month of life had size-adjusted energy expenditures
181 similar to adults, with adjusted total expenditure of $99.0 \pm 17.2\%$ ($n = 35$) and adjusted basal
182 expenditure of $78.1 \pm 15.0\%$ ($n = 34$; Figure 2). Both measures increased rapidly in the first year.
183 In segmented regression analysis, adjusted total expenditure rose $84.7 \pm 7.2\%$ per year from birth
184 to a break point at 0.7 years (95% CI: 0.6, 0.8); a similar rise ($75.5 \pm 5.6\%$) and break point (1.0
185 y, 95% CI: 0.9, 1.1) were evident in adjusted basal expenditure (Table S4). For subjects between
186 9 and 15 months, adjusted total and basal expenditures were nearly ~50% elevated compared to
187 adults (Figure 2).

188 Juveniles (1 to 20 y): Total and basal expenditure, along with fat free mass, continued to increase
189 with age throughout childhood and adolescence (Figure 1), but body size-adjusted expenditures

190 steadily declined. Adjusted total expenditure declined at a rate of $-2.8 \pm 0.1\%$ per year from
191 $147.8 \pm 22.6\%$ for subjects 1 – 2 y (n = 102) to $102.7 \pm 18.1\%$ for subjects 20 – 25 y (n = 314;
192 Tables S2, S4). Segmented regression analysis identified a breakpoint in adjusted total
193 expenditure at 20.5 y (95% CI: 19.8, 21.2), after which it plateaued at adult levels (Figure 2). A
194 similar decline ($-3.8 \pm 0.2\%$ per year) and break point (18.0 y, 95% CI: 16.8, 19.2) were evident
195 in adjusted basal expenditure (Figure 2, Text S1, Table S4). No pubertal increases in adjusted
196 total or basal expenditure were evident among subjects 10 – 15 y. In multivariate regression for
197 subjects 1 to 20 y, males had a higher total expenditure and adjusted total expenditure (Tables
198 S2, S3), but sex had no detectable effect on the rate of decline in adjusted total expenditure with
199 age (sex:age interaction $p=0.30$).

200 Adults (20 to 60 y): Total and basal expenditure and fat free mass were all stable from age 20 to
201 60 (Figure 1, 2; Tables S1, S2; Text S1). Sex had no effect on total expenditure in multivariate
202 models with fat free mass and fat mass, nor in analyses of adjusted total expenditure (Tables S2,
203 S4). Adjusted total and basal expenditures were stable even during pregnancy, the elevation in
204 unadjusted expenditures matching those expected from the gain in mothers' fat free mass and fat
205 mass (Figure 2C). Segmented regression analysis identified a break point at 63.0 y (95% CI:
206 60.1, 65.9), after which adjusted TEE begins to decline. This break point was somewhat earlier
207 for adjusted basal expenditure (46.5, 95% CI: 40.6, 52.4), but the relatively small number of
208 basal measures for 45 – 65 y (Figure 2D) reduces our precision in determining this break point.

209 Older adults (>60 y): At ~60 y, total and basal expenditure begin to decline, along with fat free
210 mass and fat mass (Figures 1, S3, Table S1). Declines in expenditure are not only a function of
211 reduced fat free mass and fat mass, however. Adjusted total expenditure declined by $-0.7 \pm 0.1\%$

212 per year, and adjusted basal expenditure fell at a similar rates (Figure 2, Figure S3, Text S1, Table
213 S4). For subjects in their nineties, adjusted TEE was ~26% below that of middle-aged adults.

214 In addition to providing empirical measures and predictive equations for total expenditure
215 from infancy to old age (Tables S1, S2), our analyses bring to light major changes in metabolic
216 rate across the life course. To begin, we can infer fetal metabolic rates from maternal measures
217 during pregnancy: if body size-adjusted expenditures were elevated in the fetus, then adjusted
218 expenditures for pregnant mothers, particularly late in pregnancy when the fetus accounts for a
219 substantial portion of a mother's weight, would be likewise elevated. Instead, the stability of
220 adjusted total and basal expenditures at ~100% during pregnancy (Figure 2B) indicates that the
221 growing fetus maintains a fat free mass- and fat mass-adjusted metabolic rate similar to adults,
222 which is consistent with adjusted expenditures of neonates (both ~100%; Figure 2) in the first
223 weeks after birth. Total and basal expenditures, both absolute and size-adjusted values, then
224 accelerate rapidly over the first year. This early period of metabolic acceleration corresponds to a
225 critical period in early development in which growth often falters in nutritionally-stressed
226 populations (19). Increasing energy demands could be a contributing factor.

227 After rapid acceleration in total and basal expenditure during the first year, adjusted
228 expenditures progressively decline thereafter, reaching adult levels at ~20 yr. Elevated adjusted
229 expenditures in this life stage may reflect the metabolic demands of growth and development.
230 Adult expenditures, adjusted for body size and composition, are remarkably stable, even during
231 pregnancy and post-partum. Declining metabolic rates in older adults could increase the risk of
232 weight gain. However, neither fat mass nor percentage increased in this period (Figure S3),
233 consistent with the hypothesis that energy intake is coupled to expenditure (20).

234 Following previous studies (21-25), we calculated the effect of organ size on basal
235 expenditure over the lifespan (Methods). At rest, the tissue-specific metabolic rates (Watts/gram)
236 of the heart, liver, brain, and kidneys are much greater than those of the muscles and other lean
237 tissue or fat (21-25). Organs with a high tissue-specific metabolic rate, particularly the brain and
238 liver, account for a greater proportion of fat free mass in young individuals, and thus organ-based
239 basal expenditure, estimated from organ size and tissue-specific metabolic rate, follows a power-
240 law relationship with fat free mass, roughly consistent with observed basal expenditures
241 (Methods, Figure S6). Still, observed basal expenditure exceeded organ-based estimates by
242 ~30% in early life (1 – 20 y) and was ~20% lower than organ-based estimates in subjects over 60
243 y (Figure S6), consistent with previous work indicating that tissue-specific metabolic rates are
244 elevated in children and adolescents (22, 24) and reduced in older adults (21, 23, 25).

245 We investigated the contributions of daily physical activity and changes in tissue-specific
246 metabolic rate to total and basal expenditure using a simple model with two components: activity
247 and basal expenditure (Figure 3; Methods). Activity expenditure was modeled as a function of
248 physical activity and body mass, assuming activity costs are proportional to weight, and could
249 either remain constant at adult levels over the lifespan or follow the trajectory of daily physical
250 activity measured *via* accelerometry, peaking at 5 – 10 y and declining thereafter (11, 26, 27)
251 (Figure 3). Similarly, basal expenditure was modeled as a power function of fat free mass
252 (consistent with organ-based BEE estimates; Methods) multiplied by a “tissue specific
253 metabolism” term, which could either remain constant at adult levels across the lifespan or
254 follow the trajectory observed in adjusted basal expenditure (Figure 2). For each scenario, total
255 expenditure was modeled as the sum of activity and basal expenditure (Methods).

256 Models that hold physical activity or tissue-specific metabolic rates constant over the
257 lifespan do not reproduce the observed patterns of age-related change in absolute or adjusted
258 measures of total or basal expenditure (Figure 3). Only when age-related changes in physical
259 activity and tissue-specific metabolism are included does model output match observed
260 expenditures, indicating that variation in both physical activity and tissue-specific metabolism
261 contribute to total expenditure and its components across the lifespan. Elevated tissue-specific
262 metabolism in early life may be related to growth or development (22, 24). Conversely, reduced
263 expenditures in later life may reflect a decline in organ level metabolism (23, 25, 28).

264 Metabolic models of life history commonly assume continuity in tissue-specific
265 metabolism over the life course, with cellular metabolic rates increasing in a power-law manner
266 ($\text{Energy} = a\text{Mass}^b$) and the energy available for growth during the juvenile period made available
267 for reproduction in adults (29, 30). Measures of humans here challenge this view, with size
268 adjusted metabolism elevated ~50% in childhood compared to adults (including pregnant
269 females), and ~25% lower in the oldest subjects. It remains to be determined whether these
270 fluctuations occur in other species. In addition to affecting energy balance, nutritional needs, and
271 body weight, these metabolic changes present a potential target for clinical investigation into the
272 kinetics of disease, pharmaceutical activity, and healing, processes intimately related to
273 metabolic rate. Further, there is considerable metabolic variation among individuals, with TEE
274 and its components varying more than $\pm 20\%$ even when controlling for fat free mass, fat mass,
275 sex, and age (Figure 1, 2, Table S2). Elucidating the processes underlying metabolic changes
276 across the life course and variation among individuals may help reveal the roles of metabolic
277 variation in health and disease.

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285 **Conflict of interest**

286 The authors have no conflicts of interest to declare.

287 **Data Availability**

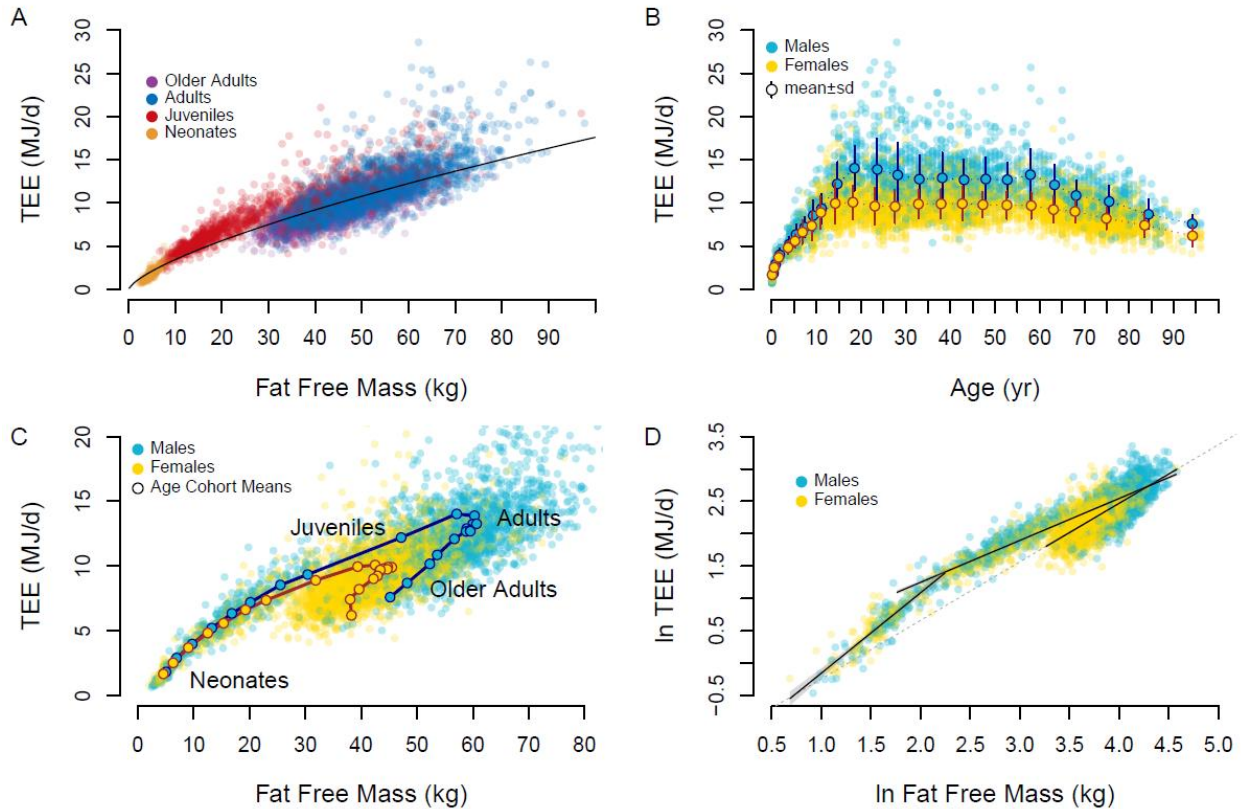
288 All data used in these analyses is freely available via the IAEA Doubly Labelled Water Database
289 (<https://doubly-labelled-water-database.iaea.org/home> or <https://www.dlwdatabase.org/>).

