Title

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Journal

American Journal of Biological Anthropology, 168(4)

ISSN

0002-9483

Authors

Rosinger, Asher Y
Pontzer, Herman
Raichlen, David A
et al.

Publication Date

2019-04-01

DOI

10.1002/ajpa.23788

Peer reviewed

HHS Public Access

Author manuscript

Am J Phys Anthropol. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Am J Phys Anthropol. 2019 April ; 168(4): 705–716. doi:10.1002/ajpa.23788.

Age-related decline in urine concentration may not be universal: Comparative study from the U.S. and two small-scale societies

Asher Y. Rosinger, PhD[1,2,*], **Herman Pontzer, PhD**[3], **David A. Raichlen, PhD**[4], **Brian M. Wood, PhD**[5], **Susan N. Tanner, PhD**[6], and **Jeff M. Sands, MD**[7]

[1]Department of Biobehavioral Health, Pennsylvania State University, State College, PA.

[2]Department of Anthropology, Pennsylvania State University, State College, PA.

[3]Department of Anthropology, Duke University, Durham, NC.

[4]School of Anthropology, University of Arizona, Tucson, AZ.

[5]Department of Anthropology, University of California Los Angeles, Los Angeles, CA.

[6]Department of Anthropology, University of Georgia, Athens, GA.

[7]Department of Medicine, Renal Division, Emory University, Atlanta, GA.

Abstract

Objectives: Evidence from industrialized populations suggest that urine concentrating ability declines with age. However, lifestyle factors including episodic protein intake and low hypertension may help explain differences between populations. Whether this age-related decline occurs among small-scale populations with active lifestyles and non-Western diets is unknown. We test the universality of age-related urine concentration decline.

Materials and Methods: We used urine specific gravity (Usg) and urine osmolality (Uosm) data from 15,055 US non-pregnant adults without kidney failure aged 18–80 in 2007–2012 participating in the National Health and Nutrition Examination Survey (NHANES). We tested the relationship of age on urine concentration biomarkers with multiple linear regressions using survey commands. We compared results to longitudinal data on Usg from 116 Tsimane' forager-horticulturalists (266 observations) adults aged 18–83 in 2013–2014 from Lowland Bolivia, and to 38 Hadza hunter-gatherers (156 observations) aged 18–75 in 2010–2015 from Tanzania using random-effects panel linear regressions.

Results: Among US adults, age was significantly negatively associated with Usg (Adjusted beta [B]=−0.0009 g/ml/10 years; SE=0.0001; p<0.001) and Uosm (B=−28.1 mOsm/kg/10yr; SE=2.4; p<0.001). In contrast, among Tsimane' (B=0.0003 g/ml/10yr; SE=0.0002; p=0.16) and Hadza (B=−0.0004 g/ml/10yr; SE=0.0004; p=0.29) age was not associated with Usg. Older Tsimane' and Hadza exhibited similar within-individual variability in Usg equivalent to younger adults.

[*]Corresponding Author: Asher Y. Rosinger, The Pennsylvania State University, 219 Biobehavioral Health Building, University Park, PA 16802, arosinger@psu.edu, Phone: 814-865-5220.

Discussion: While US adults exhibited age-related declines in urine concentration, Tsimane' and Hadza adults did not exhibit the same statistical decline in Usg. Mismatches between evolved physiology and modern environments in lifestyle may affect kidney physiology and disease risk.

Keywords

Urine concentration; kidney physiology; aging; lifestyle mismatch

Introduction

Mammals are unique in that they only have kidneys to osmoregulate or keep homeostasis of water and salt balance. Many other vertebrates, including reptiles, birds, and fish, have extra-renal functions to remove solutes without water loss (Beuchat, 1990; Cooper, 2017). Kidney function is a critical feature that helps humans maintain physiological and cognitive functioning and health (Popkin, D'Anci, & Rosenberg, 2010).

Studies over the past seven decades have shown that maximal urine concentrating ability declines with normal aging in US and European countries (Lindeman, Tobin, & Shock, 1985; Lindeman, Van Buren, & Raisz, 1960; F. Manz & Wentz, 2003; Rowe, Shock, & DeFronzo, 1976; Sands, 2012). The Baltimore Longitudinal Aging Study demonstrated that urine concentrating ability following water deprivation declined by 20% and solute conservation declined by 50% among healthy 60–79 year-olds compared with 20–39 year-olds (Lindeman et al., 1985; Rowe et al., 1976). However, low urine concentration and high urine volume are associated with faster progression of glomerular filtration rate (GFR), i.e., the ability of nephrons in the kidney to filter toxins and waste products, decline in patients with chronic renal insufficiency (Hebert, Greene, Levey, Falkenhain, & Klahr, 2003). The health implications of age-related kidney function loss are important to understand in the face of an increasing global burden of chronic kidney disease (CKD), a growing source of morbidity and mortality worldwide (Jha et al., 2013).

