This is the author's version of the work. It is posted here by permission of the AAAS for personal use, not for redistribution. The definitive version was published in *Science* on 24 November 2022, Vol 378, issue 6622, DOI: 10.1126/science.abm866.

Science

Variation in human water turnover associated with environmental and lifestyle factors

Yosuke Yamada[1,2]*†^, Xueying Zhang[3,4]^, Mary E.T. Henderson[5]^, Hiroyuki Sagayama[6]†, Herman Pontzer[7,8]†, Daiki Watenabe[1,2,9], Tsukasa Yoshida[1,2], Misaka Kimura[2], Philip N. Ainslie[10], Lene F. Andersen[11], Liam J. Anderson[12,13], Lenore Arab[14], Issaad Baddou[15], Kweku Bedu-Addo[16], Ellen E. Blaak[17], Stephane Blanc[18,19], Alberto G. Bonomi[20], Carlijn V.C. Bouten[21], Pascal Bovet[22], Maciej S. Buchowski[23], Nancy F. Butte[24], Stefan G. Camps[21,25], Graeme L. Close[12], Jamie A. Cooper[26], Richard Cooper[27], Sai Krupa Das[28], Lara R. Dugas[29,30], Simon Eaton[31], Ulf Ekelund[32,33], Sonja Entringer[34,35], Terrence Forrester[36], Barry W. Fudge[37], Annelies H Goris[21], Michael Gurven[38], Lewis G. Halsey[5], Catherine Hambly[4], Asmaa El Hamdouchi[15], Marjije B. Hoos[21], Sumei Hu[39], Noorjehan Joonas[40], Annemiek M. Joosen[21], Peter Katzmarzyk[41], Kitty P. Kempen[21], William E. Kraus[42], Wantanee Kriengsinyos[43], Robert F. Kushner[44], Estelle V. Lambert[45], William R. Leonard[46], Nader Lessan[47,48], Corby K. Martin[41], Anine C. Medin[11,49], Erwin P. Meijer[21], James C. Morehen[50,12], James P. Morton[12], Marian L. Neuhouser[51], Theresa A. Nicklas[24], Robert M. Ojiambo[52,53], Kirsi H. Pietiläinen[54], Yannis P. Pitsiladis[55], Jacob Plange-Rhule[16]**, Guy Plasqui[56], Ross L. Prentice[51], Roberto A. Rabinovich[57], Susan B. Racette[58], David A. Raichlen[59], Eric Ravussin[41], Leane M. Redman[41], John J. Reilly[60], Rebecca M. Reynolds[61], Susan B. Roberts[28], Albertine J. Schuit[62], Luis B. Sardinha[63], Analiza M. Silva[63], Anders M. Sjödin[64], Eric Stice[65], Samuel S. Urlacher[66,67], Giulio Valenti[21,20], Ludo M. Van Etten[21], Edgar A. Van Mil[68], Jonathan C. K. Wells[69], George Wilson[12], Brian M. Wood[70,71], Jack A. Yanovski[72], Alexia J. Murphy-Alford[73], Cornelia U. Loechl[73], Amy H. Luke[74]†, Jennifer Rood[41]†, Klaas R. Westerterp[75]†, William W. Wong[24]†, Motohito Miyachi[1,9]†, Dale A. Schoeller[76]†, John R. Speakman[3,4,77,78]*† and the IAEA DLW database consortium#.

*co-lead corresponding author
†co-corresponding author
** deceased
^equal contribution
See the supplementary materials.

1. National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition, Tokyo, Japan.
2. Institute for Active Health, Kyoto University of Advanced Science, Kyoto, Japan.