290 **References**

- 291 1. C. J. Henry, Basal metabolic rate studies in humans: measurement and development of new
292 equations. *Public Health Nutr* **8**, 1133-1152 (2005).
- 293 2. FAO, Human energy requirements: report of a joint FAO/ WHO/UNU Expert Consultation. *Food*
294 *Nutr Bull* **26**, 166 (2005).
- 295 3. K. R. Westerterp, J. O. de Boer, W. H. M. Saris, P. F. M. Schoffelen, F. ten Hoor, Measurement of
296 energy expenditure using doubly labelled water. *Int J Sport Med* **5**, S74-75 (1984).
- 297 4. P. D. Klein *et al.*, Calorimetric validation of the doubly-labelled water method for determination
298 of energy expenditure in man. *Hum Nutr Clin Nutr* **38**, 95-106 (1984).
- 299 5. J. R. Speakman, *Doubly Labelled Water: Theory and Practice*. (Chapman and Hall, London, 1997).
- 300 6. A. E. Black, W. A. Coward, T. J. Cole, A. M. Prentice, Human energy expenditure in affluent
301 societies: an analysis of 574 doubly-labelled water measurements. *Eur J Clin Nutr* **50**, 72-92
302 (1996).
- 303 7. L. R. Dugas *et al.*, Energy expenditure in adults living in developing compared with industrialized
304 countries: a meta-analysis of doubly labeled water studies. *Am J Clin Nutr* **93**, 427-441 (2011).
- 305 8. H. Pontzer *et al.*, Constrained Total Energy Expenditure and Metabolic Adaptation to Physical
306 Activity in Adult Humans. *Curr Biol* **26**, 410-417 (2016).
- 307 9. J. R. Speakman, K. R. Westerterp, Associations between energy demands, physical activity, and
308 body composition in adult humans between 18 and 96 y of age. *Am J Clin Nutr* **92**, 826-834
309 (2010).
- 310 10. N. F. Butte, Fat intake of children in relation to energy requirements. *Am J Clin Nutr* **72**, 1246s-
311 1252s (2000).
- 312 11. D. L. Wolff-Hughes, D. R. Bassett, E. C. Fitzhugh, Population-referenced percentiles for waist-
313 worn accelerometer-derived total activity counts in U.S. youth: 2003 - 2006 NHANES. *PLoS One*
314 **9**, e115915 (2014).
- 315 12. E. A. Schmutz *et al.*, Physical activity and sedentary behavior in preschoolers: a longitudinal
316 assessment of trajectories and determinants. *Int J Behav Nutr Phys Act* **15**, 35 (2018).
- 317 13. J. A. Hnatiuk, K. E. Lamb, N. D. Ridgers, J. Salmon, K. D. Hesketh, Changes in volume and bouts of
318 physical activity and sedentary time across early childhood: a longitudinal study. *Int J Behav Nutr*
319 *Phys Act* **16**, 42 (2019).
- 320 14. C. W. Kuzawa *et al.*, Metabolic costs and evolutionary implications of human brain development.
321 *Proc Natl Acad Sci U S A* **111**, 13010-13015 (2014).
- 322 15. H. L. Cheng, M. Amatory, K. Steinbeck, Energy expenditure and intake during puberty in
323 healthy nonobese adolescents: a systematic review. *Am J Clin Nutr* **104**, 1061-1074 (2016).
- 324 16. J. R. Speakman *et al.*, The International Atomic Energy Agency International Doubly Labelled
325 Water Database: Aims, Scope and Procedures. *Ann Nutr Metab* **75**, 114-118 (2019).
- 326 17. J. R. Speakman *et al.*, A standard calculation methodology for human doubly labeled water
327 studies. *Cell Rep Med* **2**, 100203 (2021).
- 328 18. D. B. Allison, F. Paultre, M. I. Goran, E. T. Poehlman, S. B. Heymsfield, Statistical considerations
329 regarding the use of ratios to adjust data. *Int J Obes Relat Metab Disord* **19**, 644-652 (1995).
- 330 19. H. Alderman, D. Headey, The timing of growth faltering has important implications for
331 observational analyses of the underlying determinants of nutrition outcomes. *PLoS One* **13**,
332 e0195904 (2018).
- 333 20. J. E. Blundell *et al.*, The drive to eat in homo sapiens: Energy expenditure drives energy intake.
334 *Physiol Behav* **219**, 112846 (2020).
- 335 21. D. Gallagher, A. Allen, Z. Wang, S. B. Heymsfield, N. Krasnow, Smaller organ tissue mass in the
336 elderly fails to explain lower resting metabolic rate. *Ann N Y Acad Sci* **904**, 449-455 (2000).

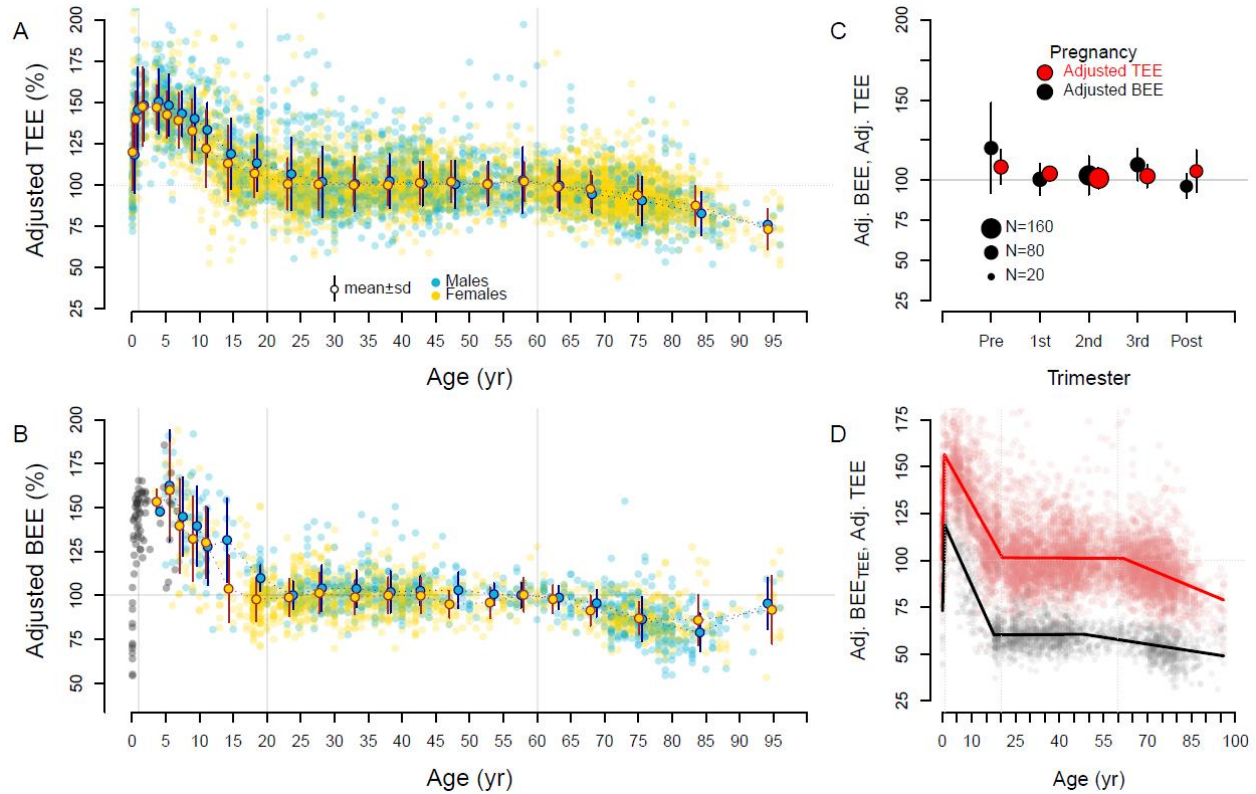
- 337 22. A. Hsu *et al.*, Larger mass of high-metabolic-rate organs does not explain higher resting energy
338 expenditure in children. *Am J Clin Nutr* **77**, 1506-1511 (2003).
- 339 23. Z. Wang *et al.*, Specific metabolic rates of major organs and tissues across adulthood: evaluation
340 by mechanistic model of resting energy expenditure. *Am J Clin Nutr* **92**, 1369-1377 (2010).
- 341 24. Z. Wang *et al.*, A cellular level approach to predicting resting energy expenditure: Evaluation of
342 applicability in adolescents. *Am J Hum Biol* **22**, 476-483 (2010).
- 343 25. Z. Wang, S. Heshka, S. B. Heymsfield, W. Shen, D. Gallagher, A cellular-level approach to
344 predicting resting energy expenditure across the adult years. *Am J Clin Nutr* **81**, 799-806 (2005).
- 345 26. D. L. Wolff-Hughes, E. C. Fitzhugh, D. R. Bassett, J. R. Churilla, Waist-Worn Actigraphy:
346 Population-Referenced Percentiles for Total Activity Counts in U.S. Adults. *J Phys Act Health* **12**,
347 447-453 (2015).
- 348 27. Y. Aoyagi, S. Park, S. Cho, R. J. Shephard, Objectively measured habitual physical activity and
349 sleep-related phenomena in 1645 people aged 1-91 years: The Nakanojo Community Study. *Prev*
350 *Med Rep* **11**, 180-186 (2018).
- 351 28. Y. Yamada *et al.*, Extracellular water may mask actual muscle atrophy during aging. *J Gerontol A*
352 *Biol Sci Med Sci* **65**, 510-516 (2010).
- 353 29. G. B. West, J. H. Brown, B. J. Enquist, A general model for ontogenetic growth. *Nature* **413**, 628-
354 631 (2001).
- 355 30. J. H. Brown, J. F. Gillooly, A. P. Allen, V. M. Savage, G. B. West, Toward a metabolic theory of
356 ecology. *Ecology* **85**, 1771-1789 (2004).
- 357 31. R. D. Montgomery, Changes in the basal metabolic rate of the malnourished infant and their
358 relation to body composition. *J Clin Invest* **41**, 1653-1663 (1962).
- 359 32. O. G. Brooke, T. Cocks, Resting metabolic rate in malnourished babies in relation to total body
360 potassium. *Acta Paediatr Scand* **63**, 817-825 (1974).
- 361 33. N. F. Butte *et al.*, Energy requirements derived from total energy expenditure and energy
362 deposition during the first 2 y of life. *Am J Clin Nutr* **72**, 1558-1569 (2000).
- 363 34. M. Hernández-Triana *et al.*, Total energy expenditure by the doubly-labeled water method in
364 rural preschool children in Cuba. *Food Nutr Bull* **23**, 76-81 (2002).
- 365 35. S. S. Summer, J. M. Pratt, E. A. Koch, J. B. Anderson, Testing a novel method for measuring
366 sleeping metabolic rate in neonates. *Respir Care* **59**, 1095-1100 (2014).
- 367 36. N. F. Butte *et al.*, Energy expenditure and deposition of breast-fed and formula-fed infants
368 during early infancy. *Pediatr Res* **28**, 631-640 (1990).
- 369 37. L. A. Gilmore *et al.*, Energy Intake and Energy Expenditure for Determining Excess Weight Gain in
370 Pregnant Women. *Obstet Gynecol* **127**, 884-892 (2016).
- 371 38. G. R. Goldberg *et al.*, Longitudinal assessment of energy expenditure in pregnancy by the doubly
372 labeled water method. *Am J Clin Nutr* **57**, 494-505 (1993).
- 373 39. N. F. Butte, W. W. Wong, M. S. Treuth, K. J. Ellis, E. O'Brian Smith, Energy requirements during
374 pregnancy based on total energy expenditure and energy deposition. *Am J Clin Nutr* **79**, 1078-
375 1087 (2004).
- 376 40. J. B. Weir, New methods for calculating metabolic rate with special reference to protein
377 metabolism. *J Physiol* **109**, 1-9 (1949).
- 378 41. R. C. Team, *R: A language and environment for statistical computing*. R Foundation for Statistical
379 Computing. (Vienna, Austria, 2020).
- 380 42. V. M. R. Muggeo, . Segmented: an R package to fit regression models with broken-line
381 relationships. *R News* **8/1**, 20-25 (2008).
- 382 43. M. Elia, in *Physiology, Stress, and Malnutrition*, J. M. Kinney, H. N. Tucker, Eds. (Raven Press,
383 Philadelphia, 1997), pp. 383-411.

