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Variation in human water turnover associated with environmental and lifestyle factors

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1 Science

2 **Variation in human water turnover associated with environmental and**
3 **lifestyle factors**

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28 # See the supplementary materials.

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146 **Abstract:**

147 **Water is essential for survival, but one in three individuals worldwide (2.2 billion**
148 **people) lack access to safe drinking water. Water intake requirements largely reflect**
149 **water turnover, the water used by the body each day. We investigated the determinants**
150 **of human water turnover in 5,604 people aged 8 days to 96 years from 26 countries**
151 **using isotope tracking (^2H) methods. Age, body size, and composition were significantly**
152 **associated with water turnover as were physical activity, athletic status, pregnancy,**
153 **socioeconomic status, and environmental characteristics (latitude, altitude, air**
154 **temperature, and humidity). People in countries with low human development index**
155 **(HDI) had higher water turnover than people who lived in countries with high HDI.**
156 **Based on this extensive dataset we provide equations to predict human water**
157 **requirements in relation to anthropometric, economic, and environmental factors.**

158

159 **One Sentence Summary:**

160 Measures of human water turnover from a large global database demonstrate the effects of
161 body size, age, lifestyle, and climate.

162

163 **Main text:**

164 Water is essential for life (1) and daily water intake is necessary to prevent
165 dehydration (i.e., net loss of body water) in most terrestrial animals, including humans (2).
166 Total body water (L) is homeostatically controlled (3) and tightly regulated day-to-day by
167 thirst and hunger drives leading to intake of fluids and food to offset water losses (4). Body
168 water is lost as urine, insensible transcutaneous evaporation and sweat loss, respiratory water
169 vapor, and water in feces (**Fig. 1A**). To maintain water balance, these losses must be matched
170 by intake of water from liquids (drinking water and beverages) and foods (5, 6), water vapor
171 in respiratory air intake, transcutaneous water uptake, and water formed during aerobic
172 respiration and metabolism (**Fig. 1A**) (2, 7). The total movement of water through the body,
173 both intake and loss, is called water turnover (L/day).

174 Despite adaptations to minimize dehydration, humans can survive for only ~3 days
175 without consuming water (1). The risk of dehydration is greater under conditions requiring
176 increased respiration, blood circulation, and sweating, such as vigorous physical activity or
177 in hot and humid environments (3). Insufficient water intake is a risk factor for heat stroke,
178 urinary and kidney diseases, and cardiovascular failure (8, 9). An understanding of water
179 turnover and its determinants is critical for global public health decision-making regarding
180 the provision of drinking water and water-enriched food (10).

181 Public health officials need to be able to anticipate future daily water intake demands
182 of their populations, especially during periods of impending crisis. Ideally this would be based
183 on scientific evidence regarding the levels of normal water intake. The current recommended

184 intakes for water (8, 9, 11), however, rely on epidemiologic self-reported surveys or
185 laboratory-based physiological studies with rather small sample sizes. Results obtained from
186 self-reported intake surveys show large variation linked to imprecision in the assessment
187 method. It is thus difficult to establish clear guidelines for worldwide public health actions
188 from these sources of information. The majority of people who lack access to safely managed
189 drinking water live in countries with a low human development index (HDI), but few studies
190 have examined water turnover in those populations (2). To develop global guidelines for
191 daily water intake, empirical measurements of water turnover under free-living conditions
192 are required across a broad range of economic and environmental conditions.

193 We report water turnover (**Fig 1**) and total body water for 5,604 (3,729 females and
194 1875 males) people, aged between 8 days to 96 years, from 26 countries around the globe,
195 across a wide range of environments and living conditions (**Fig. S1** and **Table S1**). We used
196 the hydrogen isotope dilution and elimination technique, which provides an objective,
197 accurate, reliable, and precise measurement of both total body water and water turnover under
198 free-living conditions (**Fig. 1B**) (7). This method involves the subject drinking about 100 mls
199 of water that is enriched with about 5% deuterated water (DHO). The deuterium floods into
200 the body water pool providing an estimate of total body water via the dilution principle (12).
201 The excess deuterium isotope is then eliminated from the body by the elimination routes
202 detailed in **Fig 1A**. Because there is no enriched isotope tracer entering the system the isotope
203 enrichment declines exponentially back to the baseline level. The rate constant of this
204 exponential return to baseline multiplied by the body water pool is equal to the water turnover.

205 Data were obtained from the International Atomic Energy Agency doubly labeled
206 water (DLW) Database (13, 14). The current study aimed to examine (1) the dependence of
207 water turnover and total body water on age, body size, body composition, total energy
208 expenditure (MJ/d), and physical activity level (PAL = total energy expenditure/basal energy
209 expenditure) through the human lifecourse, (2) the effects of climate, including latitude,
210 altitude, outside air temperature, and humidity; and (3) the potential influence of economic
211 development as measured by the HDI.

212 Water turnover was greatest in individuals aged 20 to 30 yr in men, and from 20 to
213 55 yr in women (**Fig. 2A** and **Table S2**). Water turnover was lower in men aged >40 and
214 women aged >65. Total body water was also highest for adults 20 to 40 years old (**Fig. 2B**).
215 As a fraction of total body water, water turnover was highest in neonates ($28.3 \pm 7.2\%$ per
216 day) and decreased with age to $9.9 \pm 3.0\%$ per day in adults aged 18 to 40 years (**Fig. 2C**).
217 Total body water as a proportion of body weight also decreased with age, from $60.0 \pm 6.4\%$
218 of body weight from birth to 6 months to $50.4 \pm 5.3\%$ (males) and $42.0 \pm 4.8\%$ (females) at
219 age 60 (**Fig. 2D**). Sex differences and the relationship with age and total body water in adults
220 largely reflected variations in percent body fat, which contains less water than muscle and
221 other organs. The ratio of water turnover to total energy expenditure was 0.33 ± 0.09 L/MJ
222 (1.4 ± 0.4 ml/kcal) for adults, comparable to previous isotope-based measures (15) (**Fig. 2E**).

223 Body size and composition, energy expenditure, and climate variables were all
224 correlated with water turnover. Limiting our analysis to adults aged 18 to 60 years to avoid
225 strong age effects (as shown in Fig. 2), bivariate analyses showed that water turnover was

226 positively correlated with fat-free mass, total energy expenditure, and PAL, and negatively
227 correlated with percent body fat ($P < 0.001$) (**Fig. 3A through D**). We found a significant
228 curvilinear relationship between outdoor air temperature and water turnover and a
229 curvilinear relationship between latitude and water turnover ($P < 0.001$) (**Fig. 3E, F**). Air
230 temperature was positively correlated with water turnover when it was higher than 10 °C
231 ($P < 0.001$). Daily water intake was highest at approximately 0° effective latitude and the
232 lowest at -50° or +50° latitude. People living above the Arctic Circle had higher water
233 turnover than those who lived at -50° or +50° latitude.

234 Linear regression analysis showed that age, fat-free mass, PAL, air temperature,
235 relative humidity, HDI, and altitude were significant predictors of water turnover in adults
236 aged 18 years and older (**Table S3**). We conducted multiple regression analysis (including
237 first- and second-order polynomial terms) to examine potential non-linear relationships
238 between water turnover and the above variables in adults aged 18 years and older (**Table S4**).
239 The positive coefficient of the second-order term of air temperature indicated a curvilinear
240 relationship between water turnover and air temperature. The negative coefficient of the
241 second-order term of age also indicated a curvilinear relationship between water turnover
242 and age. A non-linear increase of water turnover with increase of air temperature is predicted
243 from the standard Scholander curve (16) for the impact of ambient temperature on metabolic
244 rate and evaporative water loss. In an additional test of these relationships, repeated measures
245 for 72 people in spring and summer indicated higher water turnover in the summer (mean air
246 temperature of 29 °C) than in spring (mean air temperature of 18 °C) ($P < 0.001$), whereas
247 total energy expenditure did not differ seasonally (**Fig. 4A and 4B**).

248 Water turnover of pregnant and lactating women is of interest because pregnant
249 women have higher total body water and fat-free mass than do non-pregnant women (17),
250 and lactating women also lose water via milk production (11). Repeated measures of 63
251 women indicated water turnover increases in the third trimester of pregnancy (+670 mL/d)
252 and during lactation (+260 mL/d) compared to pre-pregnancy (**Fig. 4C**) (17). The increase
253 of water turnover during pregnancy is consistent with the increase in total body water.

254 The highest water turnovers in our sample are consistent with the effects of
255 temperature, climate, physical activity and body size. Nine of the 1,875 males had high water
256 turnover greater than 10 L/d; of these four were athletes, four were adult Shuar forager-
257 horticulturalists of Amazonian Ecuador (18), and one male was Caucasian with normal BMI
258 but measured in the summer with a maximal air temperature of 31.7 °C. Thirteen of 3,729
259 females had high water turnover greater than 7 L/d; of these five females were athletes, two
260 females were pregnant women who had extremely high BMI (>45 kg/m²) and were measured
261 in the summer; three females had high BMI (>30 kg/m²), in which two were measured in the
262 summer. Three females were measured in summer, with a maximal air temperature of >30°C.

263 Lifestyle had clear effects on water turnover. Athletes had higher water turnover
264 than non-athletes (P<0.001, **Fig. 5A** and **Table S5**). Hunter-gatherers, mixed farmers, and
265 subsistence agriculturalists all had higher water turnover than those in industrialized
266 economies (P<0.001, **Fig. 5B** and **Table S6**). People in countries with low HDI had higher
267 water turnover than those who lived in countries with middle and high HDI, even after
268 adjustment for physiological and environmental variables (P<0.001, **Fig. 5C** and **Table S7**).

269 The effects of body size, PAL, and air temperature were greater for people in countries with
270 low HDI (**Fig. 4D through F**). The smaller effects for these variables in high HDI
271 populations suggests water needs are buffered against environmental influences through
272 effective indoor climate control (*e.g.*, air conditioning). In high HDI countries with access to
273 air-conditioning and heating, people are exposed primarily to a narrow indoor temperature in
274 range (18 to 25 °C) (19). By comparison, people living in low HDI countries are more likely
275 to be exposed to ambient environmental temperatures without climate control. This view is
276 consistent with greater size-adjusted water turnover for hunter-gatherers and manual laborers
277 when compared to sedentary adults in industrialized countries (2). Similarly, a previous
278 comparison of regional water use (20) noted that water use is relatively high in Africa and
279 relatively low in Europe, and results from our analysis may help to explain why.