3. Shenzhen Key Laboratory of Metabolic Health, Center for Energy Metabolism and Reproduction, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China
4. Institute of Biological and Environmental Sciences, University of Aberdeen, Aberdeen, UK
5. School of Life and Health Sciences, University of Roehampton, London, UK
6. Faculty of Health and Sport Sciences, University of Tsukuba, Ibaraki, Japan.
7. Department of Evolutionary Anthropology, Duke University, Durham NC, USA
8. Duke Global Health Institute, Duke University, Durham, NC, USA
9. Faculty of Sport Sciences, Waseda University, Saitama, Japan
10. Centre for Heart, Lung and Vascular Health, School of Health and Exercise Sciences, Faculty of Health and Social Development, University of British Columbia Okanagan, Kelowna, BC, Canada
11. Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, 0317 Oslo, Norway.
12. Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK.
13. School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham UK
14. David Geffen School of Medicine, University of California, Los Angeles.
15. Unité Mixte de Recherche en Nutrition et Alimentation, CNESTEN-Université Ibn Tofail URAC39, Regional Designated Center of Nutrition Associated with AFRA/IAEA, Rabat, Morocco
16. Department of Physiology, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.
17. Department of Human Biology, Maastricht University, Maastricht, The Netherlands.
18. Nutritional Sciences, University of Wisconsin, Madison, WI, USA
19. Institut Pluridisciplinaire Hubert Curien. CNRS Université de Strasbourg, UMR7178, France.
20. Phillips Research, Eindoven, The Netherlands.
21. Maastricht University, Maastricht, The Netherlands.
22. University Center for Primary Care and Public Health (Unisanté), Lausanne, Switzerland.
23. Division of Gastroenterology, Hepatology and Nutritiion, Department of Medicine, Vanderbilt University, Nashville, Tennessee, USA
24. Department of Pediatrics, Baylor College of Medicine, USDA/ARS Children's Nutrition Research Center, Houston, Texas, USA.
25. Clinical Nutrition Research Centre (CNRC), Singapore Institute of Food and Biotechnology Innovation (SIFBI), Agency of Science, Technology and Research (A*STAR)
26. Nutritional Sciences, University of Georgia, Athens, GA, USA
27. Department of Public Health Sciences, Parkinson School of Health Sciences and Public Health, Loyola University, Maywood, IL, USA.
28. USDA Human Nutrition Research Center on Aging at Tufts University, Boston Massachusetts USA
29. Public Health Sciences, Loyola University of Chicago, Maywood, USA.
30. Division of Epidemiology and Biostatistics, School of Public Health & Family Medicine, University of Cape Town, Cape Town, South Africa

31. Developmental Biology and Cancer Department, UCL Great Ormond Street Institute of Child Health, London, UK
32. Department of Sport Medicine, Norwegian School of Sport Sciences, Oslo, Norway.
33. Department of Chronic Diseases, Norwegian Institute of Public Health, Oslo, Norway
34. Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Medical Psychology, Berlin, Germany.
35. Department of Pediatrics, University of California Irvine, Irvine, California, USA.
36. Solutions for Developing Countries, University of the West Indies, Mona, Kingston, Jamaica.
37. Department of Biomedical and Life sciences, University of Glasgow, Glasgow, UK.
38. Department of Anthropology, University of California Santa Barbara, Santa Barbara, CA, USA.
39. Beijing technology and Business university, Beijing, China.
40. Central Health Laboratory, Ministry of Health and Wellness, Mauritius.
41. Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA.
42. Department of Medicine, Duke University, Durham, North Carolina, USA.
43. Institute of Nutrition, Mahidol University, Salaya, Phutthamonthon, Nakon-Pathom 73170 Thailand.
44. Feinberg School of Medicine, Northwestern University, Chicago, IL, USA.
45. Health through Physical Activity, Lifestyle and Sport Research Centre (HPALS) Division of Exercise Science and Sports Medicine (ESSM), FIMS International Collaborating Centre of Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town
46. Department of Anthropology, Northwestern University, Evanston, IL, USA.
47. Imperial College London Diabetes Centre, Abu Dhabi, United Arab Emirates
48. Imperial College London, London, United Kingdom
49. Department of Nutrition and Public Health, Faculty of Health and Sport Sciences, University of Agder, 4630 Kristiansand, Norway.
50. The FA Group, Burton-Upon-Trent, Staffordshire, UK.
51. Division of Public Health Sciences, Fred Hutchinson Cancer Center and School of Public Health, University of Washington, Seattle, WA, USA.
52. Kenya School of Medicine, Moi University, Eldoret, Kenya.
53. Rwanda division of basic sciences, University of Global Health Equity, Rwanda.
54. Helsinki University Central Hospital, Helsinki, Finland.
55. School of Sport and Service management, University of Brighton, Eastbourne, UK.
56. Department of Nutrition and Movement Sciences, Maastricht University, Maastricht, The Netherlands.
57. The Queen's medical research Institute, University of Edinburgh, Edinburgh, UK.
58. Program in Physical Therapy and Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA.
59. Biological Sciences and Anthropology, University of Southern California, California, USA.
60. University of Starthclyde, Glasgow, Scotland.
61. Centre for Cardiovascular Sciences, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK.
62. School of Social and Behavioral Sciences, University of Tilburg, Tilburg, Netherlands.
63. Department of Sport and Health of the Faculty of Human Kinetics,University of Lisbon