- 384 44. M. A. Holliday, D. Potter, A. Jarrah, S. Bearg, The relation of metabolic rate to body weight and
385 organ size. *Pediatr Res* **1**, 185-195 (1967).
- 386 45. M. A. Holliday, Metabolic rate and organ size during growth from infancy to maturity and during
387 late gestation and early infancy. *Pediatrics* **47**, Suppl 2:169+ (1971).
- 388 46. D. K. Molina *et al.*, Organ Weight Reference Ranges for Ages 0 to 12 Years. *Am J Forensic Med*
389 *Pathol* **40**, 318-328 (2019).
- 390 47. M. Sawabe *et al.*, Standard organ weights among elderly Japanese who died in hospital,
391 including 50 centenarians. *Pathol Int* **56**, 315-323 (2006).
- 392 48. S. Kwon, K. Honegger, M. Mason, Daily Physical Activity Among Toddlers: Hip and Wrist
393 Accelerometer Assessments. *Int J Environ Res Public Health* **16**, (2019).
- 394 49. E. R. Hager *et al.*, Toddler physical activity study: laboratory and community studies to evaluate
395 accelerometer validity and correlates. *BMC Public Health* **16**, 936 (2016).
- 396 50. P. Silva *et al.*, Lifespan snapshot of physical activity assessed by accelerometry in Porto. *J Phys*
397 *Act Health* **8**, 352-360 (2011).
- 398 51. A. Doherty *et al.*, Large Scale Population Assessment of Physical Activity Using Wrist Worn
399 Accelerometers: The UK Biobank Study. *PLoS One* **12**, e0169649 (2017).
- 400 52. P. S. Blair *et al.*, Childhood sleep duration and associated demographic characteristics in an
401 English cohort. *Sleep* **35**, 353-360 (2012).
- 402 53. J. Kohyama, J. A. Mindell, A. Sadeh, Sleep characteristics of young children in Japan: internet
403 study and comparison with other Asian countries. *Pediatr Int* **53**, 649-655 (2011).
- 404 54. I. Iglowstein, O. G. Jenni, L. Molinari, R. H. Largo, Sleep duration from infancy to adolescence:
405 reference values and generational trends. *Pediatrics* **111**, 302-307 (2003).
- 406 55. P. Brambilla *et al.*, Sleep habits and pattern in 1-14 years old children and relationship with
407 video devices use and evening and night child activities. *Ital J Pediatr* **43**, 7 (2017).



408

409 **Figure 1. A.** Total expenditure (TEE) increases with fat free mass in a power-law manner, but age groups
 410 cluster about the trend line differently. **B.** Total expenditure rises in childhood, is stable through
 411 adulthood, and declines in older adults. Means \pm sd for age-sex cohorts are shown. **C.** Age-sex cohort
 412 means show a distinct progression of total expenditure and fat free mass over the life course. **D.** Neonate,
 413 juveniles, and adults exhibit distinct relationships between fat free mass and expenditure. The dashed
 414 line, extrapolated from the regression for adults, approximates the regression used to calculate adjusted
 415 total expenditure.



416

417 **Figure 2.** Fat free mass- and fat mass-adjusted expenditures over the life course. Individual subjects and

418 age-sex cohort mean \pm SD are shown. For both total (Adj. TEE) (A) and basal (Adj. BEE) expenditure (B),

419 adjusted expenditures begin near adult levels (~100%) but quickly climb to ~150% in the first year.

420 Adjusted expenditures decline to adult levels ~20y, then decline again in older adults. Basal expenditures

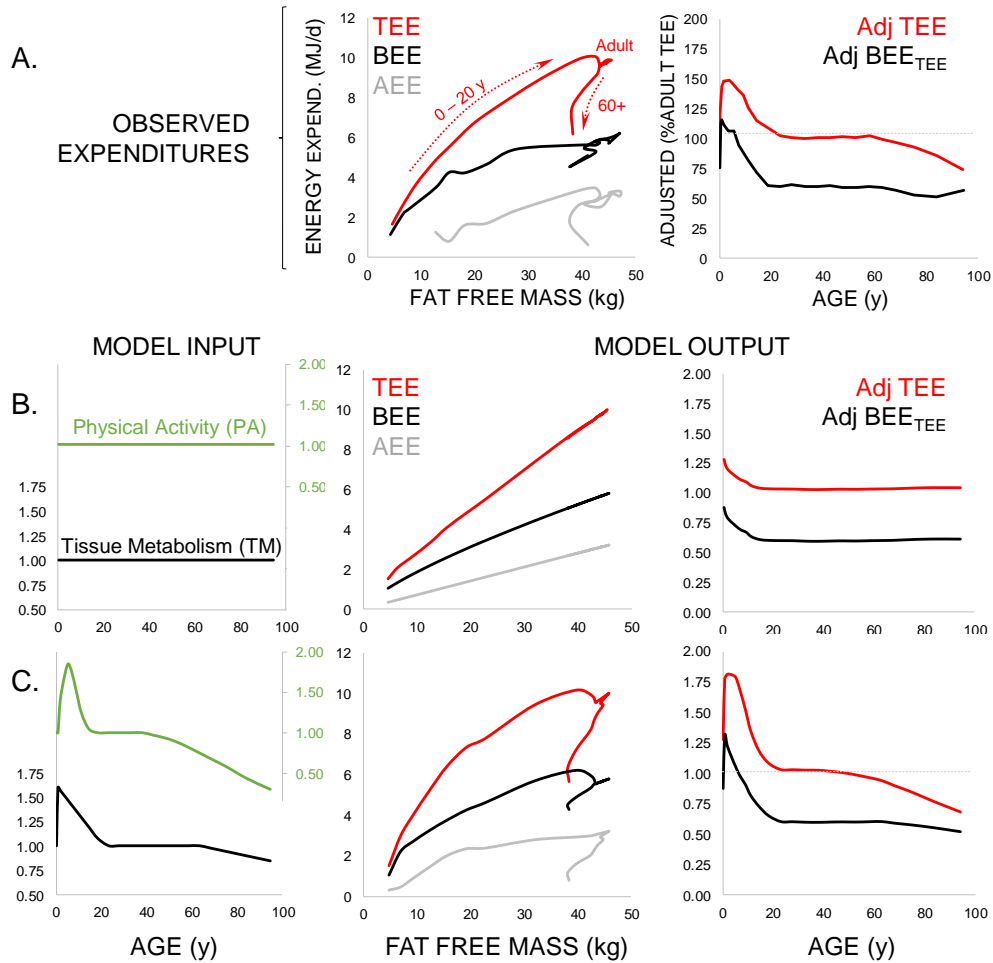
421 for infants and children not in the doubly labeled water database are shown in gray. C. Pregnant mothers

422 exhibit adjusted total and basal expenditures similar to non-reproducing adults (Pre: prior to pregnancy;

423 Post: 27 weeks post-partum). D. Segmented regression analysis of adjusted total (red) and adjusted

424 basal expenditure (calculated as a portion of total; Adj. BEE_{TEE}; black) indicates a peak at ~1 y, adult

425 levels at ~20 y, and decline at ~60 y (see text).



426

427 **Figure 3.** Modeling the contribution of physical activity and tissue-specific metabolism to daily
 428 expenditures. **A.** Observed total (TEE, red), basal (BEE, black), and activity (AEE, gray) expenditures
 429 (Table S1) show age-related variation with respect to fat free mass (see Figure 1C) that is also evident in
 430 adjusted values (Table S3; see Figure 2D). **B.** These age effects do not emerge in models assuming
 431 constant physical activity (PA, green) and tissue-specific metabolic rate (TM, black) across the life course.
 432 **C.** When physical activity and tissue-specific metabolism follow the life course trajectories evident from
 433 accelerometry and adjusted basal expenditure, respectively, model output is similar to observed
 434 expenditures.

435 **Supplementary Materials:**

436 Pontzer et al. *Daily Energy Expenditure through the Human Life Course*

437 **Contents:**

438 Materials and Methods

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 - 441 3. Predictive Models for TEE, BEE, AEE, and PAL
 - 442 4. Adjusted TEE, Adjusted BEE, and Adjusted BEE_{TEE}
 - 443 5. Segmented Regression Analysis
 - 444 6. Organ Size and BEE
 - 445 7. Modeling the Effects of PA and Cellular Metabolism
 - 446 8. Physical Activity, Activity Expenditure and PAL
 - 447 9. The IAEA DLW database consortium
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450 **Material and Methods**

451 1. Doubly Labeled Water Database

452 Data were taken from IAEA Doubly Labelled Water (DLW) Database, version 3.1,
453 completed April, 2020 (16). This version of the database comprises 6,743 measurements of total
454 expenditure using the doubly labeled water method. Of these, a total of 6,421 had valid data for
455 total expenditure, fat free mass, fat mass, sex, and age. These 6,421 measurements were used in
456 this analysis. This dataset was augmented with published basal expenditure measurements for
457 $n=136$ neonates and infants (31-36) that included fat free mass and fat mass. Malnourished or

458 preterm infants were excluded. For sources that provided cohort means rather than individual
459 subject measurements (33, 36) means were entered as single values into the dataset without
460 reweighting to reflect sample size. This approach resulted in 77 measures of basal expenditure,
461 fat free mass, and fat mass for n=136 subjects. We also added to the dataset published basal and
462 total expenditure measurements of n=141 women before, during, and after pregnancy (37-39)
463 that included fat free mass and fat mass. These measurements were grouped as pre-pregnancy, 1st
464 trimester, 2nd trimester, 3rd trimester, and post-partum for analysis.

465 In the doubly labeled water method (5), subjects were administered a precisely measured
466 dose of water enriched in $^2\text{H}_2\text{O}$ and H_2^{18}O . The subject's body water pool is thus enriched in
467 deuterium (^2H) and ^{18}O . The initial increase in body water enrichment from pre-dose values is
468 used to calculate the size of the body water pool, measured as the dilution space for deuterium
469 (N_d) and ^{18}O (N_o). These isotopes are then depleted from the body water pool over time: both
470 isotopes are depleted *via* water loss, whereas ^{18}O is also lost *via* carbon dioxide production.
471 Subtracting the rate (%/d) of deuterium depletion (k_d) from the rate of ^{18}O depletion (k_o), and
472 multiplying the size of the body water pool (derived from N_d and N_o) provided the rate of carbon
473 dioxide production, $r\text{CO}_2$. Entries in the DLW database include the original k and N values for
474 each subject, which were then used to calculate CO_2 using a common equation that has been
475 validated in subjects across the lifespan (17). The rate of CO_2 production, along with each
476 subject's reported food quotient, was then used to calculate energy expenditure (MJ/d) using the
477 Weir equation (40). We used the food quotients reported in the original studies to calculate total
478 energy expenditure from $r\text{CO}_2$ for each subject.

479 The size of the body water pool, determined from N_d and N_o , was used to establish FFM,
480 using hydration constants for fat free mass taken from empirical studies. Other anthropometric

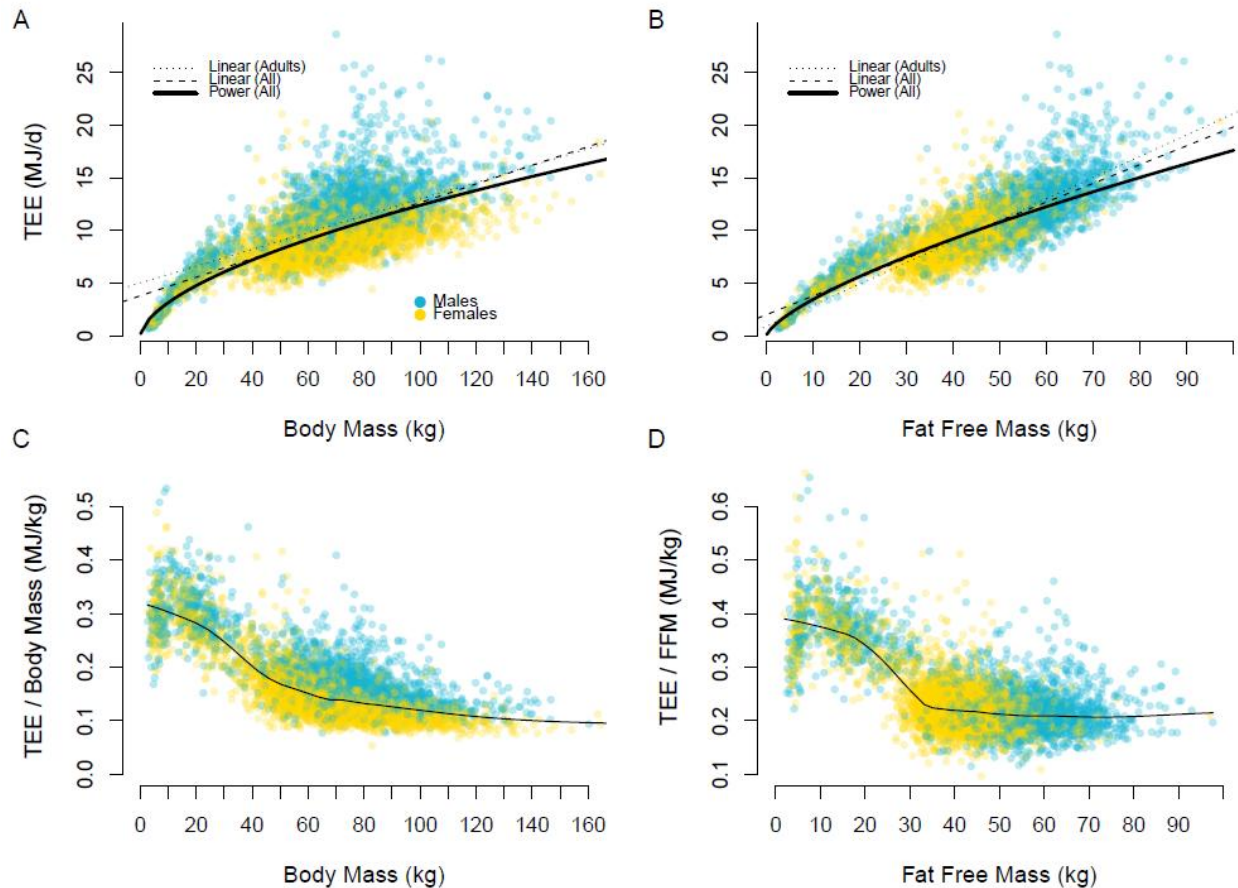
481 variables (age, height, body mass, sex) were measured using standard protocols. Fat mass was
482 calculated as (body mass) – (fat free mass).