280 We obtained the following equation to predict water turnover (**Fig. 6**):

$$\begin{aligned} 281 \text{ Water turnover (mL/d)} &= 1076 \times \text{PAL} + 14.34 \times \text{Body weight (kg)} + 374.9 \times \text{Sex} \\ 282 &+ 5.823 \times \text{Humidity (\%)} + 1070 \times \text{Athlete status} + 104.6 \times \text{HDI} + 0.4726 \times \text{Altitude (m)} - \\ 283 &0.3529 \times \text{Age}^2 + 24.78 \times \text{Age (y)} + 1.865 \times \text{Temperature}^2 - 19.66 \times \text{Temperature (}^\circ\text{C)} - 713.1 \\ 284 &[\text{eq.1}] \end{aligned}$$

285 Sex is 0 for female and 1 for male; Athlete status is 0 for non-athlete and 1 for athlete; HDI
286 is 0 for high HDI countries, 1 for middle HDI countries, and 2 for low HDI countries. This
287 equation explains 47.1% of the variation in water turnover. An increase in PAL of 1.0 induces
288 a ~1000 ml increase in water turnover; a 50 kg increase in body weight induces a ~700 ml
289 increases in water turnover; a 50% increase in relative humidity induces a ~300 ml increase

290 in water turnover; and a 1000 m increase in altitude induces a ~500 ml increase in water
291 turnover. Males exhibit ~400 ml more water turnover than do females of the same weight
292 because males have greater fat-free mass and a lower percentage body fat. People who live
293 in low HDI countries exhibit ~200 ml more water turnover than people who live in high HDI
294 countries after controlling for the other measured variables. Athletes have ~1000 ml more
295 water turnover than do non-athletes with everything else being equal. A U-shaped
296 relationship between water turnover and air temperature shows ~1000 ml more water
297 turnover at +30 °C air temperature than the nadir between ±0 and +10 °C air temperature,
298 and also ~400 ml more water turnover at –10 °C air temperature than that nadir. A curvilinear
299 relationship between water turnover and age shows the peak water turnover is shown between
300 20's and 40's and decrease after 50's and ~700 ml less water turnover at age 80 than at age
301 30.

302 A 20-year-old male weighing 70 kg, who is not athletic and exhibits a PAL of 1.75,
303 and who lives in a high HDI country at 0 m altitude where mean air temperature is 10°C and
304 relative humidity is 50%, has a predicted water turnover of 3.2 L/d. A non-athletic 20-year-
305 old female weighing 60 kg living at the same location will have a water turnover of 2.7 L/d.
306 In contrast, a 20-year-old athletic male weighing 70 kg, with a PAL of 2.5, who lives in a
307 high HDI country at a location 2000 m above sea level, where air temperature is 30°C and
308 relative humidity is 90%, has a water turnover of 7.3 L/d; for a 60 kg athletic female in the
309 same scenario, water turnover is 6.8 L/d. In this equation, we used weight and sex as a proxy
310 of fat-free mass because body composition is not easily measured in daily setting. If body

311 composition can be assessed, the following equation can be used to predict water turnover

312 **(Fig. 6):**

$$\begin{aligned} 313 \text{ Water turnover (mL/d)} &= 861.9 \times \text{PAL} + 37.34 \times \text{Fat-free mass (kg)} + 4.288 \times \text{Humidity (\%)} \\ 314 &+ 699.7 \times \text{Athlete status} + 105.0 \times \text{HDI} + 0.5140 \times \text{Altitude (m)} - 0.3625 \times \text{Age}^2 + 29.42 \times \text{Age (y)} \\ 315 &+ 1.937 \times \text{Temperature}^2 - 23.15 \times \text{Temperature (}^\circ\text{C)} - 984.8 \quad [\text{eq.2}] \end{aligned}$$

316 TEE was not included into the equations because sex, body weight or PAL capture the
317 variance explained by TEE. When fat-free mass was included in the model, the effect of sex
318 was not significant. The sex difference of water turnover can be explained by the sex
319 difference of the fat-free mass/body weight ratio.

320 Values of water turnover in this study represented average values under normal
321 conditions. Many health conditions, including parasitic infections and diarrhea, affect water
322 loss and intake (21). Additionally, the current study did not assess any indicators of hydration
323 status and did not indicate whether the participants were adequately hydrated. Older adults
324 or vulnerable individuals have a higher risk of both acute and chronic dehydration (22, 23)
325 because they have a decreased thirst response. Medications, anorexia or frailty, and low total
326 body water (storage) are associated with a lower skeletal muscle mass (*i.e.*, sarcopenia).
327 Skeletal muscle tissues contain a large volume of water, particularly in the intracellular space
328 (24). Mean water turnover values presented here are not necessarily representative of all
329 people or conditions (21) but provide a comparative framework for investigating water
330 intakes in populations with greater needs.

331 Objective measures of water turnover from a large global dataset indicate that water
332 turnover is strongly related to anthropometric, lifestyle, and environmental factors. We found
333 significant correlations between water turnover and several known markers of health,
334 wellness, and disease risks: Water turnover is positively correlated with fat-free mass, TEE,
335 PAL, athletic status, and negatively correlated with percent body fat and age in adults. Water
336 turnover may therefore provide a useful, integrative biomarker of metabolic health.
337 Biomarkers that capture global metabolic health are generally lacking and of potentially
338 enormous value for public health and medical management.

339 As shown in Figure 1, we need to be aware that water turnover obtained by the
340 hydrogen isotope dilution and elimination technique is not equal to daily water intake from
341 liquids and foods. Metabolic water accounts for ~10% of water turnover, and respiratory
342 water uptake and transcutaneous water uptake each account for 2 to 3% of water turnover.
343 Therefore, daily water intake from liquids and foods is equivalent to ~85% of water turnover
344 (7). An unsolved question is, what percentage of water intake comes from food? Self-reported
345 surveys around the world suggested 20-50% of daily water intake is from food (5, 6, 11).
346 These estimates, however, are questionable because many studies that have demonstrated
347 self-reported surveys underestimate energy, protein and salt intake. Thus, dietary survey
348 methods probably also underestimate the water intake in food and overestimate from drinking
349 water and beverages. Conversely, if people consume a higher energy density diet with lower
350 water content (25, 26), they may need more water from drinks and beverages. Without
351 measured water intakes from food, it is not possible to assess the relative contributions of
352 food and drinking water or beverages to water turnover in this study, and indeed no studies

353 to date have adequately addressed this issue. Nonetheless, the current study clearly indicates
354 that one size does not fit all for drinking water guidelines, and the common suggestion that
355 we should drink 8×8 oz glasses of water per day (approx. 2 L) is not backed by objective
356 evidence.

357 We provide equations to predict human water turnover by environmental, lifestyle
358 and anthropometric factors guided by a large dataset. Improved guidelines are of increasing
359 importance because of the explosive population growth and climate change the world
360 currently faces, which will affect the availability of water for human consumption (27, 28)
361 and non-ingestive uses, such as irrigation, cooling, and manufacturing (29). Presently, 2.2
362 billion people lack access to safe drinking water (30). The water turnover measures here can
363 help shape strategies for drinking water and water-enriched food management as the global
364 population and climate changes.

365

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367 References

- 368 1. B. M. Popkin, K. E. D'Anci, I. H. Rosenberg, Water, hydration, and health. *Nutr Rev* **68**, 439-
369 458 (2010).
- 370 2. H. Pontzer *et al.*, Evolution of water conservation in humans. *Current biology : CB* **31**,
371 1804-1810.e1805 (2021).
- 372 3. T. Morimoto, T. Itoh, Thermoregulation and body fluid osmolality. *J Basic Clin Physiol*
373 *Pharmacol* **9**, 51-72 (1998).
- 374 4. C. A. Zimmerman *et al.*, Thirst neurons anticipate the homeostatic consequences of eating
375 and drinking. *Nature* **537**, 680-684 (2016).
- 376 5. A. Rosinger, S. Tanner, Water from fruit or the river? Examining hydration strategies and
377 gastrointestinal illness among Tsimane' adults in the Bolivian Amazon. *Public Health Nutr*
378 **18**, 1098-1108 (2015).
- 379 6. Y. Tani *et al.*, The influence of season and air temperature on water intake by food groups
380 in a sample of free-living Japanese adults. *Eur J Clin Nutr* **69**, 907-913 (2015).
- 381 7. A. Raman *et al.*, Water turnover in 458 American adults 40-79 yr of age. *American journal*
382 *of physiology. Renal physiology* **286**, F394-401 (2004).
- 383 8. R. J. Johnson *et al.*, Metabolic and Kidney Diseases in the Setting of Climate Change, Water
384 Shortage, and Survival Factors. *Journal of the American Society of Nephrology : JASN* **27**,
385 2247-2256 (2016).
- 386 9. J. Glaser *et al.*, Climate Change and the Emergent Epidemic of CKD from Heat Stress in
387 Rural Communities: The Case for Heat Stress Nephropathy. *Clinical journal of the American*
388 *Society of Nephrology : CJASN* **11**, 1472-1483 (2016).
- 389 10. P. H. Gleick, Water strategies for the next administration. *Science* **354**, 555-556 (2016).
- 390 11. Food and Nutrition Board, Institute of Medicine, *Dietary Reference Intakes for Water,*
391 *Potassium, Sodium, Chloride, and Sulfate.*, (National Academies Press, Washington, DC,
392 2005).
- 393 12. International Atomic Energy Agency, *IAEA Human Health Series No. 3. Assessment of Body*
394 *Composition and Total Energy Expenditure in Humans Using Stable Isotope Techniques.*
395 (Vienna International Centre, Vienna, Austria, 2009).
- 396 13. J. R. Speakman *et al.*, A standard calculation methodology for human doubly labeled water
397 studies. *Cell reports. Medicine* **2**, 100203 (2021).
- 398 14. H. Pontzer *et al.*, Daily energy expenditure through the human life course. *Science* **373**,
399 808-812 (2021).
- 400 15. K. R. Westerterp, G. Plasqui, A. H. Goris, Water loss as a function of energy intake, physical
401 activity and season. *Br J Nutr* **93**, 199-203 (2005).
- 402 16. P. F. Scholander, R. Hock, V. Walters, F. Johnson, L. Irving, Heat regulation in some arctic
403 and tropical mammals and birds. *The Biological bulletin* **99**, 237-258 (1950).
- 404 17. N. F. Butte, W. W. Wong, M. S. Treuth, K. J. Ellis, E. O'Brian Smith, Energy requirements
405 during pregnancy based on total energy expenditure and energy deposition. *Am J Clin Nutr*
406 **79**, 1078-1087 (2004).
- 407 18. L. Christopher *et al.*, High energy requirements and water throughput of adult Shuar
408 forager-horticulturalists of Amazonian Ecuador. *American journal of human biology : the*
409 *official journal of the Human Biology Council*, e23223 (2019).