64. Department of Nutrition, Exercise and Sports, Copenhagen University, Copenhagen, Denmark.
65. Department of Psychiatry and Behavioural Sciences, Stanford University, Stanford CA, USA.
66. Department of Anthropology, Baylor University, Waco, TX, USA.
67. Child and Brain Development Program, CIFAR, Tronto, Canada
68. Maastricht University, Brightlands Campus Greenport Venlo and Lifestyle Medicine Center for Children, Jeroen Bosch Hospital’s-Hertogenbosch, The Netherlands.
69. Population, Policy and Practice Research and Teaching Department, UCL Great Ormond Street Institute of Child Health, London, UK.
70. Department of Anthropology, University of California Los Angeles, Los Angeles, USA.
71. Max Planck Institute for Evolutionary Anthropology, Department of Human Behavior, Ecology, and Culture.
72. Section on Growth and Obesity, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA.
73. Nutritional and Health-Related Environmental Studies Section, Division of Human Health, International Atomic Energy Agency, Vienna, Austria.
74. Department of Public Health Sciences, Parkinson School of Health Sciences and Public Health, Loyola University Chicago, Chicago, IL, USA.
75. NUTRIM, Maastricht University, Maastricht, The Netherlands.
76. Biotech Center and Nutritional Sciences University of Wisconsin, Madison, Wisconsin, USA.
77. State Key Laboratory of Molecular developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing, China
78. CAS Center of Excellence in Animal Evolution and Genetics, Kunming, China.

Abstract:

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

One Sentence Summary:

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

Main text:

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

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

Public health officals need to be able to anticipate future daily water intake demands of their populaions, especially during periods of impeding crisis. Ideally this would be based on scientific evidence regarding the levels of normal water intake. The current recommended intakes for water (*8, 9, 11*), however, rely on epidemiologic self-reported surveys or laboratory-based physiological studies with rather small sample sizes. Results obtained from self-reported intake surveys show large variation linked to imprecision in the assessment method. It is thus difficult to establish clear guidelines for worldwide public health actions from these sources of information. The majority of people who lack access to safely managed drinking water live in countries with a low human development index (HDI), but few studies have examined water turnover in those populations (*2*). To develop global guidelines for daily water intake, empirical measurements of water turnover under free-living conditions are required across a broad range of economic and environmental conditions.