483 2. Basal Expenditure, Activity Expenditure, and Physical Activity Level (PAL)

484 A total of 2,008 subjects in the database had associated basal expenditure, measured *via*
485 respirometry. For these subjects, we analyzed basal expenditure, activity expenditure, and
486 “physical activity level” (PAL). Activity expenditure was calculated as $[0.9(\text{total expenditure}) -$
487 $(\text{basal expenditure})]$ which subtracts basal expenditure and the assumed thermic effect of food
488 $[\text{estimated at } 0.1(\text{total expenditure})]$ from total expenditure. The PAL ratio was calculated as
489 $(\text{total expenditure})/(\text{basal expenditure})$. As noted above, the basal expenditure dataset was
490 augmented with measurements from neonates and infants, but these additional measures do not
491 have associated total expenditure and could not be used to calculate activity expenditure or PAL.

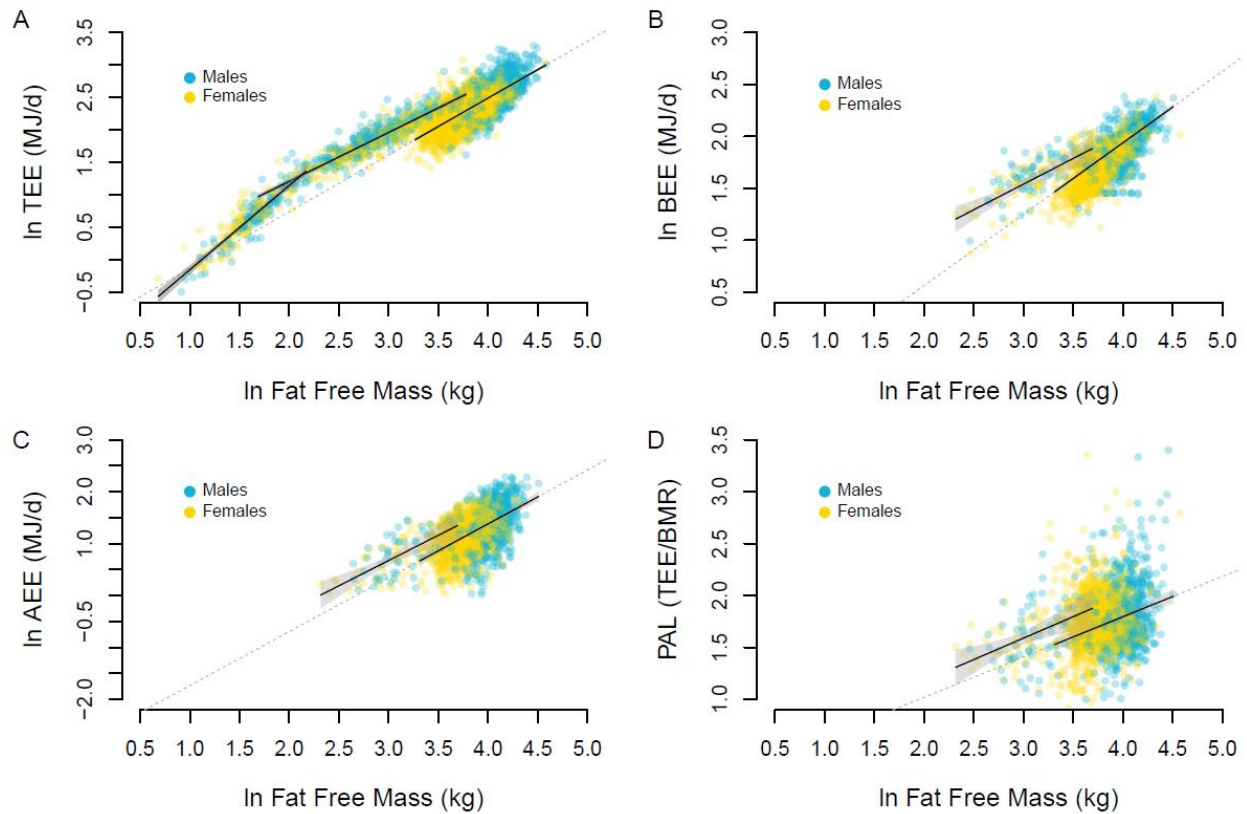
492 3. Predictive Models for Total, Basal, and Activity Expenditures and PAL

493 We used general linear models to regress measures of energy expenditure against
494 anthropometric variables. We used the base package in R version 4.0.3 (41) for all analyses.
495 General linear models were implemented using the `lm` function. These models were used to
496 develop predictive equations for total expenditure for clinical and research applications, and to
497 determine the relative contribution of different variables to total expenditure and its components.
498 Given the marked changes in metabolic rate over the lifespan (Figure 1, Figure 2) we calculated
499 these models separately for each life history stage: infants (0 – 1 y), juveniles (1 – 20 y), adults
500 (20 – 60 y), and older adults (60+ y). These age ranges were identified using segmented
501 regression analysis. Results of these models are shown in Table S2.



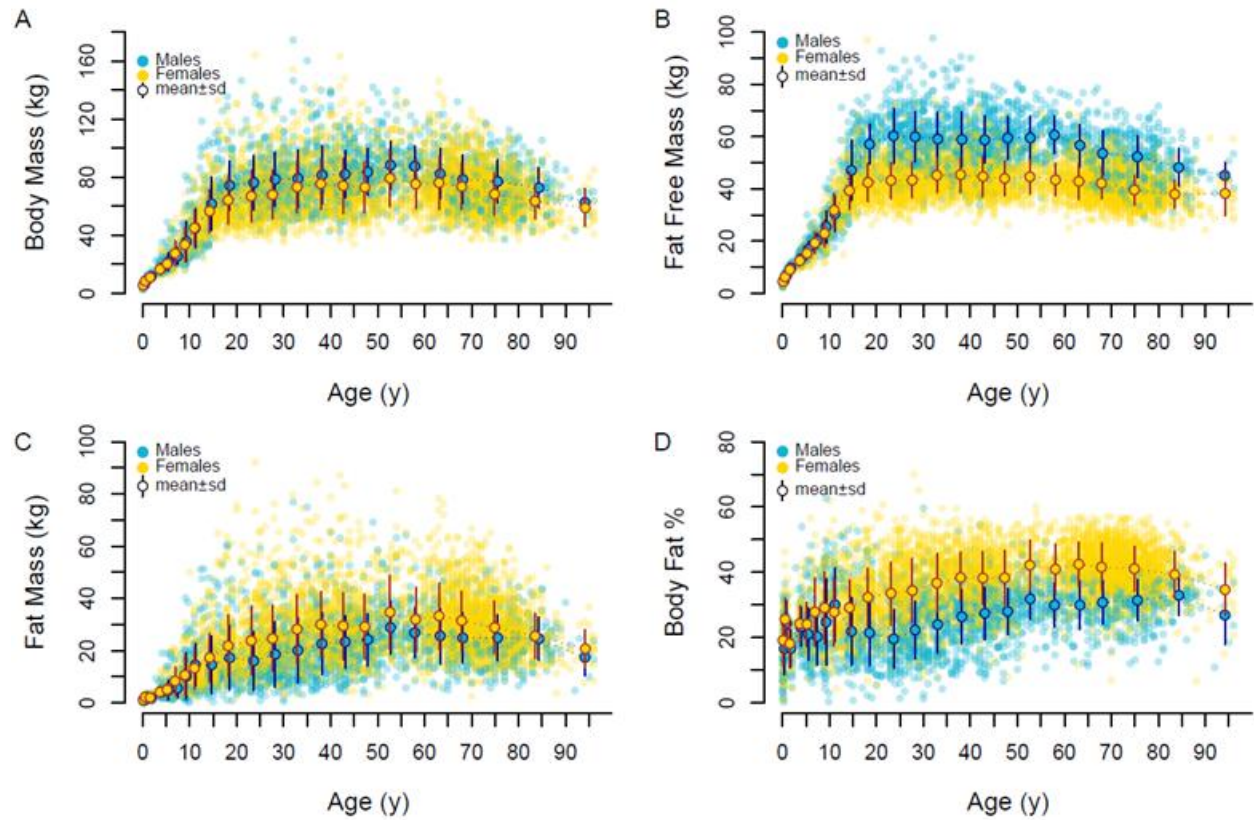
502

503 **Figure S1.** Total expenditure (TEE) increases with body size in a power-law manner. For the entire
 504 dataset ($n = 6,407$): **A.** the power-law regression for total body mass ($\ln TEE = 0.593 \pm 0.004 \ln Mass -$
 505 0.214 ± 0.018 , $p < 0.001$, adj. $r^2 = 0.73$, model std. err. = 0.223, $df = 6419$) is less predictive than the
 506 regression for **B.** fat free mass ($\ln TEE = 0.708 \pm 0.004 \ln FFM - 0.391 \pm 0.015$, $p < 0.001$, adj. $r^2 = 0.83$,
 507 model std. err. = 0.176, $df = 6419$). For both body mass and fat free mass regressions, power-law
 508 regressions outperform linear models, particularly at the smallest body sizes. For all models, for both
 509 body mass and fat free mass, children have elevated total expenditure, clustering above the trend line.
 510 Children also exhibit elevated basal and activity expenditures (Figure S2). Power-law regressions have
 511 an exponent < 1.0 , and linear regressions (dashed: linear regression through all data; dotted: linear
 512 regression through adults only) have a positive intercept, indicating that simple ratios of **C.** (total
 513 expenditure)/(body mass) or **D.** (total expenditure)/(fat free mass) do not adequately control for
 514 differences in body size (18) as smaller individuals will tend to have higher ratios. Lines in **C** and **D**
 515 are lowess with span 1/6. In body mass regressions (panel **A**, power and linear models) and the ratio of (total
 516 expenditure)/(body mass) (**C**), adult males cluster above the trend line while females cluster below due to
 517 sex differences in body composition. In contrast, males and females fit the fat free mass regressions (**B**)
 518 and ratio (**D**) equally well.



519

520 **Figure S2.** Infants and children exhibit different relationships between fat free mass and expenditure and
 521 the PAL ratio. **A:** For total expenditure (TEE), regressions for infants (age <1 y, left regression line) and
 522 adults (right regression line) intersect for neonates, at the smallest body size. However, the slopes differ,
 523 with the infants' regression and 95% CI (gray region) falling outside of that for adults (age 20 – 60 y,
 524 extrapolated dashed line). Juvelines (age 1 – 20 y, middle regression line) are elevated, with a regression
 525 outside the 95% CI of adults. Juvenile (1 – 20 y) regressions (with 95%CI) are also elevated for basal
 526 expenditure (BEE) (**B**), activity expenditure (AEE) (**C**), and PAL (**D**) compared to adults (20 – 60 y). Sex
 527 differences in expenditure (**A-D**) are attributable to differences in fat free mass. Note that total and basal
 528 expenditures are measured directly. Activity expenditure is calculated as $(0.9TEE - BEE)$, and PAL is
 529 calculated as (TEE/BEE) ; see Methods.



530

531 **Figure S3.** Changes in body composition over the lifespan: **A.** Body mass; **B.** Fat free mass; **C.** Fat Mass;

532 and **D.** Body fat percentage.

533 4. Adjusted Expenditures

534 We used general linear models with fat free mass and fat mass in adults (20 – 60 y) to
535 calculate adjusted total expenditure and adjusted basal expenditure. The 20 – 60 y age range was
536 used as the basis for analyses because segmented regression analysis consistently identified this
537 period as stable with respect to size-adjusted total expenditure (see below).