- 410 19. X. Zhang *et al.*, Human total, basal and activity energy expenditures are independent of
411 ambient environmental temperature. *iScience* **25**, 104682 (2022).
- 412 20. S. Pande, A. Pandit, Hydro-social metabolism: scaling of birth rate with regional water use.
413 *Palgrave Communications* **4**, 85 (2018).
- 414 21. A. Y. Rosinger, Biobehavioral variation in human water needs: How adaptations, early life
415 environments, and the life course affect body water homeostasis. *American journal of*
416 *human biology : the official journal of the Human Biology Council* **32**, e23338 (2020).
- 417 22. A. M. El-Sharkawy *et al.*, Hydration and outcome in older patients admitted to hospital
418 (The HOOP prospective cohort study). *Age Ageing* **44**, 943-947 (2015).
- 419 23. R. J. Maughan, Hydration, morbidity, and mortality in vulnerable populations. *Nutr Rev* **70**
420 **Suppl 2**, S152-155 (2012).
- 421 24. Y. Yamada *et al.*, Extracellular Water May Mask Actual Muscle Atrophy During Aging. *The*
422 *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* **65A**, 510-516
423 (2010).
- 424 25. A. Drewnowski, Energy Density, Palatability, and Satiety: Implications for Weight Control.
425 *Nutrition Reviews* **56**, 347-353 (1998).
- 426 26. J. H. Ledikwe *et al.*, Dietary energy density is associated with energy intake and weight
427 status in US adults. *The American Journal of Clinical Nutrition* **83**, 1362-1368 (2006).
- 428 27. UNESCO World Water Assessment Programme, *The United Nations world water*
429 *development report 2020: water and climate change*. (2020).
- 430 28. G. Woodward, D. M. Perkins, L. E. Brown, Climate change and freshwater ecosystems:
431 impacts across multiple levels of organization. *Philos Trans R Soc Lond B Biol Sci* **365**, 2093-
432 2106 (2010).
- 433 29. F. Jaramillo, G. Destouni, Local flow regulation and irrigation raise global human water
434 consumption and footprint. *Science* **350**, 1248-1251 (2015).
- 435 30. UN Stats, *Sustainable Development Goals*. (2019).
- 436 31. J. R. Speakman *et al.*, The International Atomic Energy Agency International Doubly
437 Labelled Water Database: Aims, Scope and Procedures. *Annals of Nutrition and*
438 *Metabolism* **75**, 114-118 (2019).
- 439 32. International Atomic Energy Agency. (Vienna, Austria, 2019), vol. 2020.
- 440 33. J. R. Speakman, *Doubly labelled water: theory and practice*. (Chapman and Hall, London,
441 1997).
- 442 34. D. A. Schoeller *et al.*, Energy expenditure by doubly labeled water: validation in humans
443 and proposed calculation. *Am J Physiol Regul Integr Comp Physiol* **250**, R823-830 (1986).
- 444 35. W. W. Wong, L. L. Clarke, A hydrogen gas-water equilibration method produces accurate
445 and precise stable hydrogen isotope ratio measurements in nutrition studies. *J Nutr* **142**,
446 2057-2062 (2012).
- 447 36. N. Ripoché, V. Ferchaud-Roucher, M. Krempf, P. Ritz, D and ¹⁸O enrichment
448 measurements in biological fluids in a continuous-flow elemental analyser with an isotope-
449 ratio mass spectrometer using two configurations. *Journal of mass spectrometry : JMS* **41**,
450 1212-1218 (2006).
- 451 37. K. R. Westerterp, Doubly labelled water assessment of energy expenditure: principle,
452 practice, and promise. *Eur J Appl Physiol* **117**, 1277-1285 (2017).
- 453 38. M. D. Mifflin *et al.*, A new predictive equation for resting energy expenditure in healthy
454 individuals. *Am J Clin Nutr* **51**, 241-247 (1990).

- 455 39. W. N. Schofield, Predicting basal metabolic rate, new standards and review of previous
456 work. *Hum Nutr Clin Nutr* **39 Suppl 1**, 5-41 (1985).
- 457 40. D. A. Schoeller, E. van Santen, Measurement of energy-expenditure in humans by doubly
458 labeled water method. *J. Appl. Physiol.* **53**, 955-959 (1982).
- 459 41. C. R. Fjeld, K. H. Brown, D. A. Schoeller, Validation of the deuterium oxide method for
460 measuring average daily milk intake in infants. *Am J Clin Nutr* **48**, 671-679 (1988).
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- 462

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475 were freely available via the IAEA DLW Database, which can be found at [https://doubly-labelled-](https://doubly-labelled-water-database.iaea.org/home)
476 [water-database.iaea.org/home](https://doubly-labelled-water-database.iaea.org/home) and www.dlwdatabase.org.

477

478 **Figure legends**

479

480 **Fig. 1. (A)** Conceptual diagram showing sources of water influx and efflux on human body. *
481 Metabolic water produced inside a living organism as an end product of the oxidation of energy-
482 containing substances in their food. **(B)** Hydrogen isotope dilution and elimination provides an
483 objective measure of total body water (TBW) and water turnover (WT). DLW; doubly labeled
484 water.

485

486 **Fig. 2.** Relationships between age and total body water (TBW) or water turnover (WT) in 3729
487 females (orange) and 1875 males (blue) aged 0 to 96 years with mean and SD. **(A)** displays WT
488 (L/d), **(B)** TBW (kg), **(C)** WT per TBW (%), **(D)** TBW per body weight (%), **(E)** WT per total energy
489 expenditure (TEE) (L/MJ), or **(F)** TEE (MJ/d). Water turnover increases with age until about 30 years
490 and is higher in men (4.3 L/d) than women (3.4 L/d). Water turnover significantly decreases after
491 30 years in men and 55 years in women, reaching an average water turnover of 3.1 and 2.8 L/d in
492 men and women aged over 70 years, respectively. The average water turnover rate as a percent of
493 total body water is a maximum of ~25% in neonates, decreases with development, and is ~15% in
494 5-year-old children. At puberty, water turnover falls to ~10% and remains constant until age 40
495 years in men and 65 years in women, after which it decreases. The average water turnover per TEE
496 is about 0.33 L/MJ (~1.4 ml/kcal) in adults. Note that the variation in water turnover is incredibly
497 large – the low end for men and women is ~1-1.5 L/day while the upper end is around ~6 L/day –
498 and the outliers lie in the 10L/d range. On average, water accounts for 60% of the body weight in
499 infants, 50% in older adults, and only 42% in women at 60 years of age, reflecting a larger % body
500 fat.

501

502 **Fig. 3.** Relationships between water turnover (WT) against (A) fat-free mass (FFM), (B) percent
503 body fat, (C) total energy expenditure (TEE), (D) physical activity level (PAL), (E) air temperature,
504 and (F) effective latitude in 1657 females (upper panels; red) and 1013 males (lower panels; blue)
505 aged 20 to 60 years. The blue line represents generalized additive models with integrated
506 smoothness (GAM). Pearson correlation analysis shows positive correlations between water
507 turnover and fat-free mass ($r = 0.442$, $P < 0.001$), TEE ($r = 0.488$, $P < 0.001$), PAL ($r = 0.388$, $P <$
508 0.001), and altitude ($r = 0.100$, $P < 0.001$). Water turnover was negatively correlated with percent
509 body fat (-0.311 , $P < 0.001$). Outdoor air temperature was only weakly correlated with water
510 turnover in the whole sample ($r = 0.160$, $P < 0.001$). A significant curvilinear relationship between
511 water turnover and the air temperature and a significant curvilinear relationship between water
512 turnover and effective latitude was observed (see text for details). Average water turnover
513 reached the highest values at around 0° and the lowest at around -50° or $+50^\circ$ of effective latitude.
514 People who lived near the Arctic Circle had higher average water turnover than those who lived
515 around -50° or $+50^\circ$ of effective latitude.

516

517 **Fig. 4. (A)** Repeated measures of 72 people (31 females and 41 males) shows water turnover (WT)
518 was significantly higher in the summer (3.7 ± 1.0 L/d) with an average temperature of 29°C than in
519 the spring (3.0 ± 0.7 L/d) with 18°C ($P < 0.001$). **(B)** In contrast, total energy expenditure (TEE) was
520 not significantly different between summer and spring ($P = 0.233$). **(C)** Repeated measures of 63
521 pregnant women show that total water turnover was significantly higher during late pregnancy
522 and lactation (data from Butte *et al.* 2005). (Pre = Before pregnancy; Post = 27 weeks postpartum).