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

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

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

Body size and composition, energy expenditure, and climate variables were all correlated with water turnover. Limiting our analysis to adults aged 18 to 60 years to avoid strong age effects (as shown in Fig. 2), bivariate analyses showed that water turnover was positively correlated with fat-free mass, total energy expenditure, and PAL, and negatively correlated with percent body fat ($P<0.001$) (**Fig. 3A through D**). We found a significant curvelinear relationship between outdoor air temperature and water turnover and a curvelinear relationship between latitude and water turnover ($P<0.001$) (**Fig. 3E, F**). Air temperature was positively correlated with water turnover when it was higher than 10 °C ($P<0.001$). Daily water intake was highest at approximately 0° effective latitude and the lowest at -50° or +50° latitude. People living above the Arctic Circle had higher water turnover than those who lived at -50° or +50° latitude.

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

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

The highest water turnovers in our sample are consistent with the effects of temperature, climate, physical activity and body size. Nine of the 1,875 males had high water turnover greater than 10 L/d; of these four were athletes, four were adult Shuar forager-horticulturalists of Amazonian Ecuador (*18*), and one male was Caucasian with normal BMI but measured in the summer with a maximal air temperature of 31.7 °C. Thirteen of 3,729 females had high water turnover greater than 7 L/d; of these five females were athletes, two females were pregnant women who had extremely high BMI (>45 kg/m^2) and were measured in the summer; three females had high BMI (>30 kg/m^2), in which two were measured in the summer. Three females were measured in summer, with a maximal air temperature of >30°C.

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

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

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

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

Sex is 0 for female and 1 for male; Athlete status is 0 for non-athlete and 1 for athlete; HDI is 0 for high HDI countries, 1 for middle HDI countries, and 2 for low HDI countries. This equation explains 47.1% of the variation in water turnover. An increase in PAL of 1.0 induces a ~1000 ml increase in water turnover; a 50 kg increase in body weight induces a ~700 ml increases in water turnover; a 50% increase in relative humidity induces a ~300 ml increase in water turnover; and a 1000 m increase in altitude induces a ~500 ml increase in water turnover. Males exhibit ~400 ml more water turnover than do females of the same weight because males have greater fat-free mass and a lower percentage body fat. People who live in low HDI countries exhibit ~200 ml more water turnover than people who live in high HDI countries after controlling for the other measured variables. Athletes have ~1000 ml more water turnover than do non-athletes with everything else being equal. A U-shaped relationship between water turnover and air temperature shows ~1000 ml more water turnover at +30 °C air temperature than the nadir between ±0 and +10 °C air temperature, and also ~400 ml more water turnover at –10 °C air temperature than that nadir. A curvilinear relationship between water turnover and age shows the peak water turnover is shown between 20's and 40's and decrease after 50's and ~700 ml less water turnover at age 80 than at age 30.

A 20-year-old male weighing 70 kg, who is not athletic and exhibits a PAL of 1.75, and who lives in a high HDI country at 0 m altitude where mean air temperature is 10°C and relative humidity is 50%, has a predicted water turnover of 3.2 L/d. A non-athletic 20-year-old female weighing 60 kg living at the same location will have a water turnover of 2.7 L/d. In contrast, a 20-year-old athletic male weighing 70 kg, with a PAL of 2.5, who lives in a high HDI country at a location 2000 m above sea level, where air temperature is 30°C and relative humidity is 90%, has a water turnover of 7.3 L/d; for a 60 kg athletic female in the same scenario, water turnover is 6.8 L/d. In this equation, we used weight and sex as a proxy of fat-free mass because body composition is not easily measured in daily setting. If body composition can be assessed, the following equation can be used to predict water turnover (**Fig. 6**):