While age-related decline in urine concentrating ability is not explained by deterioration in vasopressin (anti-diuretic hormone) response or decrease in filtration rate (GFR) (O'neill & McLean, 1992; Rowe et al., 1976), other potential mechanisms have been examined, including reductions in transport proteins, water channels or aquaporins, type 2 vasopressin receptor, sodium transporters, and urea transporters (Phillips et al., 1984; Rolls & Phillips, 1990; Sands & Layton, 2014). High protein intake and high blood pressure are both associated with faster deterioration of renal function and may exacerbate this process (Brenner, Meyer, & Hostetter 1982; Hostetter et al., 1986; Lindeman, Tobin, & Shock, 1984). Moreover, aging negatively affects physiological responses to heat, including decoupling of thirst and body water homeostatic mechanisms, which increase dehydration risk (W. Larry Kenney & Hodgson, 1987; W. L. Kenney et al., 1990).

The majority of research illustrating the age-related decline in urine concentrating ability has taken place in industrialized populations and in animal models (F. Manz & Wentz, 2003; Sands, 2012). However, work from small-scale and non-Western societies have found that some age-related physiological processes, including cardiovascular function and hormone levels, thought to be inevitable, may in fact not be (Ellison et al., 2002; Gurven, Blackwell,

Eid Rodríguez, Stieglitz, & Kaplan, 2012; Kaplan et al., 2017; Kurita et al., 2016; Mueller, Noya-Alarcon, Contreras, Appel, & Dominguez-Bello, 2018; Raichlen et al., 2017; Uchida et al., 2006). When lifestyle, nutrition, energetic status, and population variation of biomarker levels have been explored, the biological inevitability of senescence as exhibited in Western populations comes into question (Campbell, Leslie, & Campbell, 2006a, 2006b; Ellison et al., 2002; Uchida et al., 2006).

Some of the same processes affecting physiological processes into late adulthood may also be acting on kidney function. For example, low testosterone as well as regular high protein intake are linked to kidney function and lower filtration rate (Brenner et al., 1982; Kurita et al., 2016). Whether urine concentration ability declines with age among populations with traditional lifestyles is unknown. Examining urine concentration variability, i.e., diluting and concentrating urine, in naturalistic settings with traditional lifestyles outside of industrialized populations provides critical information about human variation in kidney function and body water homeostasis with aging that have implications for potential lifestyle recommendations for prolonging kidney health. Examining variation of urine concentration among different populations in different environments is critical to understanding natural variation in kidney function.

Therefore, we aimed to compare urine concentration between adults from the U.S. and two highly-remote, small-scale populations with non-Western lifestyles in different thermic environments to test the hypothesis that urine concentration declines with age across populations.

Material and Methods

US NHANES

Data for U.S. adults comes from the nationally-representative cross-sectional National Health and Nutrition Examination Survey (NHANES) 2007–2008, 2009–2010, and 2011–2012 cycles. The NHANES uses a complex, stratified multi-stage probability design to create a nationally representative sample of the non-institutionalized, civilian US population. This survey uses both in-person interviews alongside physical examinations which take place in Mobile Examination Centers (MECs). Data collection takes place year-round in 30 sampling sites throughout the US per two-year cycle. Further description of NHANES methodology and sampling procedures is described in-depth elsewhere (National Center for Health Statistics, 2015, 2016). Since 1999, NHANES has been continuously conducted with data released in two-year cycles by the National Center for Health Statistics (NCHS). The examination response rate varied between 64.4% and 72.2% during these cycles for adults. The National Center for Health Statistics Research Ethics Review Board approved NHANES and participants gave written informed consent.

Tsimane’ (Lowland Bolivia)

Currently, approximately 16,000 people who identify as Tsimane’ live in the Beni Department of Bolivia (Gurven et al., 2017). Tsimane’ traditionally practice forager-horticulturalist subsistence strategies and live in ~100 villages, the majority of which are

riverine. This region has an annual mean of 26.8°C, high humidity, and high rainfall (Godoy et al., 2008). Tsimane' subsistence practices include slash-and-burn horticulture, fishing, hunting, and purchased market foods. Longitudinal data collection took place in two villages between September 2013–June 2014 encompassing wet and dry seasons. Procedures are described in detail elsewhere (Rosinger, 2015).