523

524 **Fig. 5. (A)** Athletes had higher water turnover (WT) than non-athletes, even after adjusting for
525 physiological and environmental variables ($P < 0.001$). **(B)** Hunter-gatherers (HG), mixed farmer
526 and hunter-gatherer (HGF), and subsistence agriculturalists (SA) had higher water turnover than
527 other people (C), even after adjusting for physiological and environmental variables ($P < 0.001$).
528 Note that there are no males in the database who fell into the SA category. **(C)** People who lived in
529 countries with a low Human Development Index (HDI) had higher WT than people who lived in
530 countries with high or middle HDI, even after adjusting for physiological and environmental
531 variables ($P < 0.001$). **(D-F)** Relationship between water turnover and outdoor air temperature,
532 physical activity level (PAL), or fat-free mass. The countries were categorized as high (red), middle
533 (green), and low (blue) HDI. **(D)** A significant interaction ($P < 0.001$) was observed between
534 outdoor air temperature and HDI in water turnover. The association between outdoor air
535 temperature and water turnover is weak in high HDI countries ($r = 0.086$, $P < 0.001$) but strong in
536 men in low HDI countries ($r = 0.604$, $P < 0.001$). **(E, F)** A significant interaction ($P < 0.001$) was
537 observed between HDI and PAL or FFM in water turnover. Correlation coefficients were
538 significantly higher ($P < 0.001$) in low HDI countries ($r = 0.484$ to 0.670 , $P < 0.001$) than in high HDI
539 countries ($r = 0.367$ to 0.510 , $P < 0.001$).

540

541 **Fig. 6.** Determinants of human water turnover. Objective measures of water turnover from a large
542 global dataset indicate that water turnover is strongly related to anthropometric, lifestyle, and
543 environmental factors. PAL = Physical activity level (Total energy expenditure/Basal energy
544 expenditure), HDI = Human development index.

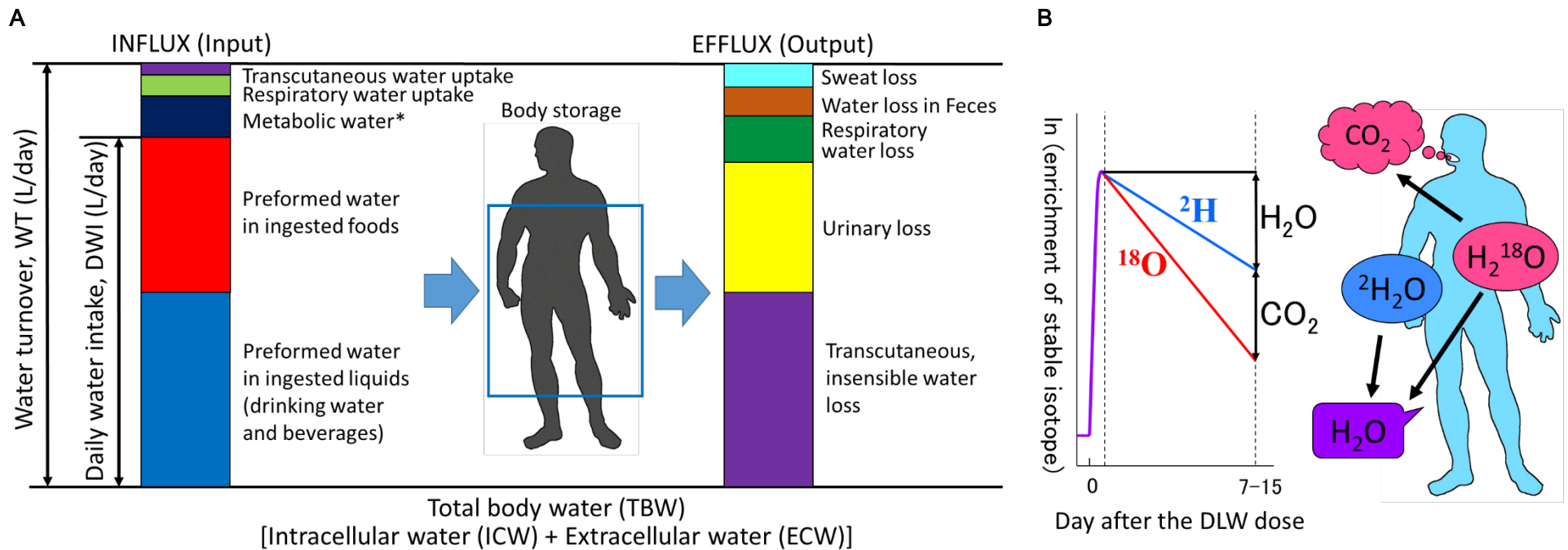


Fig. 1. (A) Conceptual diagram showing sources of water influx and efflux on human body. * Metabolic water produced inside a living organism as an end product of the oxidation of energy-containing substances in their food. **(B)** Hydrogen isotope dilution and elimination provides an objective measure of total body water (TBW) and water turnover (WT). DLW; doubly labeled water.

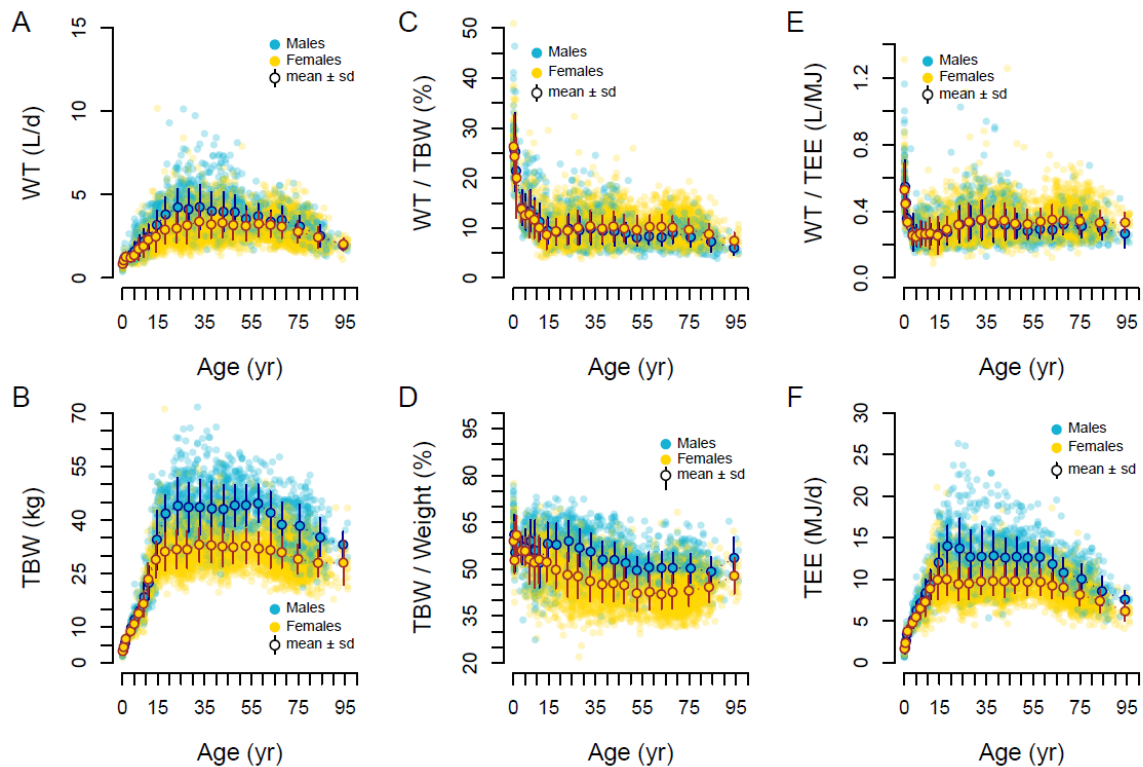


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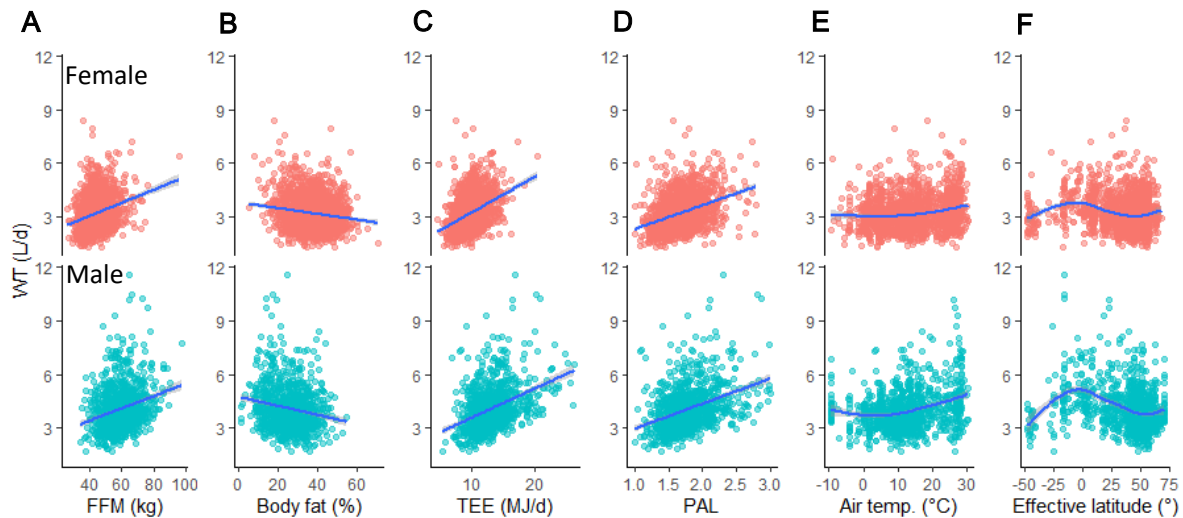