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

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

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

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

As shown in Figure 1, we need to be aware that water turnover obtained by the hydrogen isotope dilution and elimination technique is not equal to daily water intake from liquids and foods. Metabolic water accounts for ~10% of water turnover, and respiratory water uptake and transcutaneous water uptake each account for 2 to 3% of water turnover. Therefore, daily water intake from liquids and foods is equivalent to ~85% of water turnover (*7*). An unsolved question is, what percentage of water intake comes from food? Self-reported surveys around the world suggested 20-50% of daily water intake is from food (*5, 6, 11*). These estimates, however, are questionable because many studies that have demonstrated self-reported surveys underestimate energy, protein and salt intake. Thus, dietary survey methods probably also underestimate the water intake in food and overestimate from drinking water and beverages. Conversely, if people consume a higher energy density diet with lower water content (*25, 26*), they may need more water from drinks and beverages. Without measured water intakes from food, it is not possible to assess the relative contributions of food and drinking water or beverages to water turnover in this study, and indeed no studies to date have adequately addressed this issue. Nonetheless, the current study clearly indicates that one size does not fit all for drinking water guidelines, and the common suggestion that we should drink 8 × 8oz glasses of water per day (approx. 2 L) is not backed by objective evidence.

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

References

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

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

39. W. N. Schofield, Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr* **39 Suppl 1**, 5-41 (1985).

40. D. A. Schoeller, E. van Santen, Measurement of energy-expenditure in humans by doubly labeled water method. *J. Appl. Physiol.* **53**, 955-959 (1982).

41. C. R. Fjeld, K. H. Brown, D. A. Schoeller, Validation of the deuterium oxide method for measuring average daily milk intake in infants. *Am J Clin Nutr* **48**, 671-679 (1988).

Acknowledgments

We are grateful to the International Atomic Energy Agency (IAEA), Taiyo Nippon Sanso, and SERCON for their support and to Takashi Oono for his tremendous efforts at fundraising on our behalf. Y.Y. and M.K. would like to pay gratitude and respect to their mentor, Prof. Taketoshi Morimoto, an emeritus professor of the Department of Physiology, Kyoto Prefectural University of Medicine, who passed away in July 2019. Y.Y., T.Y., and M.M. are grateful to Keiichi Abe for his support. **Funding:** The IAEA Doubly Labeled Water (DLW) Database is generously supported by the IAEA, Taiyo Nippon Sanso, and SERCON. The authors also gratefully acknowledge funding from the US National Science Foundation (BCS-1824466) awarded to H.P. and the Chinese Academy of Sciences (grant CAS 153E11KYSB20190045) to J.R.S. The funders played no role in the content of this manuscript. **Conflict of interest:** Y.Y. has a patent pending that is partly related to the publication. The other authors have no conflicts of interest to declare. **Data Availability:** All data used in these analyses were freely available via the IAEA DLW Database, which can be found at https://doubly-labelled-water-database.iaea.org/home and www.dlwdatabase.org.

Figure legends

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.

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

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

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

Fig. 5. (A) Athletes had higher water turnover (WT) than non-athletes, even after adjusting for physiological and environmental variables ($P < 0.001$). **(B)** Hunter-gatherers (HG), mixed farmer and hunter-gatherer (HGF), and subsistence agriculturalists (SA) had higher water turnover than other people (C), even after adjusting for physiological and environmental variables ($P < 0.001$). Note that there are no males in the database who fell into the SA category. **(C)** People who lived in countries with a low Human Development Index (HDI) had higher WT than people who lived in countries with high or middle HDI, even after adjusting for physiological and environmental variables ($P < 0.001$). **(D-F)** Relationship between water turnover and outdoor air temperature, physical activity level (PAL), or fat-free mass. The countries were categorized as high (red), middle (green), and low (blue) HDI. **(D)** A significant interaction ($P < 0.001$) was observed between outdoor air temperature and HDI in water turnover. The association between outdoor air temperature and water turnover is weak in high HDI countries ($r = 0.086$, $P < 0.001$) but strong in men in low HDI countries ($r = 0.604$, $P < 0.001$). **(E, F)** A significant interaction ($P < 0.001$) was observed between HDI and PAL or FFM in water turnover. Correlation coefficients were significantly higher ($P < 0.001$) in low HDI countries ($r = 0.484$ to 0.670, $P < 0.001$) than in high HDI countries ($r = 0.367$ to $0,510$, $P < 0.001$).

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