538 We used models 2 and 5 in Table S2, which have the form $\ln(\text{Expenditure}) \sim \ln(\text{FFM}) +$
539 $\ln(\text{Fat Mass})$ and were implemented using the `lm` function in base R version 4.0.3 (41). We
540 used \ln -transformed variables due to the inherent power-law relationship between body size and
541 both total and basal expenditure (ref. 2; see Figure 1, Figure S1). Predicted values for each
542 subject, given their fat free mass and fat mass, were calculated from the model using the
543 `pred()` function; these \ln -transformed values were converted back into MJ as $\exp(\text{Predicted})$.
544 Residuals for each subject were calculated as (Observed – Predicted) expenditure, and were then
545 used to calculate adjusted expenditures as:

$$546 \quad \text{Adjusted Expenditure} = 1 + \text{Residual} / \text{Predicted} \quad [1]$$

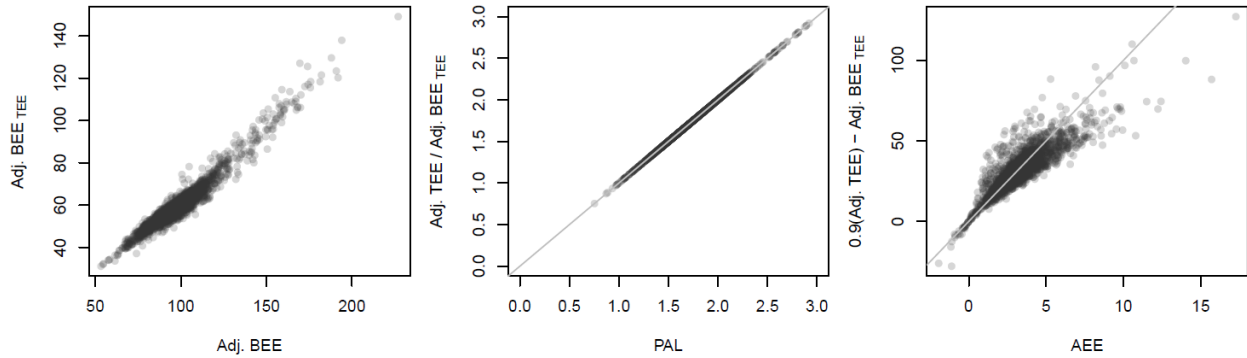
547 The advantage of expressing residuals as a percentage of the predicted value is that it allows us
548 to compare residuals across the range of age and body size in the dataset. Raw residuals (MJ) do
549 not permit direct comparison because the relationship between size and expenditure is
550 heteroscedastic; the magnitude of residuals increases with size (see Figure S1). Ln-transformed
551 residuals ($\ln\text{MJ}$) avoid this problem but are more difficult to interpret. Adjusted expenditures,
552 used here, provide an easily interpretable measure of deviation from expected values. An
553 adjusted expenditure value of 100% indicates that a subject's observed total or basal expenditure
554 matches the value predicted for their fat free mass and fat mass, based on the general linear
555 model derived for adults. An adjusted expenditure of 120% indicates an observed total or basal

556 expenditure value that exceeds the predicted value for their fat free mass and fat mass by 20%.
557 Similarly, an adjusted expenditure of 80% means the subject's measured expenditure was 20%
558 lower than predicted for their fat free mass and fat mass using the adult model. Adjusted total
559 expenditure and adjusted basal expenditure values for each age-sex cohort are given in Table S3.
560 Within each metabolic life history stage we used general linear models (`lm` function in R) to
561 investigate the effects of sex and age on adjusted total and basal expenditure.

562 This same approach was used to calculate adjusted basal expenditure as a proportion of
563 total expenditure (Figure 2D), hereafter termed adjusted BEE_{TEE} . $Residual_{BEE-TEE}$, the deviation
564 of observed basal expenditure from the adult total expenditure regression (eq. 2 in Table S2),
565 was calculated as (Observed Basal Expenditure – Predicted Total Expenditure) and then used to
566 calculate adjusted BEE_{TEE} as

$$567 \quad \text{Adjusted } BEE_{TEE} = 1 + \text{Residual}_{BEE-TEE} / \text{Predicted Total Expenditure} \quad [2]$$

568 When adjusted $BEE_{TEE} = 80\%$, observed basal expenditure is equal to 80% of predicted total
569 expenditure given the subject's fat free mass and fat mass. Adjusted BEE_{TEE} is equivalent to
570 adjusted basal expenditure (Figure S4) but provides some analytical advantages. The derivation
571 of adjusted BEE_{TEE} approach applies identical manipulations to observed total expenditure and
572 observed basal expenditure and therefore maintains them in directly comparable units. The ratio
573 of (adjusted total expenditure)/(adjusted basal expenditure) is identical to the PAL ratio of (total
574 expenditure)/(basal expenditure), and the difference (0.9adjusted total expenditure– adjusted
575 basal expenditure) is proportional to activity expenditure (Figure S4). Plotting adjusted total
576 expenditure and adjusted BEE_{TEE} over the lifespan (Figure 2D) therefore shows both the relative
577 magnitudes of total and basal expenditure and their relationship to one another in comparable
578 units.



579

580 **Figure S4.** Left: Adjusted BEE_{TEE} corresponds strongly to adjusted basal expenditure (Adj. BEE). Center:
 581 The ratio of adjusted total expenditure (adj. TEE) to adjusted BEE_{TEE} is identical to the PAL ratio. Right:
 582 The difference (0.9adjusted total expenditure – adjusted BEE_{TEE}) is proportional to activity energy
 583 expenditure (AEE). Gray lines: center panel: $y = x$, right panel: $y = 10x$.

584 5. Segmented Regression Analysis

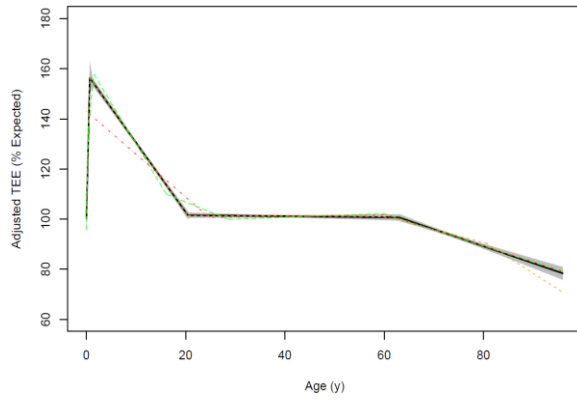
585 We used segmented regression analysis to determine the change points in the relationship
 586 between adjusted expenditure and age. We used the Segmented (version 1.1-0) package in R
 587 (42). For adjusted total expenditure, we examined a range of models with 0 to 5 change points,
 588 using the `npsi=` term in the `segmented()` function. This approach does not specify the
 589 location or value of change points, only the number of them. Each increase in the number of
 590 change points from 0 to 3 improved the model adj. R^2 and standard error considerably.
 591 Increasing the number of change points further to 4 or 5 did not improve the model, and the
 592 additional change points identified by the `segmented()` function fell near the change points for
 593 the 3-change point model. We therefore selected the 3-change point model as the best fit for
 594 adjusted total expenditure in this dataset. Segmented regression results are shown in Table S4. A
 595 similar 3-change point segmented regression approach was conducted for adjusted basal
 596 expenditure (Figure S4) and adjusted BEE_{TEE} (Figure 2D). We note that the decline in adjusted
 597 basal expenditure and adjusted BEE_{TEE} in older adults begins earlier (as identified by segmented

598 regression analysis) than does the decline in adjusted total expenditure among older adults.
599 However, this difference may reflect the relative paucity of basal expenditure measurements for
600 subjects 40 – 60 y. Additional measurements are needed to determine whether the decline in
601 basal expenditure does in fact begin earlier than the decline in total expenditure. Here, we view
602 the timing as essentially coincident and interpret the change point in adjusted total expenditure
603 (~60 y), which is determined with a greater number of measurements, as more accurate and
604 reliable.

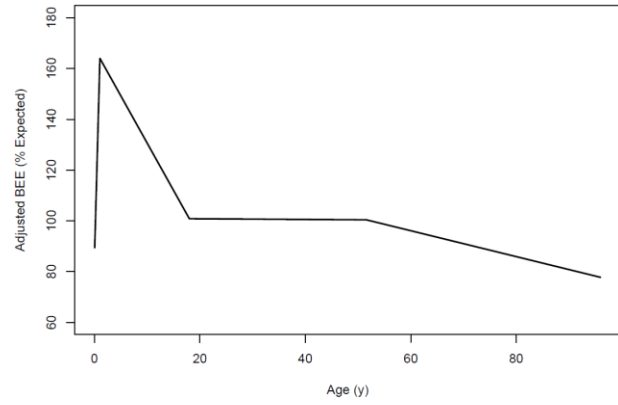
605 Having established that 3 break points provided the best fit for this dataset, we examined
606 whether changes in the age range used to calculate adjusted total energy expenditure affected the
607 age break-points identified by segmented regression. When the age range used to calculate
608 adjusted expenditure was set at 20 – 60 y, the set of break point (95% CI) was: 0.69 (0.61-0.76),
609 20.46 (19.77-21.15), 62.99 (60.14-65.85). When the age range was expanded to 15 – 70 y, break
610 points determined through segmented regression were effectively unchanged: 0.69 (0.62 – 0.76),
611 21.40 (20.60-22.19), 61.32 (58.60-64.03). Break points were also unchanged when the initial age
612 range for adjusted expenditure was limited to 30 – 50 y: 0.69 (0.62-0.77), 20.56 (19.84-21.27),
613 62.85 (59.97-65.74).

614

A



B



615

616 **Figure S5.** Segmented regression analysis of adjusted TEE (**A**) and adjusted BEE (**B**). In both panels,
617 the black line and gray shaded confidence region depicts the 3 change-point regression. For adjusted
618 TEE, segmented regressions are also shown for 2 change points (red), 4 change points (yellow), and 5
619 change points (green). Segmented regression statistics are given in Table S4.

620 6. Organ Size and Basal Expenditure

621 Measuring the metabolic rate of individual organs is notoriously challenging, and the
622 available data come from only a small number of studies. The available data indicate that organs
623 differ markedly in their mass-specific metabolic rates at rest (43). The heart ($1848 \text{ kJ kg}^{-1} \text{ d}^{-1}$),
624 liver ($840 \text{ kJ kg}^{-1} \text{ d}^{-1}$), brain ($1008 \text{ kJ kg}^{-1} \text{ d}^{-1}$), and kidneys ($1848 \text{ kJ kg}^{-1} \text{ d}^{-1}$) have much greater
625 mass-specific metabolic rates at rest than do muscle ($55 \text{ kJ kg}^{-1} \text{ d}^{-1}$), other lean tissue (50 kJ kg^{-1}
626 d^{-1}), and fat ($19 \text{ kJ kg}^{-1} \text{ d}^{-1}$). Consequently, the heart, liver, brain, and kidneys combined account
627 for ~60% of basal expenditure in adults (21, 22, 44, 45). In infants and children, these
628 metabolically active organs constitute a larger proportion of body mass. The whole body mass-
629 specific basal expenditure [i.e., (basal expenditure)/(body mass), or (basal expenditure)/(fat free
630 mass)] for infants and children is therefore expected to be greater than adults' due to the greater
631 proportion of metabolically active organs early in life adults (21, 22, 44, 45). Similarly, reduced
632 organ sizes in elderly subjects may result in declining basal expenditure (21).

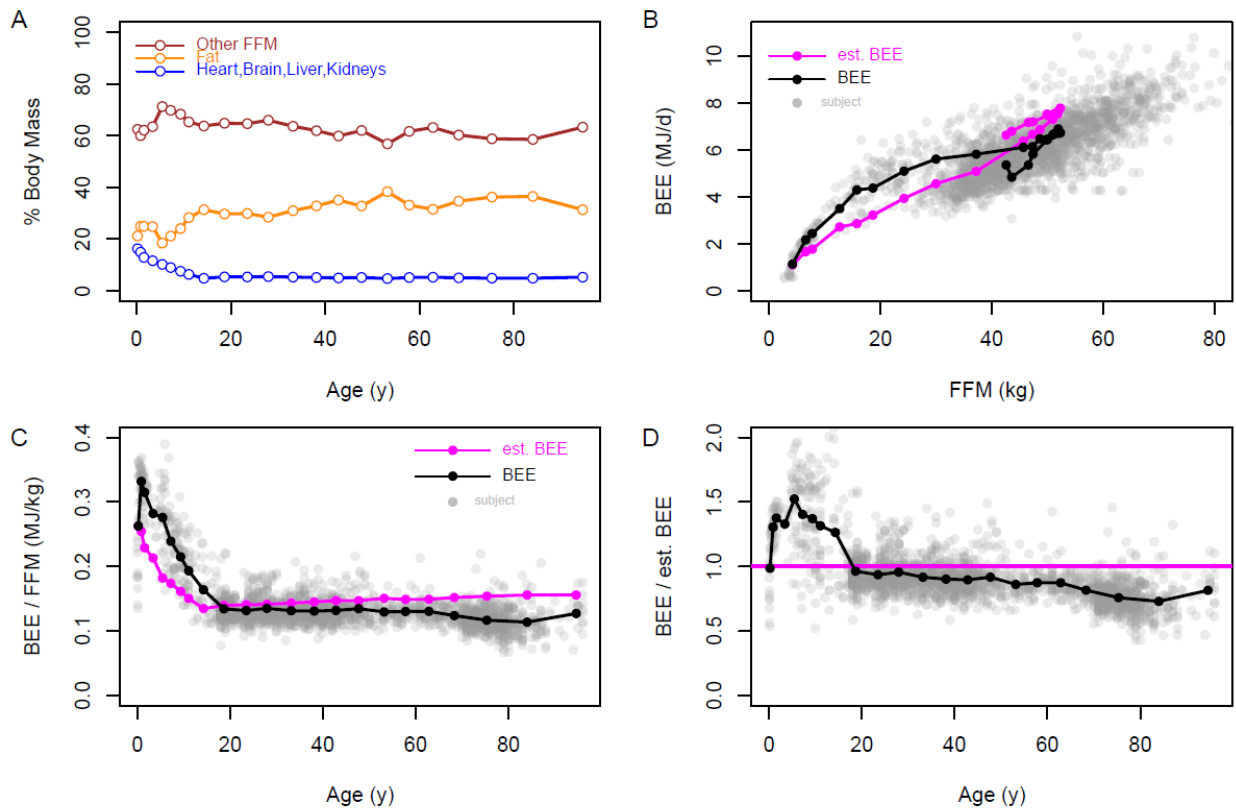
633 To examine this effect of organ size on basal expenditure in our dataset, we used
634 published references for organ size to determine the mass of the metabolically active organs
635 (heart, liver, brain, and kidneys) as a percentage of body mass or fat free mass for subjects 0 – 12
636 y (22, 44-46), 15 to 60 y (21, 22), and 60 to 100 y (21, 47). We used these relationships to
637 estimate the combined mass of the metabolically active organs (heart, liver, brain, kidneys) for
638 each subject in our dataset. We then subtracted the mass of the metabolically active organs from
639 measured fat free mass to calculate the mass of “other fat free mass”. These two measures, along
640 with measured fat mass, provided a three-compartment model for each subject: metabolically
641 active organs, other fat free mass, and fat (Figure S6A).