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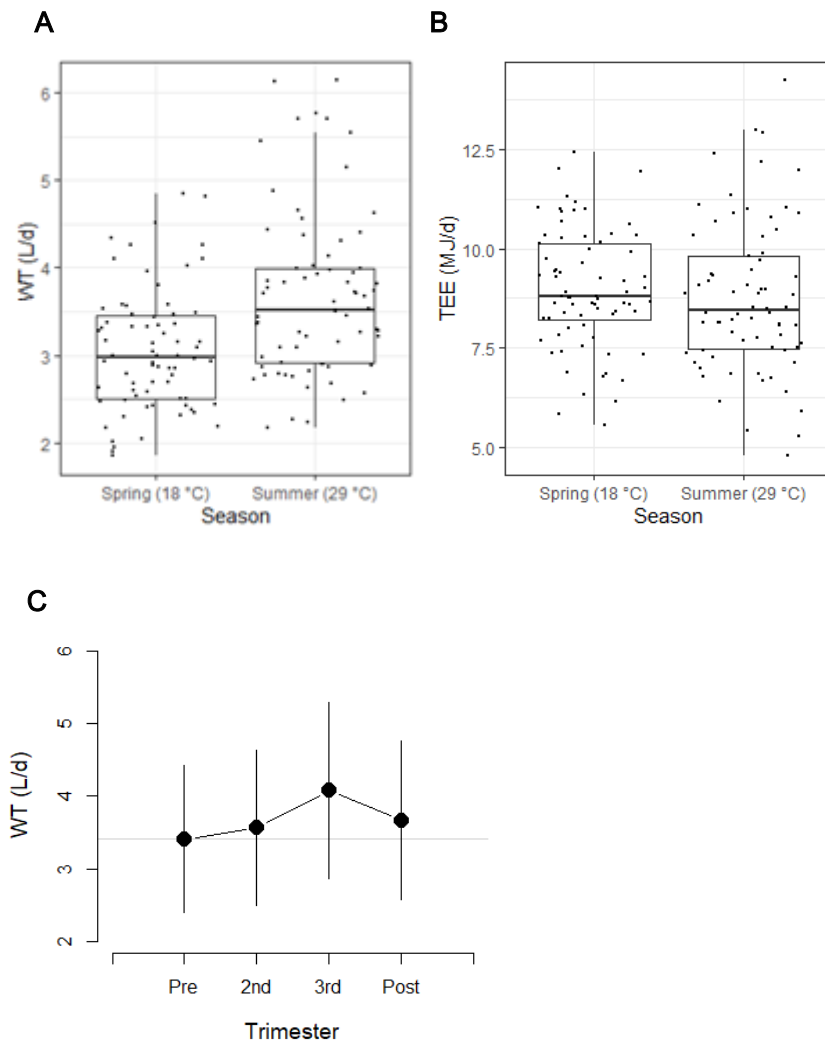


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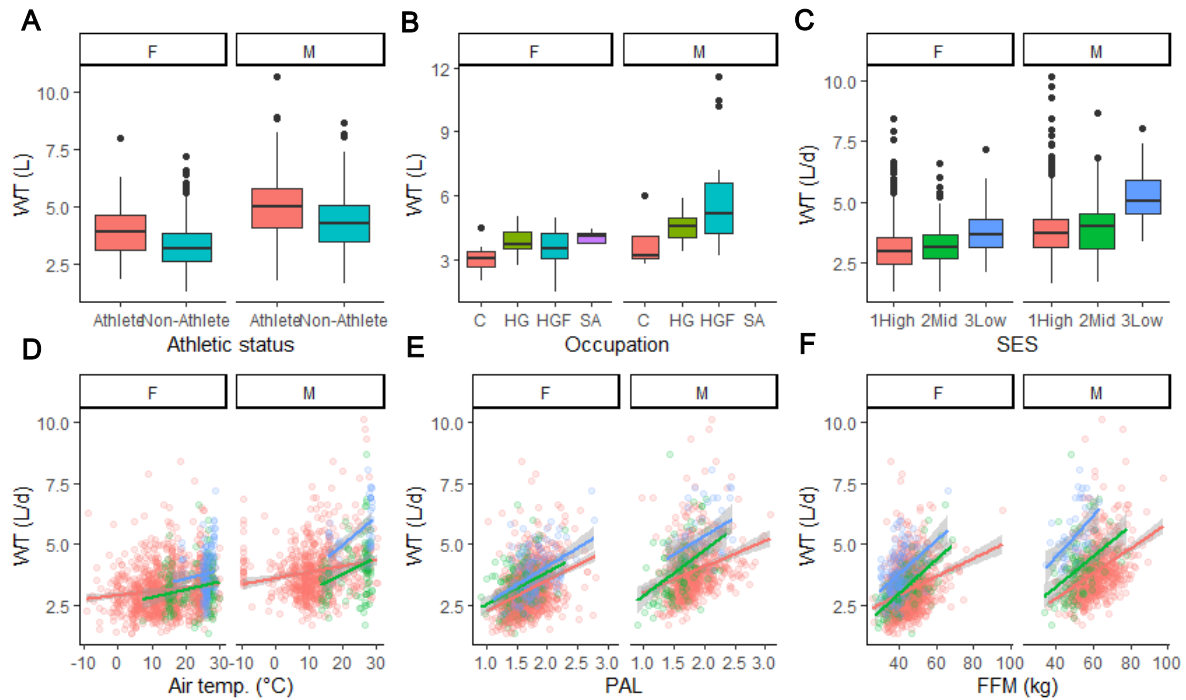


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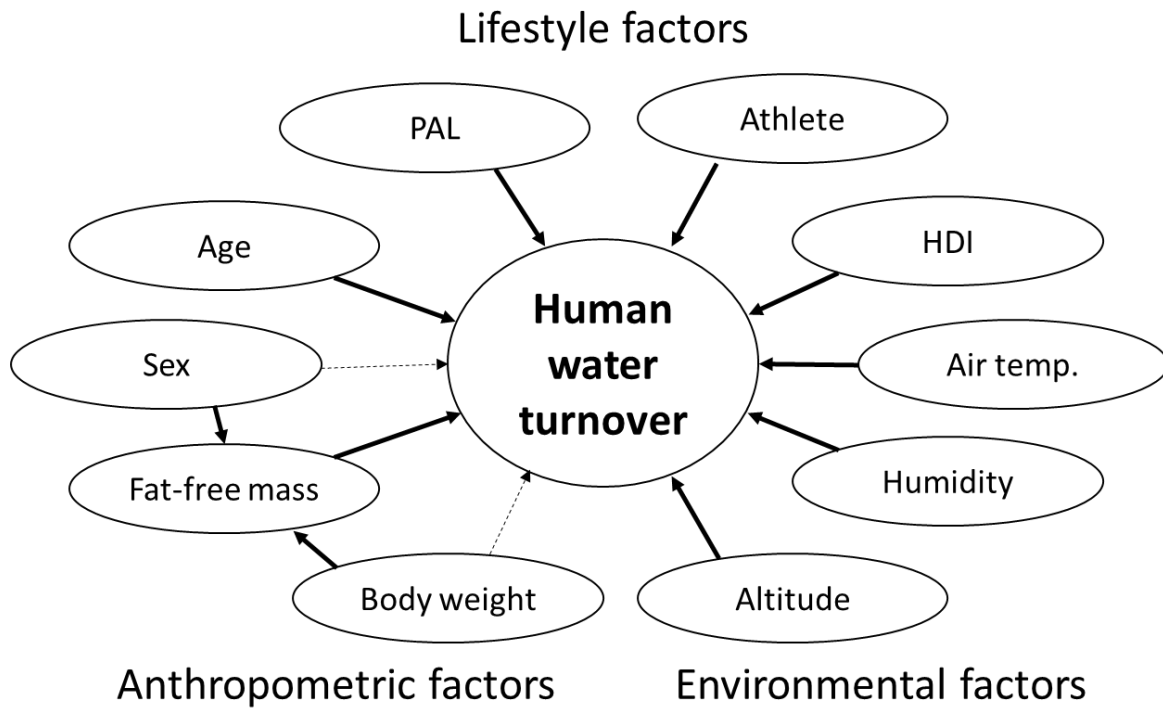


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Supplementary Materials for

Variation in human water intake associated with environmental and lifestyle factors

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The PDF file includes:

Materials and Methods

Fig. S1

Tables S1 to S9

IAEA DLW Database Consortium Collaborators List

References

Other Supplementary Material for this manuscript includes the following:

MDAR Reproducibility Checklist

Materials and Methods

Participants

This analysis was conducted using the International Atomic Energy Agency International Doubly Labeled Water database (IAEA DLW database). The details of the database have been described elsewhere (31), and the information is available on the IAEA website (32). We used the database version 3.5.3, which had a total of 7049 measurements, of which we analyzed a total of 5604 subjects (3729 females and 1875 males). These subjects had no missing information on age, sex, height, weight, dilution spaces, and elimination rates of ^{18}O and ^2H , total energy expenditure (TEE), water turnover (WT), fat-free mass (FFM), fat mass (FM), measurement data, latitude, longitude, and climate data.

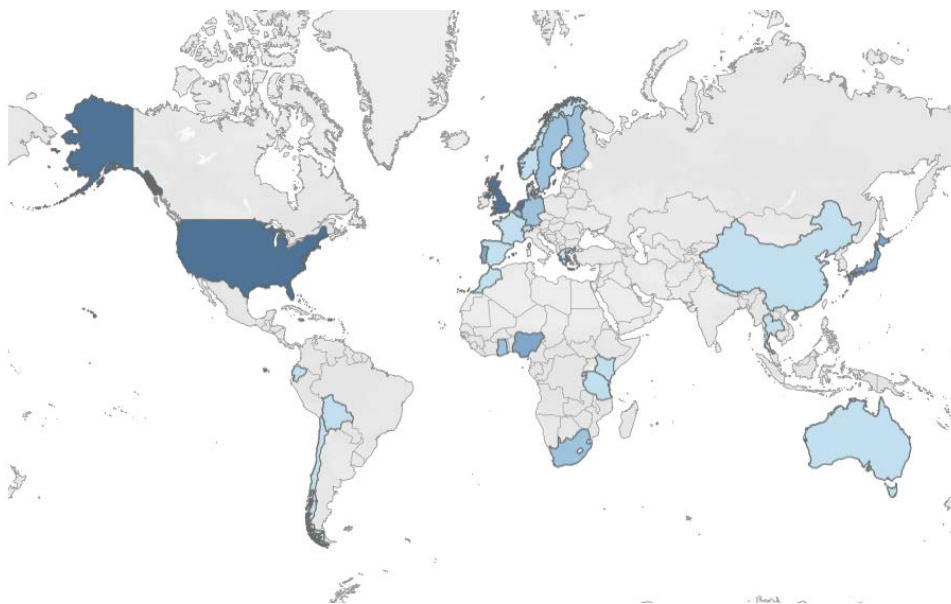


Fig. S1. Measurement locations of the IAEA DLW Database. Darker shading indicates a larger sample size from that country. Data were divided by country on the basis of the world bank coding classification.

Water turnover, body composition, and energy expenditure

Water turnover, energy expenditure, and body composition were measured using the DLW method (33). Details of the methods have been described in previous papers (13, 34). Briefly, each participant was given a drink that containing a weighed premixed dose of $^2\text{H}_2\text{O}$ and H_2^{18}O (DLW) based on body size. Predose and postdose samples of urine, blood or saliva were collected and analyzed mostly by isotope-ratio mass spectrometry, with some samples analysed by laser spectroscopy. There is no significant effect of the analysis method on the estimated isotope enrichments (35-37). The dilution spaces of ^2H and ^{18}O (N_D and N_O , respectively) and the elimination rates of ^2H and ^{18}O (k_D and k_O , respectively) were obtained. Total body water was calculated from the average of the two dilution spaces, $N_D/1.043$ and $N_O/1.007$, which corrects for isotopic sequestration in non-aqueous tissues (3, 41-43). FFM was calculated by assuming a hydration coefficient of 73.2% in adults. Age-specific hydration coefficients were applied to children. The carbon dioxide production rate ($r\text{CO}_2$) was calculated using a common equation across all studies, specifically equation 1 from Speakman *et al.* (2021) (13). TEE was calculated using Wier's equation (equation 5 in reference 13, Speakman *et al.* 2021), using respiratory quotients for each specific study.

For $n = 1439$ subjects we also had measures of basal energy expenditure (BEE: $n = 181$ females and $n = 621$ males). Because only ~30% of subjects had measured BEE, the predicted BEE was used in this study with the Mifflin *et al.* equation for adults aged 18 years and older (38) and Schofield equation for those under 18 years old (39). The physical activity level (PAL) was calculated as TEE divided by BEE

The rate of daily water turnover ($r\text{H}_2\text{O}$, L/d) was calculated using the following equation(40):

$$r\text{H}_2\text{O} = k_D N_D \quad [1]$$

When body water is maintained constant, $r\text{H}_2\text{O}$ is equal to the total water efflux and total water influx (41).

Ambient temperature and other weather related variables

Weather related data were extracted differently for locations within and outside the USA. For measurements inside the USA, we used the National Centers for Environmental Information (NCEI)'s FTP site (<ftp://ftp.ncdc.noaa.gov/pub/data/daily-grids/>). This dataset contains averages of daily maximum, minimum, and average temperature (TMAX, TMIN, and TAVG) and precipitation (PRCP) for the contiguous USA between January 1, 1951, and the present (46). These data cover gridded fields that cover the land area between 24°N and 49°N and between 67°W and 125°W. The grids are approximately 4 km square. These data are compiled into averages for US counties. For each DLW measurement we used the known geographical location to identify the county where the person was measured and then extracted the daily averages for the duration of the measurement, which was also provided from the IAEA DLW database. We then generated an average maximum, minimum and mean temperature and precipitation exposure for each individual measurement.

For data outside the USA we matched the individual estimates for each study participant, based on reported dates and locations for each measurement in the database, to the local average ambient temperature (TAVG), relative humidity (RH), precipitation (PRCP) and windspeed (WDSP) extracted from the National Oceanic and Atmospheric Administration's (NOAA) National Centers for Environmental Information (NCEI) online data repository and NOAA's Global Surface Summary of the Day (GSOD; <https://www.ncei.noaa.gov/metadata/geoportal/rest/metadata/item/gov.noaa.ncdc:C00516/html>) records using the R package GSODR. The GSOD is derived from The Integrated Surface Hourly (ISH) dataset available from National Centers for Environmental Information. This database contains global averages of daily weather elements between 1929 and the present calculated on an hourly basis. For each participant, daily weather data were extracted from the database from the nearest weather station within a 50km

radius of the study coordinates for the days of each DLW measurement and then averaged across those days.

Statistical analyses

We used the base package in R version 4.0.2 (R Core Team 2020-06-22) with RStudio version 1.2.5019 (2019-10-24) for all analyses. The mean and standard deviation (SD) were calculated for descriptive statistics. General linear models were implemented using the `lm` function for multiple regression analysis with WT as the dependent variable. Pearson correlation coefficients were calculated between log-transformed WT and log-transformed FFM, percent body fat, log-transformed TEE, PAL, or air temperature. Scatter plots were generated using the `ggplot` function with generalized additive models with integrated smoothness.

Table S1-1. Distribution of Observations by Economy & Country

Low HDI*		259
Ghana	GHA	59
Kenya	KEN	35
Nigeria	NGA	116
Tanzania	TZA	49
Middle HDI		368
China	CHN	16
Ecuador	ECU	44
Jamaica	JAM	72
Morocco	MAR	22
Mauritius	MUS	51
Seychelles	SYC	72
South Africa	ZAF	91
High HDI		4977
Belgium	BEL	50
Denmark	DNK	27
Finland	FIN	48
France	FRA	6
Germany	DEU	79
Great Britain	GBR	163
Japan	JPN	159
Netherlands	NLD	415
Norway	NOR	26
Spain	ESP	31
Sweden	SWE	97
United States	USA	3876
Total		5604

*HDI, human development index.

Table S1-2. Distribution of Observations by Country in Adults Aged 60 Years and Older

Tanzania	TZA	8
Germany	DEU	10
Japan	JPN	159
Netherlands	NLD	50
Norway	NOR	2
Sweden	SWE	49
United States	USA	1579
Total		1857

Table S1-3. Distribution of Observations by Country in People Aged <18 Years

Kenya	KEN	27
Nigeria	NGA	6
Ecuador	ECU	44
Morocco	MAR	22
Mauritius	MUS	51
Belgium	BEL	31
Denmark	DNK	27
Great Britain	GBR	111
Netherlands	NLD	95
Spain	ESP	31
Sweden	SWE	30
United States	USA	651
Total		1126