642 Following previous studies (21-25), we assigned mass-specific metabolic rates to each
643 compartment and estimated basal expenditure for each subject. We used reported mass-specific
644 metabolic rates for the heart, liver, brain, and kidneys (see above; (43)) and age-related changes
645 in the proportions of these organs for subjects 0 – 12 y (22, 46), 15 to 60 y (21-25), and 60 to 100
646 y (21, 23, 25, 47) to calculate an age-based weighted mass-specific metabolic rate for the
647 metabolically active organ compartment. We averaged the mass-specific metabolic rates of
648 resting muscle and other lean tissue (see above; (21, 22)) and assigned a value of 52.5 kJ kg⁻¹ d⁻¹
649 to “other fat free mass”, and we used a mass-specific metabolic rate of 19 kJ kg⁻¹ d⁻¹ for fat.

650 Results are shown in Figure S6. Due to the greater proportion of metabolically active
651 organs in early life, the estimated basal expenditure from the three-compartment model follows a
652 power-law relationship with FFM (using age cohort means, BEE= 0.38 FFM^{0.75}; Figure S6B)
653 that is similar to that calculated from observed basal expenditure in our dataset (see Table S2 and
654 *7. Modeling the Effects of Physical Activity and Tissue Specific Metabolism*, below). Estimated
655 BEE from the three-compartment model produced mass-specific metabolic rates that are
656 considerably higher for infants and children than for adults and roughly consistent with observed
657 age-related changes in (basal expenditure)/(fat free mass) (Figure S6C). Thus, changes in organ
658 size can account for much of the variation in basal expenditure across the lifespan observed in
659 our dataset.

660 Nonetheless, observed basal expenditure was ~30% greater early in life, and ~20% lower
661 in older adults, than estimated basal expenditure from the three-compartment model (Figure
662 S6D). The departures from estimated basal expenditure suggest that the mass-specific metabolic
663 rates of one or more organ compartments are considerably higher early in life, and lower late in
664 life, than they are in middle-aged adults, consistent with previous assessments (21-25). It is

665 notable, in this context, that observed basal expenditure for neonates is nearly identical to basal
 666 expenditure estimated from the three-compartment model, which assumes adult-like tissue
 667 metabolic rates (Figure S6B,C,D). Observed basal expenditure for neonates is thus consistent
 668 with the hypothesis that the mass-specific metabolic rates of their organs are similar to those of
 669 other adults, specifically the mother.



670
 671 **Figure S6. Organ sizes and BEE.** **A.** The relative proportions of metabolically active organs (heart,
 672 brain, liver, kidneys), other fat free mass (FFM), and fat changes over the life course. Age cohort means
 673 are shown. **B.** Consequently, estimated basal expenditure (BEE) from the three-compartment model
 674 increases with fat free mass (FFM) in a manner similar to observed basal expenditure, with **C.** greater
 675 whole body mass-specific basal expenditure (BEE/FFM) early in life. **D.** Observed basal expenditure is
 676 ~30% greater early in life, and ~20% lower after age 60 y, than estimated basal expenditure from the
 677 three-compartment model (shown as the ratio of BEE/est.BEE). In panels **B**, **C**, and **D**, age-cohort means
 678 for observed (black) and estimated (magenta) basal expenditure are shown.

679 7. Modeling the Effects of Physical Activity and Tissue Specific Metabolism

680 We constructed two simple models to examine the contributions of physical activity and
681 variation in tissue metabolic rate to total and basal expenditure. In the simplest version, we used
682 the observed relationship between basal expenditure and fat free mass for all adults 20 – 60 y
683 determined from linear regression of $\ln(\text{basal expenditure})$ and $\ln(\text{fat free mass})$ (untransformed
684 regression equation: $\text{basal expenditure} = 0.32 (\text{fat free mass})^{0.75}$, $\text{adj. } r^2 = 0.60$, $\text{df} = 1684$, $p <$
685 0.0001) to model basal expenditure as

$$686 \quad \text{Basal expenditure} = 0.32 \text{ TM}_{\text{age}} (\text{fat free mass})^{0.75} \quad [3]$$

687 The TM_{age} term is tissue metabolic rate, a multiplier between 0 and 2 reflecting a relative
688 increase ($\text{TM}_{\text{age}} > 1.0$) or decrease ($\text{TM}_{\text{age}} < 1.0$) in organ metabolic rate relative that expected
689 from the power-law regression for adults. Note that, even when $\text{TM}_{\text{age}} = 1.0$, smaller individuals
690 are expected to exhibit greater mass-specific basal expenditure (that is, a greater basal
691 expenditure per kg body weight) due to the power-law relationship between basal expenditure
692 and fat free mass. Further, we note that the power-law relationship between basal expenditure
693 and fat free mass for adults is similar to that produced when estimating basal expenditure from
694 organ sizes (see *Organ Size and Basal Expenditure*, above). Thus, variation in TM_{age} reflects
695 modeled changes in tissue metabolic rate *in addition* to power-law scaling effects, and also, in
696 effect, in addition to changes in basal expenditure due to age-related changes in organ size and
697 proportion. To model variation in organ activity over the lifespan, we either 1) maintained TM_{age}
698 at adult levels ($\text{TM}_{\text{age}} = 1.0$) over the entire lifespan, or 2) had TM_{age} follow the trajectory of
699 adjusted basal expenditure with age (Figure S8).

700 To incorporate effects of fat mass into the model, we constructed a second version of the
701 model in which basal expenditure was modeled following the observed relationship with FFM
702 and fat mass for adults 20 – 60 y,

$$703 \quad \text{Basal expenditure} = 0.32 \text{ TM}_{\text{age}} (\text{fat free mass})^{0.7544} (\text{fat mass})^{0.0003} \quad [4]$$

704 As with the fat free mass model (eq. 3), we either maintained TM_{age} at 1.0 over the life span or
705 modeled it using the trajectory of adjusted basal expenditure.

706 Activity expenditure was modeled as a function of physical activity and body mass
707 assuming larger individuals expend more energy during activity. We began with activity
708 expenditure, calculated as $[0.9(\text{total expenditure}) - (\text{basal expenditure})]$ as described above. The
709 observed ratio of $(\text{activity expenditure})/(\text{fat free mass})$ for adults 20 – 60 y was $0.07 \text{ MJ d}^{-1} \text{ kg}^{-1}$.
710 We therefore modeled activity expenditure as

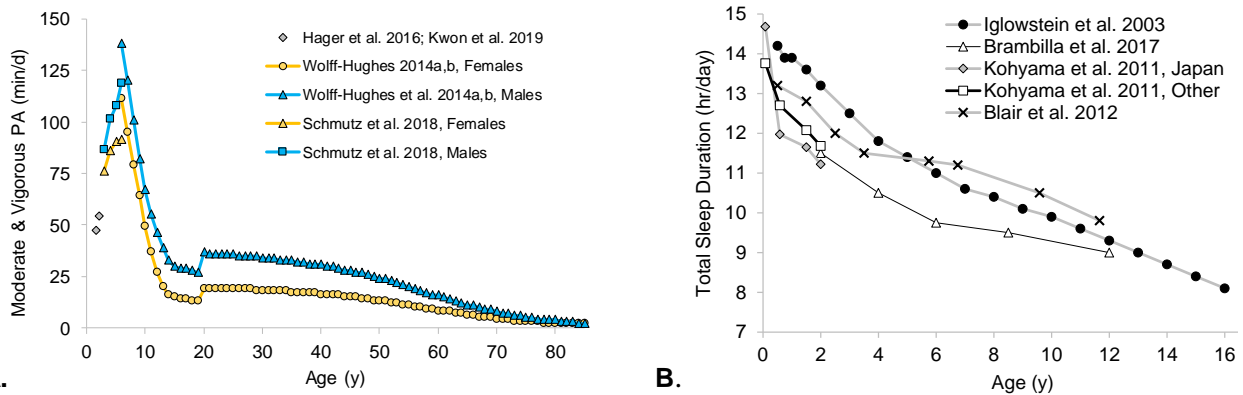
$$711 \quad \text{Activity expenditure} = 0.07 \text{ PA}_{\text{age}} (\text{fat free mass}) \quad [5]$$

712 To incorporate effects of fat mass, we constructed a second version using the ratio of (activity
713 expenditure)/(body weight) for adults 20 – 60y,

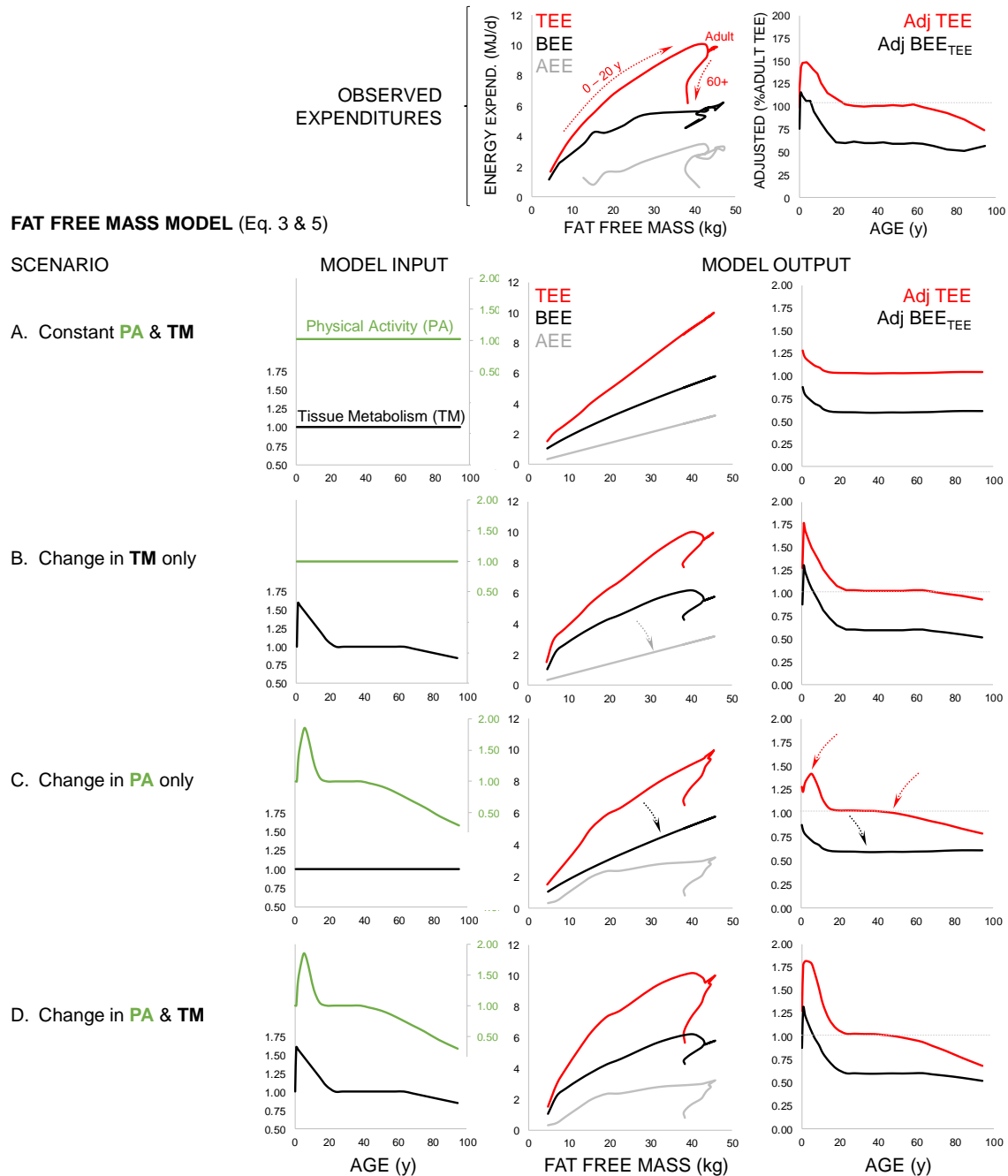
$$714 \quad \text{Activity expenditure} = 0.04 \text{ PA}_{\text{age}} (\text{body weight}) \quad [6]$$