Male		Age (y)		Height (cm)		Weight (kg)		BMI		Fat (%)		FFM (kg)		TEE (MJ/d)		TBW (kg)		TBW (%)		WT (L/d)		WT/TEE (mL/kcal)	
Age group	N	mean	sd	mean	Sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
(0,0.5]	78	0.2	0.1	59.6	5.9	6.0	1.7	16.3	2.2	23.9	7.8	4.4	1.1	1.8	0.6	3.6	0.8	61.1	6.4	0.9	0.2	2.29	0.67
(0.5,1]	15	0.7	0.2	69.7	3.8	8.4	0.8	17.4	1.0	30.4	7.5	5.9	0.9	2.6	0.8	4.7	0.7	55.3	5.9	1.2	0.4	1.89	0.43
(1,2]	6	1.0	0.0	75.7	2.5	9.8	0.7	17.1	0.9	26.7	6.3	7.2	0.6	3.5	0.8	5.7	0.5	58.0	4.9	1.2	0.2	1.49	0.21
(2,4]	25	3.6	0.3	102.3	7.2	17.7	3.4	16.9	3.1	27.5	5.8	12.7	1.9	5.1	1.0	9.8	1.4	56.1	4.5	1.4	0.4	1.15	0.47
(4,6]	91	5.1	0.7	112.9	7.8	21.6	5.7	16.8	2.8	25.5	7.3	15.8	2.8	6.3	1.1	12.1	2.2	57.2	5.6	1.6	0.6	1.07	0.27
(6,8]	30	7.2	0.6	124.9	8.4	25.4	6.0	16.2	2.6	22.5	8.9	19.3	2.7	7.2	1.1	14.7	2.0	59.0	6.8	2.0	0.6	1.13	0.29
(8,10]	67	9.1	0.5	136.4	9.6	34.6	13.1	18.1	4.6	26.0	12.8	24.3	5.7	8.4	1.6	18.4	4.3	56.0	9.7	2.2	0.7	1.09	0.28
(10,12]	29	11.0	0.5	143.7	9.6	44.5	13.2	21.2	4.4	30.9	10.5	29.8	6.3	9.4	1.8	22.4	4.7	52.0	7.9	2.5	0.7	1.10	0.26
(12,16]	119	14.5	1.2	168.7	12.0	60.6	17.8	21.0	5.2	22.2	9.1	46.2	11.0	12.0	2.3	34.5	8.2	58.1	6.8	3.2	0.9	1.11	0.27
(16,20]	93	18.3	1.1	178.2	7.1	73.7	15.1	23.1	4.2	21.7	9.2	56.7	7.2	14.0	2.5	41.8	5.2	57.8	6.8	3.8	1.1	1.15	0.33
(20,25]	100	23.5	1.4	177.7	9.5	76.0	19.3	23.9	5.0	19.5	8.9	60.1	10.8	13.7	3.6	44.0	7.9	59.0	6.5	4.2	1.1	1.35	0.46
(25,30]	145	28.0	1.4	177.2	8.8	77.7	15.6	24.6	4.0	22.4	8.1	59.5	9.4	12.7	3.2	43.6	6.9	56.9	5.9	4.1	1.2	1.40	0.41
(30,35]	103	32.8	1.4	176.8	8.0	79.7	19.5	25.4	5.3	24.1	8.1	59.5	10.6	12.7	3.6	43.6	7.7	55.6	5.9	4.3	1.3	1.45	0.50
(35,40]	135	38.0	1.5	177.0	7.7	83.0	19.8	26.4	5.5	27.6	8.1	59.0	10.4	12.8	2.9	43.2	7.6	53.0	6.0	4.0	1.1	1.35	0.46
(40,45]	155	42.9	1.4	176.4	7.7	82.5	16.1	26.4	4.3	27.7	7.8	58.8	9.1	12.6	2.3	43.1	6.6	52.9	5.7	4.0	1.2	1.33	0.38
(45,50]	129	47.8	1.5	176.8	7.1	85.8	15.1	27.4	4.3	29.1	6.2	60.2	7.8	12.7	2.3	44.1	5.7	51.9	4.6	3.9	1.0	1.31	0.31
(50,55]	87	52.5	1.5	177.3	6.5	89.9	15.7	28.6	4.8	32.3	6.0	60.3	7.9	12.6	1.9	44.2	5.7	49.6	4.4	3.5	0.8	1.18	0.21
(55,60]	64	57.7	1.4	177.4	7.5	89.1	14.0	28.2	3.8	30.9	6.6	61.0	7.2	12.7	2.0	44.6	5.3	50.6	4.8	3.7	0.7	1.23	0.22
(60,65]	70	63.1	1.6	174.8	7.8	84.8	17.4	27.6	4.6	31.2	7.2	57.4	8.1	11.9	2.0	42.0	5.9	50.4	5.3	3.4	0.7	1.21	0.24
(65,70]	71	67.8	1.2	171.4	6.9	78.1	17.3	26.4	4.8	31.2	6.7	52.9	8.4	10.8	1.8	38.7	6.2	50.4	4.9	3.5	0.8	1.35	0.26
(70,80]	194	75.5	3.0	171.0	8.3	77.3	15.8	26.3	4.5	31.4	6.5	52.4	8.3	10.1	1.8	38.4	6.1	50.3	4.7	3.1	0.6	1.30	0.28
(80,90]	61	84.2	2.5	168.1	7.4	72.3	13.9	25.5	4.4	32.8	6.3	48.0	7.3	8.6	1.7	35.2	5.3	49.2	4.6	2.5	0.7	1.23	0.27
(90,100]	8	94.0	1.9	168.8	3.0	62.6	9.5	22.0	3.4	26.8	8.9	45.2	4.9	7.6	1.0	33.1	3.6	53.6	6.5	2.0	0.3	1.12	0.36
Female	N	mean	sd	mean	Sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
(0,0.5]	78	0.2	0.1	59.2	5.3	5.7	1.4	15.9	1.7	26.4	7.6	4.1	0.9	1.7	0.5	3.3	0.7	59.0	6.2	0.8	0.2	2.21	0.67
(0.5,1]	12	0.6	0.2	67.5	4.3	8.4	1.6	18.4	1.9	33.6	5.2	5.6	0.9	2.4	0.3	4.4	0.7	52.8	4.1	1.1	0.2	1.86	0.33
(1,2]	6	1.5	0.5	80.7	5.8	11.0	1.9	16.7	0.6	22.6	8.0	8.5	1.9	3.8	0.7	6.7	1.4	60.9	6.2	1.3	0.3	1.40	0.16
(2,4]	29	3.6	0.3	101.0	5.7	16.0	3.1	15.6	1.7	27.7	4.8	11.5	1.7	4.8	0.6	8.9	1.3	55.9	3.7	1.2	0.2	1.07	0.23
(4,6]	73	5.1	0.6	111.2	6.8	19.7	3.3	15.8	1.7	27.3	5.8	14.2	2.2	5.5	0.8	10.9	1.6	55.8	4.4	1.4	0.4	1.04	0.21
(6,8]	36	7.0	0.6	121.7	9.2	26.8	7.8	17.8	3.8	30.2	10.1	18.1	3.5	6.5	1.2	13.8	2.7	53.2	7.7	1.7	0.6	1.11	0.32
(8,10]	72	9.1	0.5	133.5	9.3	33.0	11.2	18.2	4.5	31.1	10.8	21.9	4.7	7.3	1.7	16.6	3.6	52.1	8.2	1.9	0.7	1.10	0.30
(10,12]	69	11.1	0.6	148.5	8.0	45.1	11.6	20.3	4.1	29.5	10.2	31.1	6.2	8.9	1.9	23.4	4.6	53.1	7.7	2.3	0.6	1.12	0.39
(12,16]	218	14.4	1.2	160.8	7.9	56.5	14.0	21.7	4.6	30.1	8.2	38.7	6.9	10.0	2.3	28.9	5.1	52.3	6.2	2.5	0.9	1.07	0.47
(16,20]	195	18.3	1.0	164.2	7.1	63.9	15.2	23.6	5.3	32.6	8.2	42.2	7.0	10.0	1.9	31.2	5.2	49.8	6.0	2.9	0.8	1.22	0.31
(20,25]	220	23.3	1.4	164.7	7.4	68.1	18.6	25.1	6.6	34.2	9.5	43.4	7.2	9.5	1.9	31.8	5.3	48.2	6.9	3.0	0.9	1.34	0.36
(25,30]	252	27.7	1.5	164.0	6.9	68.4	17.0	25.4	6.0	34.9	9.5	43.3	7.0	9.5	1.9	31.7	5.1	47.7	7.0	3.2	1.1	1.41	0.47
(30,35]	206	32.9	1.3	164.6	6.2	73.5	17.5	27.1	6.2	36.9	8.8	45.2	6.5	9.8	1.6	33.1	4.8	46.2	6.5	3.4	1.0	1.47	0.45
(35,40]	213	38.0	1.5	164.0	6.6	74.7	17.7	27.8	6.6	38.4	7.7	45.0	6.6	9.8	1.7	32.9	4.8	45.1	5.6	3.2	0.8	1.39	0.35
(40,45]	275	42.8	1.4	163.7	7.2	73.4	18.7	27.3	6.3	37.9	8.0	44.5	7.6	9.8	1.9	32.6	5.6	45.5	5.8	3.3	0.9	1.44	0.43
(45,50]	159	47.4	1.5	164.5	6.1	73.8	17.0	27.3	6.2	38.7	7.9	44.2	6.2	9.8	1.5	32.4	4.5	44.9	5.8	3.2	0.9	1.37	0.38
(50,55]	102	52.8	1.5	163.4	5.9	79.6	19.5	29.8	7.0	42.2	7.8	44.7	6.6	9.7	1.6	32.7	4.8	42.3	5.7	3.1	0.9	1.35	0.37
(55,60]	99	58.3	1.5	164.0	6.0	76.7	17.0	28.4	5.7	41.7	7.5	43.7	6.1	9.7	1.5	32.0	4.5	42.7	5.5	3.3	0.7	1.42	0.32
(60,65]	239	63.3	1.5	161.5	7.2	76.9	18.4	29.5	6.9	42.7	6.6	43.1	6.8	9.3	1.6	31.6	5.0	42.0	4.8	3.2	0.7	1.47	0.37
(65,70]	361	68.1	1.5	161.3	6.8	74.0	15.8	28.4	5.7	41.8	7.3	42.3	5.9	9.0	1.3	31.0	4.4	42.7	5.3	3.1	0.7	1.44	0.31
(70,80]	653	75.0	2.8	159.4	6.8	68.7	14.4	27.0	5.2	41.1	6.7	39.7	5.6	8.2	1.3	29.1	4.1	43.1	4.9	2.8	0.7	1.43	0.34
(80,90]	140	83.6	2.4	157.4	7.3	64.1	12.4	25.9	4.7	39.5	6.5	38.2	5.2	7.4	1.4	28.0	3.8	44.3	4.8	2.4	0.6	1.39	0.31
(90,100]	22	94.4	1.8	158.0	9.1	59.0	12.8	23.5	4.1	34.6	7.9	38.3	8.5	6.2	1.2	28.0	6.2	47.9	5.8	2.0	0.4	1.39	0.26

Table S2. Key characteristics by age-sex group (mean and SD). BMI, body mass index; Fat, percent body fat; FFM, fat-free mass; TEE, total energy expenditure; TBW, total body water; WT, water turnover.

Table S3. Multiple regression analysis to predict water turnover in adults aged 18 years and older.

	β	std. err.	t-value	p	
(Intercept)	-0.059	0.036	-1.635	0.102	
Age (yr)	-0.203	0.051	-3.982	0.00007	***
Height (cm)	0.003	0.047	0.064	0.949	
FFM (kg)	0.454	0.076	5.947	0.00000	***
% body fat (%)	0.050	0.049	1.020	0.308	
Sex (F=0, M=1)	0.075	0.045	1.691	0.091	
TEE (MJ/d)	-0.094	0.128	-0.734	0.463	
PAL	0.309	0.083	3.725	0.0002	***
Air temp. (°C)	0.240	0.035	6.887	0.00000	***
Relative humidity (%)	0.093	0.030	3.137	0.0018	**
Wind speed (m/s)	-0.027	0.025	-1.067	0.286	
precipitation (mm)	0.018	0.027	0.655	0.513	
HDI (H=0, M=1, L=2)	0.158	0.028	5.678	0.00000	***
Effective latitude (°)	0.038	0.024	1.544	0.123	
Altitude (m)	0.062	0.025	2.448	0.0145	*
	SEE	R2	adj R2	P	
	0.7944	0.456	0.4496	< 2.2e-16	

FFM, fat-free mass; TEE, total energy expenditure; PAL, physical activity level; HDI, Human Development Index. * P<0.05, ** P<0.01, *** P<0.001

Table S4. Multiple regression analysis including first and second-order terms to predict water turnover (WT) in adults aged 18 years and older.

	β	std. err.	t-value	p	
(Intercept)	0.032	0.032	0.987	0.32389	
PAL	0.237	0.019	12.307	0.00000	***
FFM (kg)	0.386	0.031	12.348	0.00000	***
Sex (F=0, M=1)	0.018	0.026	0.701	0.48348	
Air temp. (°C)	-0.192	0.063	-3.048	0.00236	**
Air temp. * Air temp	0.479	0.065	7.339	0.00000	***
Relative humidity (%)	0.067	0.028	2.399	0.01660	*
Athlete (No=0, Athlete=1)	0.041	0.012	3.357	0.00081	***
HDI (H=0, M=1, L=2)	0.052	0.025	2.051	0.04044	*
Altitude (m)	0.133	0.025	5.443	0.00000	***
Age (year)	0.611	0.123	4.986	0.00000	***
Age * Age	-0.800	0.125	-6.401	0.00000	***
	SEE	R2	adj R2	P	
	0.7618	0.486	0.484	< 2.2e-16	

The positive coefficient of Air temp.² indicated an U-shaped relationship between water turnover and air temp.. The negative coefficient of Age² indicated an inverse U-shaped relationship between water turnover and age. Eleven subjects who engaged in the DLW experiment at an altitude over 3000 m were excluded from the analysis (7490 m [n = 3], 5390 m [n = 6], and 3263 m [n = 2]).