715 In both equations, PA_{age} represents the level of physical activity relative to the mean value for 20
716 – 60 y adults. PA_{age} could either remain constant at adult levels ($\text{PA}_{\text{age}}=1.0$) over the lifespan or
717 follow the trajectory of physical activity measured *via* accelerometry, which peaks between 5 –
718 10 y, declines rapidly through adolescence, and then declines more slowly beginning at ~40 y
719 (11-13, 26, 27, 48-51). Different measures of physical activity (*e.g.*, moderate and vigorous PA,
720 mean counts per min., total accelerometry counts) exhibit somewhat different trajectories over
721 the lifespan, but the patterns are strongly correlated; all measures show the greatest activity at 5-
722 10 y and declining activity in older adults (Figure S7). We chose total accelerometry counts (11,

723 26), which sum all movement per 24-hour period, to model age-related changes in PA_{age} . We
 724 chose total counts because activity energy expenditure should reflect the summed cost of all
 725 activity, not only activity at moderate and vigorous intensities. Further, the amplitude of change
 726 in moderate and vigorous activity over the lifespan is considerably larger than the observed
 727 changes in adjusted total expenditure or adjusted activity expenditure (Figure S10). Determining
 728 the relative contributions of different measures of physical activity to total expenditure is beyond
 729 the scope of the simple modeling approach here and remains an important task for future
 730 research.
 731

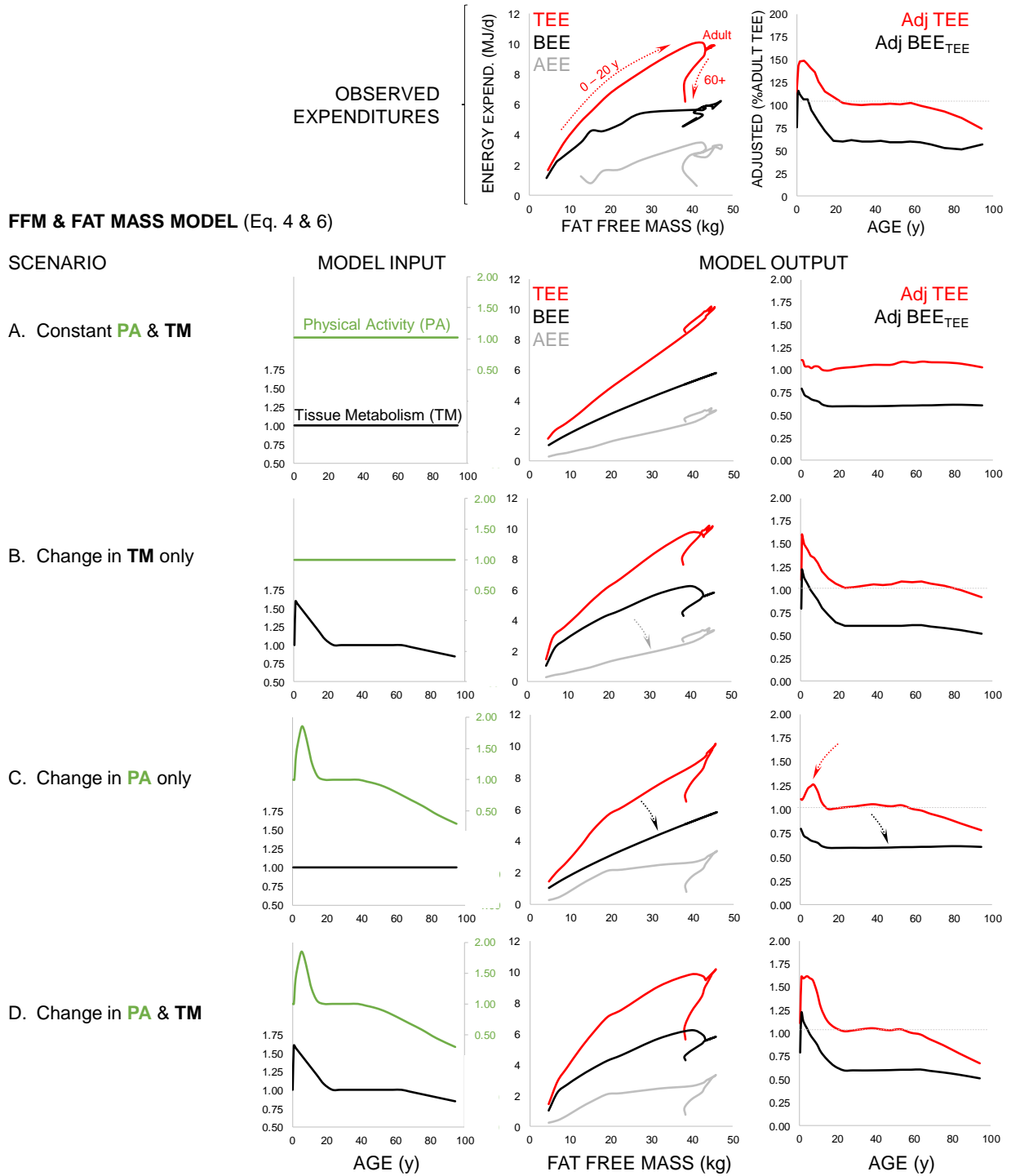


732 **A.** **Figure S7.** Modeling physical activity across the lifespan. **A.** Across studies and countries,
 733 accelerometer-measured physical activity rises through infancy and early childhood, peaking between 5
 734 and 10y before declining to adult levels in the teenage years (11-13, 26, 27, 48-51). Physical activity
 735 declines again, more slowly, in older adults. The onset of decline in older adults varies somewhat across
 736 studies, beginning between ~40 y and ~60 y. Here, physical activity is shown as minutes/day of moderate
 737 and vigorous physical activity. Other measures (e.g., total accelerometer counts; mean counts/min, vector
 738 magnitude) follow a similar pattern of physical activity over the life span (11, 26). **B.** The increase in
 739 physical activity from 0 to ~10 y is mirrored by the steady decline in total daily sleep duration during this
 740 period (52-55).
 741



742

743 **Figure S8.** Results of the fat free mass model. Observed expenditures exhibit a marked age effect on the
 744 relationship between expenditure and fat free mass that is evident in both absolute (Figure 1C) and
 745 adjusted (Figure 2D) measures. **A.** If physical activity (PA) and cellular metabolism (TM) remain constant
 746 at adult levels, age effects do not emerge from the model. **B.** When only TM varies, age effects emerge
 747 for total expenditure (TEE) and basal expenditure (BEE), but not activity expenditure (AEE; gray arrow).
 748 **C.** Conversely, if only physical activity varies age effects emerge for AEE and TEE but not BEE (black
 749 arrows). Adjusted TEE also peaks later in childhood and declines earlier in adulthood (red arrows) than
 750 observed. **D.** Varying both PA and TM gives model outputs similar to observed expenditures.



751

752 **Figure S9.** Results of the fat free mass and fat mass model. Model outputs are similar to those of the fat

753 free mass model (Figure S8). The scenario that best matches the observed relationships between fat free

754 mass, age, and expenditure is D, in which AEE is influenced by age-related variation in both physical

755 activity and cellular metabolism. Abbreviations as in Fig S8.

756 8. Physical Activity, Activity Expenditure and PAL

757 To further interrogate our simple model of expenditure and the contribution of physical
758 activity, we examined the agreement between accelerometry-measured physical activity,
759 adjusted activity expenditure, and modeled PAL over the lifespan. First, as noted in our
760 discussion of the simple expenditure model (see above; Figures 3, S8, S9), moderate and
761 vigorous physical activity and total accelerometry counts show a similar shape profile when
762 plotted against age, but moderate and vigorous physical activity shows a greater amplitude of
763 change over the lifespan (Figure S10). Moderate and vigorous physical activity reach a peak ~4-
764 times greater than the mean values observed for 20 – 30 y men and women, far greater than the
765 amplitude of change in adjusted total expenditure.

766 We used adjusted total and basal expenditures to model activity expenditure and PAL
767 over the lifespan for comparison with published accelerometry measures of physical activity.
768 Modeling activity expenditure and PAL was preferable because our dataset has no subjects less
769 than 3 y with measures of both total and basal expenditure, and only 4 subjects under the age of 6
770 y with both measures (Table S1). Using values of adjusted total expenditure and adjusted
771 BEE_{TEE} (basal expenditure expressed as a percentage of total expenditure) for age cohorts from
772 Table S3 enabled us to model activity expenditure and PAL for this critical early period of
773 development, in which both physical activity and expenditure change substantially. We modeled
774 adjusted activity expenditure as $[(\text{adjusted total expenditure}) - (\text{adjusted } BEE_{TEE})]$ and PAL as
775 $[(\text{adjusted total expenditure}) / (\text{adjusted } BEE_{TEE})]$, which as we show in Figure S4 correlate
776 strongly with unadjusted measures of activity expenditure and PAL, respectively.

777 Modeled adjusted activity expenditure and PAL showed a somewhat different pattern of
778 change over the lifecourse than either total counts or moderate and vigorous activity measured via

779 accelerometry (Figure S10). Modeled activity expenditure was most similar to total counts, rising
780 through childhood, peaking between 10 and 20 y before falling to a stable adult level; the adult
781 level was stable from ~30 – 75 y before declining (Figure S10). Modeled PAL rose unevenly
782 from birth through age 20, then remained largely stable thereafter.

783 The agreement, and lack thereof, between the pattern of accelerometry-measured physical
784 activity and modeled activity expenditure and PAL must be assessed with caution. These
785 measures are from different samples; we do not have paired accelerometry and energy
786 expenditure measures in the present dataset. The life course pattern of accelerometry-measured
787 physical activity, particularly total counts, is broadly consistent with that of modeled activity
788 expenditure. However, more work is clearly needed to determine the effects of physical activity
789 and other factors to variation in activity expenditure and PAL over the lifecourse.

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802 **9.IAEA DLW database consortium**

803 This group authorship contains the names of people whose data were contributed into the
804 database by the analysis laboratory but they later could not be traced, or they did not respond to
805 emails to assent inclusion among the authorship. The list also includes some researchers who did
806 not assent inclusion because they felt their contribution was not sufficient to merit authorship

807 **Dr Stefan Branth**

808 University of Uppsala, Uppsala, Sweden

809

810 **Dr Niels C. De Bruin**

811 Erasmus University, Rotterdam, The Netherlands

812

813 **Dr Lisa H. Colbert**

814 Kinesiology, University of Wisconsin, Madison, WI,

815

816 **Dr Alice E. Dutman**

817 TNO Quality of Life, Zeist, The Netherlands

818

819 **Dr Simon D. Eaton,**

820 University college London, London, UK

821

822 **Dr Cara Ebbeling**

823 Boston Children's Hospital, Boston, Massachusetts, USA.

824

825 **Dr Sölve Elmståhl**

826 Lund University, Lund, Sweden

827

828 **Dr Mikael Fogelholm**

829 Dept of Food and Nutrition, Helsinki, Finland

830

831 **Dr Tamara Harris**

832 Aging, NIH, Bethesda, MD,

833

834 **Dr Rik Heijligenberg**

835 Academic Medical Center of Amsterdam University, Amsterdam, The Netherlands

836

837 **Dr Hans U. Jorgensen**

838 Bispebjerg Hospital, Copenhagen, Denmark

839

840 **Dr Christel L. Larsson**

841 University of Gothenburg, Gothenburg, Sweden

842

843 **Dr David S. Ludwig**

844 Boston Children's Hospital, Boston, Massachusetts, USA.
845
846 **Dr Margaret McCloskey**
847 Royal Belfast Hospital for Sick Children, Belfast, Northern Ireland
848

849 **Dr Gerwin A. Meijer**
850 Maastricht University, Maastricht, The Netherlands
851

852 **Dr Daphne L. Pannemans**
853 Maastricht University, Maastricht, The Netherlands
854

855 **Dr Renaat M. Philippaerts**
856 Catholic University Leuven, Leuven, Belgium
857

858 **Dr John J. Reilly**
859 University of Strathclyde, Glasgow, UK

860 **Dr Elisabet M. Rothenberg**
861 Göteborg University, Göteborg, Sweden
862

863 **Dr Sabine Schulz**
864 University of Maastricht, Maastricht, The Netherlands

865 **Dr Amy Subar**
866 Epidemiology and Genomics, Division of Cancer Control, NIH, Bethesda, MD,
867

868 **Dr Minna Tanskanen**
869 University of Jyväskylä, Jyväskylä, Finland
870

871 **Dr Ricardo Uauy**
872 Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago Chile.
873

874 **Dr Rita Van den Berg-Emons**
875 Maastricht University, Maastricht, The Netherlands
876

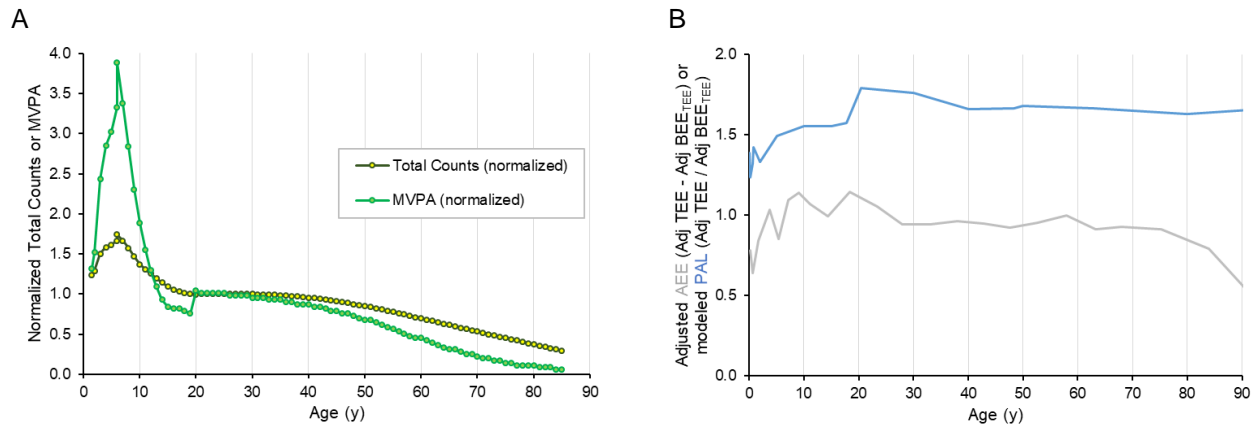
877 **Dr Wim G. Van Gemert**
878 Maastricht University, Maastricht, The Netherlands
879

880 **Dr Erica J. Velthuis-te Wierik**
881 TNO Nutrition and Food Research Institute, Zeist, The Netherlands
882

883 **Dr Wilhelmine W. Verboeket-van de Venne**
884 Maastricht University, Maastricht, The Netherlands
885

886 **Dr Jeanine A. Verbunt**
887 Maastricht University, Maastricht, The Netherlands

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Figure S10. A. Physical activity measured via accelerometry from published analyses (11-13, 26, 27, 48-51) and **B.** modeled activity expenditure and PAL calculated from cohort means for adjusted total expenditure and adjusted BEE_{TEE} in Table S3. Accelerometry measures and modeled activity expenditure are normalized to mean values for 20 – 30 y subjects.

Table S3. Adjusted total expenditure (TEE), Adjusted basal expenditure (BEE), and Adjusted BEE_{TEE}. *Infant data from the literature, males and females pooled. N values for infant BEE (0 to 2 years) indicate number of entries and (number of individuals).

| | | Adjusted TEE - Female & Male Cohorts | | | | | | | | Adjusted BEE and Adjusted BEE _{TEE} | | | | | | | | | | | |
|----------|--|--------------------------------------|-----|----------|------|--------------|------|-------|------|--|-----|----------|------|--------------|-------|-------|------|-----------------------------|------|-------|------|
| | | N | | mean Age | | Adjusted TEE | | | | N | | mean Age | | Adjusted BEE | | | | Adjusted BEE _{TEE} | | | |
| Age | | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | | |
| Cohort | | F | M | F | M | mean | sd | mean | sd | F | M | F | M | mean | sd | mean | sd | mean | sd | mean | sd |
| (0,0.5] | | 103 | 93 | 0.2 | 0.2 | 120.0 | 23.2 | 118.4 | 23.2 | 22 (111)* | | 0.2 | | 100.47 | 33.89 | | | 86.03 | 28.9 | | |
| (0.5,1] | | 18 | 23 | 0.7 | 0.7 | 139.8 | 17.0 | 145.5 | 25.7 | 20 (88)* | | 0.9 | | 142.89 | 11.62 | | | 115.47 | 9.2 | | |
| (1,2] | | 33 | 35 | 1.7 | 1.6 | 147.4 | 23.9 | 148.2 | 21.6 | 18 (86)* | | 1.6 | | 142.02 | 13.52 | | | 111.94 | 9.6 | | |
| (2,4] | | 54 | 48 | 3.8 | 3.8 | 147.0 | 13.4 | 150.3 | 19.6 | 3 | 1 | 3.8 | 4.0 | 150.2 | 6.0 | 144.3 | NA | 108.6 | 7.4 | 100.7 | NA |
| (4,6] | | 99 | 121 | 5.3 | 5.3 | 142.5 | 14.0 | 148.2 | 18.5 | 9 | 5 | 5.7 | 5.4 | 156.4 | 26.3 | 158.8 | 30.9 | 110.1 | 19.9 | 108.1 | 19.9 |
| (6,8] | | 42 | 42 | 7.0 | 7.2 | 139.2 | 16.7 | 143.2 | 13.6 | 18 | 12 | 7.2 | 7.4 | 136.9 | 25.8 | 141.9 | 21.8 | 94.6 | 17.7 | 94.6 | 15.1 |
| (8,10] | | 79 | 75 | 9.1 | 9.1 | 132.8 | 19.2 | 140.2 | 18.7 | 22 | 16 | 9.2 | 9.5 | 130.0 | 23.4 | 137.3 | 21.8 | 87.2 | 15.2 | 88.8 | 14.2 |
| (10,12] | | 68 | 34 | 11.1 | 11.0 | 122.0 | 23.4 | 133.4 | 16.3 | 5 | 5 | 11.1 | 11.1 | 128.3 | 19.9 | 126.3 | 21.2 | 82.6 | 12.3 | 81.8 | 15.0 |
| (12,16] | | 229 | 128 | 14.4 | 14.5 | 113.1 | 22.9 | 118.9 | 21.4 | 18 | 16 | 14.4 | 13.9 | 103.1 | 18.6 | 130.0 | 23.3 | 64.9 | 12.2 | 82.4 | 15.7 |
| (16,20] | | 209 | 103 | 18.3 | 18.4 | 107.1 | 14.4 | 113.3 | 17.1 | 155 | 148 | 18.5 | 18.9 | 97.5 | 12.9 | 109.3 | 7.5 | 60.2 | 8.1 | 62.9 | 5.3 |
| (20,25] | | 252 | 123 | 23.2 | 23.5 | 100.6 | 15.5 | 106.7 | 21.9 | 135 | 116 | 23.4 | 23.8 | 98.3 | 10.5 | 99.6 | 8.1 | 60.6 | 7.1 | 57.0 | 5.2 |
| (25,30] | | 280 | 182 | 27.8 | 28.0 | 100.5 | 15.3 | 102.0 | 21.2 | 115 | 104 | 27.9 | 27.9 | 100.8 | 11.5 | 104.0 | 13.4 | 62.5 | 7.8 | 59.6 | 8.3 |
| (30,35] | | 235 | 146 | 33.0 | 32.8 | 100.0 | 11.9 | 100.7 | 16.5 | 96 | 94 | 33.2 | 33.1 | 98.7 | 9.7 | 103.3 | 10.4 | 60.9 | 6.3 | 59.7 | 7.0 |
| (35,40] | | 231 | 165 | 38.0 | 38.0 | 100.0 | 11.9 | 102.3 | 16.3 | 112 | 110 | 38.1 | 38.2 | 99.7 | 10.2 | 101.6 | 11.7 | 61.4 | 6.9 | 59.1 | 7.2 |
| (40,45] | | 301 | 165 | 42.8 | 42.9 | 101.3 | 12.6 | 100.8 | 13.2 | 100 | 96 | 42.9 | 42.6 | 99.8 | 10.4 | 102.9 | 9.1 | 61.6 | 6.9 | 59.7 | 6.1 |
| (45,50] | | 171 | 144 | 47.4 | 47.8 | 102.0 | 12.4 | 100.5 | 14.3 | 42 | 41 | 47.3 | 48.1 | 99.0 | 14.7 | 108.1 | 14.6 | 61.4 | 9.6 | 62.7 | 8.9 |
| (50,55] | | 105 | 93 | 52.8 | 52.6 | 100.5 | 11.4 | 100.8 | 13.2 | 33 | 33 | 53.1 | 53.4 | 96.1 | 9.1 | 103.1 | 9.2 | 59.8 | 5.5 | 60.3 | 5.9 |
| (55,60] | | 111 | 76 | 58.2 | 57.8 | 102.2 | 11.7 | 102.9 | 20.0 | 23 | 23 | 58.1 | 57.5 | 100.3 | 9.5 | 100.0 | 7.1 | 62.5 | 6.1 | 57.9 | 4.5 |
| (60,65] | | 252 | 90 | 63.2 | 63.2 | 98.8 | 12.4 | 99.8 | 15.3 | 23 | 21 | 62.4 | 63.1 | 99.5 | 12.8 | 99.2 | 8.5 | 62.6 | 8.3 | 58.3 | 5.2 |
| (65,70] | | 387 | 90 | 68.0 | 68.0 | 97.6 | 10.9 | 94.4 | 11.1 | 40 | 40 | 68.0 | 68.7 | 91.0 | 8.6 | 95.2 | 7.6 | 56.9 | 5.9 | 56.4 | 4.8 |
| (70,80] | | 681 | 232 | 75.1 | 75.4 | 93.9 | 12.1 | 90.6 | 14.6 | 188 | 173 | 75.2 | 75.4 | 86.8 | 9.9 | 86.4 | 12.9 | 55.2 | 6.6 | 51.5 | 8.0 |
| (80,90] | | 149 | 66 | 83.6 | 84.2 | 87.6 | 12.2 | 82.8 | 13.0 | 47 | 38 | 84.1 | 84.0 | 86.5 | 16.0 | 78.6 | 10.8 | 55.3 | 10.8 | 47.6 | 6.8 |
| (90,100] | | 22 | 8 | 94.4 | 94.0 | 73.2 | 12.4 | 76.0 | 9.6 | 14 | 5 | 94.9 | 94.0 | 91.2 | 19.1 | 94.8 | 14.6 | 57.1 | 12.9 | 57.3 | 8.6 |

906 **Table S4.** Segmented Regression Analyses

| adjTEE | Segments | | | | Break Points | | |
|---------------|-----------------|-----------|-----------------|-----------------|---------------------|-----------------|-----------------|
| | <i>beta</i> | <i>SE</i> | <i>CI_lower</i> | <i>CI_upper</i> | <i>Estimate</i> | <i>CI_lower</i> | <i>CI_upper</i> |
| | 84.70 | 7.15 | 70.69 | 98.71 | 0.69 | 0.61 | 0.76 |
| | -2.77 | 0.07 | -2.91 | -2.63 | 20.46 | 19.77 | 21.15 |
| | -0.02 | 0.02 | -0.07 | 0.03 | 62.99 | 60.13 | 65.85 |
| | -0.68 | 0.06 | -0.79 | -0.57 | | | |

| adjBEE | Segments | | | | Break Points | | |
|---------------|-----------------|-----------|-----------------|-----------------|---------------------|-----------------|-----------------|
| | <i>beta</i> | <i>SE</i> | <i>CI_lower</i> | <i>CI_upper</i> | <i>Estimate</i> | <i>CI_lower</i> | <i>CI_upper</i> |
| | 75.51 | 5.59 | 64.55 | 86.46 | 1.04 | 0.94 | 1.14 |
| | -3.75 | 0.22 | -4.17 | -3.33 | 18.00 | 16.82 | 19.18 |
| | 0.02 | 0.05 | -0.07 | 0.12 | 46.46 | 40.57 | 52.35 |
| | -0.45 | 0.04 | -0.53 | -0.37 | | | |

907