Table S5. Participant characteristics by Athletic status & Sex (mean \pm SD; [range])*

	Male		Female	
	Athlete (n = 95)	Non-athlete (n = 720)	Athlete (n = 19)	Non-athlete (n = 1100)
Age (y)	23.5 \pm 5 [18-45]	38.1 \pm 12.1 [18-59]	24.8 \pm 5.6 [18-36]	35.5 \pm 12.1 [18-59]
Height (cm)	183.2 \pm 10 [155-204.7]	178.6 \pm 7.1 [153-204]	173.1 \pm 11.4 [162.4-195]	164.7 \pm 6.5 [142.1-186]
Weight (kg)	78.2 \pm 12.3 [51.8-108.9]	85.9 \pm 18.8 [49.9-189.9]	66.5 \pm 11.4 [52.2-84.3]	79.5 \pm 23.6 [38.3-192.4]
BMI (kg/m ²)	23.2 \pm 2.3 [18.9-29.9]	26.9 \pm 5.7 [15.7-61.4]	22.0 \pm 1.7 [19.6-25.0]	29.3 \pm 8.5 [12.5-71.9]
Fat (%)	17.4 \pm 5.4 [3.2-40.4]	27.3 \pm 9.1 [3.4-56.2]	28.9 \pm 8 [9.8-40.0]	38.5 \pm 9.3 [6.9-70.1]
FFM (kg)	64.7 \pm 11.2 [38.3-96.9]	61.3 \pm 8.8 [36.3-97.8]	46.7 \pm 5.6 [35.7-56.2]	47.2 \pm 9.0 [26.3-89.8]
TEE (MJ/d)	17.3 \pm 3.3 [7.7-26.3]	13.6 \pm 2.8 [6.7-26.1]	12.8 \pm 1.9 [10.2-17.1]	10.2 \pm 1.9 [4.7-19.9]
WT (L/d)	5.1 \pm 1.6 [1.8-10.6]	3.9 \pm 1.1 [1.7-10.1]	4.1 \pm 1.5 [1.8-8.0]	3.2 \pm 0.9 [1.3-8.6]
WT/Weight (L/kg/d)	66.2 \pm 21.1 [26.9-141.0]	47.1 \pm 14.6 [17.9-139.2]	61.7 \pm 19.8 [29.6-100.9]	43.0 \pm 16.8 [10.5-194.8]

*BMI, body mass index; FFM, fat-free mass; TEE, total energy expenditure; WT, water turnover.

Table S6. Participant characteristics by Occupation & Sex (mean ± SD; [range])*

	Male			Female			
	C (n = 589)	HG (n = 21)	HGF (n = 19)	C (n = 809)	HG (n = 19)	HGF (n = 22)	SA (n = 7)
Age (y)	38.4 ± 12.3 [18-59]	32.2 ± 12.3 [18-58]	41.1 ± 10.7 [18-54]	37.3 ± 11.7 [18-59]	32.8 ± 12.1 [18-59]	40 ± 12.8 [18-57]	30 ± 6.4 [21-38]
Height (cm)	178.5 ± 7.3 [153.0-204.0]	159.6 ± 7.2 [144.5-171.1]	165 ± 5.6 [155.2-178.1]	164.3 ± 6.8 [142.1-186]	149.7 ± 8 [137.4-164.5]	150.2 ± 5 [141.5-160.6]	161.1 ± 7.8 [152-177.5]
Weight (kg)	85.5 ± 18.7 [49.9-189.9]	51.5 ± 4.8 [42.8-58.2]	69.1 ± 9.6 [53.8-84.9]	80.8 ± 24.6 [38.3-192.4]	45.5 ± 6.4 [34-55]	54.9 ± 7.7 [42.8-66.5]	59.6 ± 5.5 [51.3-65.4]
BMI (kg/m ²)	26.8 ± 5.6 [15.7-61.4]	20.2 ± 1.7 [18.1-23.8]	25.3 ± 2.7 [20.6-31.1]	29.9 ± 8.9 [12.5-71.9]	20.2 ± 2 [16.7-23.9]	24.3 ± 2.8 [19.9-29]	23.1 ± 2.7 [20-26.2]
Fat (%)	27.7 ± 9.2 [3.4-56.2]	14.0 ± 5.5 [2.2-23.9]	21.5 ± 7.6 [12.4-42.3]	39.0 ± 9.5 [6.9-70.1]	23.1 ± 5 [13.3-31.9]	29.1 ± 6.1 [15.5-40.6]	30.7 ± 5.7 [22.4-38.2]
FFM (kg)	60.6 ± 8.5 [36.3-92.3]	44.2 ± 3.9 [34.8-52.2]	54.2 ± 8.8 [41.1-73.1]	47.5 ± 9.5 [26.3-89.8]	34.8 ± 4.1 [29.5-43.6]	38.8 ± 4.8 [26.2-46]	41.2 ± 4.0 [35.5-45.3]
TEE (MJ/d)	13.8 ± 3.0 [6.7-26.1]	10.5 ± 1.6 [7.5-14.3]	14.1 ± 3.3 [8.2-20.8]	10.3 ± 2.0 [4.7-19.9]	8.0 ± 1.5 [6.1-12.0]	9.9 ± 1.3 [7.5-12.7]	13.9 ± 1.9 [10-15.8]
WT (L/d)	3.9 ± 1.1 [1.7-10.1]	4.5 ± 0.6 [3.4-5.9]	6.2 ± 2.3 [3.2-11.6]	3.3 ± 0.9 [1.3-8.6]	3.9 ± 0.6 [2.7-5]	3.6 ± 0.9 [1.5-5]	4.0 ± 0.3 [3.7-4.4]
WT/Weight (L/kg)	47.0 ± 15.0 [17.9-142.2]	89.4 ± 16.7 [64.7-134.9]	88.1 ± 24.7 [47.5-136.2]	43.8 ± 17.4 [10.5-194.8]	85.5 ± 12.2 [64.8-105.3]	66.9 ± 16.8 [27.6-102.2]	68.1 ± 3.6 [62.7-73.9]

*BMI, body mass index; FFM, fat-free mass; TEE, total energy expenditure; WT, water turnover; C, control; HG, hunter-gatherers; HGF, mixed farmer and hunter-gatherer; SA, subsistence agriculturalists.

Table S7. Participant characteristics by Human Development Index (HDI) & Sex (mean ± SD; [range])*

	Male			Female		
	High HDI (n = 813)	Middle HDI (n = 103)	Low HDI (n = 57)	High HDI (n = 1339)	Middle HDI (n = 148)	Low HDI (n = 161)
Age (y)	38.7 ± 11.4 [18-59]	32.8 ± 5.7 [21-44]	32.1 ± 9.7 [18-58]	36.3 ± 11.3 [18-59]	31.9 ± 6.5 [20-45]	32.1 ± 10.2 [18-59]
Height (cm)	178.5 ± 7.0 [153-204]	171.8 ± 6.6 [157-187]	165.8 ± 8.7 [144.5-182.8]	165 ± 6.4 [146-186]	162.3 ± 6.2 [147-183.3]	158.9 ± 7.1 [137.4-176.5]
Weight (kg)	85.1 ± 16.2 [49.9-174.6]	68.4 ± 14.4 [47.6-127]	57.1 ± 8 [41.6-74.7]	73.0 ± 17.4 [38.3-164.5]	76.1 ± 22.8 [36.9-148.2]	57.4 ± 12.3 [34-106.9]
BMI (kg/m ²)	26.7 ± 4.7 [15.7-57.1]	23.1 ± 4.3 [15.5-38.4]	20.7 ± 2.3 [16.7-26.4]	26.8 ± 6.2 [12.5-55.3]	28.8 ± 8.2 [14.5-54.8]	22.7 ± 4.7 [15.4-47.8]
Fat (%)	27.3 ± 8.1 [3.4-54.5]	22.6 ± 7.8 [1.3-44.1]	13.3 ± 5.8 [1.2-28]	37.4 ± 8.4 [8-70.1]	40.4 ± 9.2 [19.7-59.6]	29.4 ± 8.1 [5.5-51.8]
FFM (kg)	61.1 ± 8.6 [36.3-97.8]	52.3 ± 8.4 [33.9-77.9]	49.3 ± 6.3 [34.8-63.3]	44.6 ± 6.8 [26.3-95.7]	43.7 ± 8.5 [27.5-68.3]	39.8 ± 5.5 [29.5-66.4]
TEE (MJ/d)	13.3 ± 2.8 [6.7-34.3]	10.8 ± 2.3 [5.4-18.3]	11.9 ± 2.0 [7.5-15.4]	9.8 ± 1.7 [4.7-20.4]	9.3 ± 2.0 [4.6-15]	9.3 ± 1.6 [6.1-17.4]
WT (L/d)	3.9 ± 1.1 [1.7-10.1]	4.0 ± 1.2 [1.7-8.7]	5.2 ± 1.1 [3.3-8.0]	3.1 ± 0.9 [1.3-8.4]	3.2 ± 0.9 [1.3-6.6]	3.8 ± 0.9 [2.1-7.2]
WT/Weight (L/kg/d)	47.0 ± 13.5 [17.9-139.2]	59.6 ± 16.9 [24.8-142.2]	91.3 ± 17.5 [61-134.9]	44.5 ± 16.2 [14-194.8]	44.2 ± 12.0 [14.5-80.2]	67.0 ± 16.4 [36-114]

*BMI, body mass index; FFM, fat-free mass; TEE, total energy expenditure; WT, water turnover.

The IAEA DLW database group authorship (database version 3.5.3).

This group authorship contains the names of people whose data were contributed into the IAEA DLW database by the analysis laboratory but they later could not be traced, or they did not respond to emails to assent inclusion among the authorship. The list also includes some researchers who did not assent inclusion to the main authorship because they felt their contribution was not sufficient to merit authorship, or their specific data was not used in the present analysis (eg pediatric data)

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