Research communities were selected to provide variation in distance to the main market town, water sources (surface and wells), and lifestyle. During phase one (September 2013–January 2014), anthropometrics and focal-follows took place with a stratified, representative sample of both communities with 33 household heads aged 18+, which allowed for physical activity levels to be observed using the factorial method. Urine samples were collected twice that day. During phase two (March–April 2014) and three (May–June 2014), follow-up surveys, anthropometrics, doctor-conducted health examinations, and urine collection were conducted at the participant's household using exhaustive sampling in both communities. Tsimane' had access to ad-libitum food and water. Permission was granted by the Grand Tsimane' Council, community leaders, and participants gave informed oral consent. University of Georgia IRB approved the study.

Hadza (Northern Tanzania)

Hadza live in semi-arid woodland-savannah habitat in northern Tanzania. Several hundred Hadza continue to live as hunter-gatherers, acquiring food from wild plants, game, and honey (Marlowe, 2010). The equatorial region (3–4°S latitude) is often hot (mean temperature ~28°C, mean maximum ~35°C), with pronounced dry (June–November) and rainy (December–May) seasons (Marlowe, 2010). Water typically comes from streams and springs near camp, but sometimes from shallow, hand-dug wells or baobab cisterns. Residence camps are relatively remote and the residents at each site hunted and gathered daily, with wild foods accounting for over 90% of calories.

Longitudinal urine samples and anthropometrics were collected during the morning or evening in 2010 and 2015 at Sengeli and Setako camps as part of ongoing research into Hadza energy expenditure and health (Pontzer et al., 2012; Raichlen et al., 2017). All data was collected during the dry season. Both camps were remote, undeveloped, with similar distance to water sources and had very limited contact with non-Hadza during the study though Setako was more arid than Sengeli. Hadza had access to ad-libitum food and water. Permissions were obtained from Tanzanian authorities (National Institute for Medical Research, Commission for Science and Technology, regional and local governments) and U.S. institutions (Washington University; Hunter College; Yale University; University of Arizona). Subjects gave informed oral consent.

Urine Concentration Biomarkers

In NHANES, two biomarkers were measured. Participants provided spot urine samples in mobile examination centers (MEC) with urine specific gravity (Usg) measured in 2007–2008 and urine osmolality (Uosm) measured in 2009–2012. Usg was measured among Tsimane' and Hadza due to remote conditions.

Usg, the density of urine compared to water, is commonly used for laboratory and field measurements of urine concentration (L. Armstrong, 2007). NHANES urine samples were measured in the MEC for Usg using a digital refractometer (Atago). In Bolivia and Tanzania, samples were covered and measured in the field with digital refractometers (Atago) within 30 minutes of collection. Usg values vary between 1.000–1.040 g/ml with inadequate hydration >1.020 g/ml (Cheuvront, Ely, Kenefick, & Sawka, 2010).

Urine osmolality (Usom), total concentration of dissolved particles per kg of water in urine, was determined by freezing point depression osmometry in the MEC, calculated as milliosmoles per kilogram (mOsm/kg). Urine osmolality is highly correlated with Usg and values >800 mOsm/kg used inadequate hydration (Lawrence E. Armstrong et al., 2012; L. E. Armstrong et al., 2010).

Some differences existed in urine sample timing across sites. NHANES collected samples in the morning (44–48%), noon (33–34%) and afternoon (18%−23%) across cycles. Among Tsimane', 52% of samples were collected between 8 am and noon and the rest 12 pm to 6:45 pm. Among Hadza, samples were collected in mornings (7:00–8:45 am) (22%) and afternoon/evenings (3:45–7:30 pm) (78%).

Main predictor: Age

In NHANES, age was measured via government-issued identification cards. Age is more challenging to measure in populations with high illiteracy and less record keeping. To estimate age in Bolivia, participants were interviewed, supplemented by long-term field records(Leonard et al., 2015). For Hadza, ages were determined through interviews and long-term field records, as described previously (Marlowe, 2010).

Covariates

Covariates differed by site based on data availability, but were selected a-priori for analyses based on associations with hydration. In NHANES, sex (male, female), race/Hispanic origin, body mass index (BMI; kg/m^2), alcohol intake (g), caffeine intake (<, ≥400mg), protein intake (gm), total water intake (ml), physical activity (<, ≥150 minutes per week of moderate or vigorous physical activity), lactating status, and time of exam (morning, afternoon, evening) were included as covariates (Eisenhofer & Johnson, 1982; Killer, Blannin, & Jeukendrup, 2014; Friedrich Manz & Wentz, 2005; Perrier et al., 2013; Stookey, 1999).

In NHANES, participants self-reported race and Hispanic origin and were categorized as non-Hispanic white, non-Hispanic black, Hispanic, and other (including all non-Hispanic individuals reporting more than one race group). Alcohol, caffeine, protein, and water intakes were derived from the in-person 24-hour dietary recall using the Automated Multiple Pass Method (AMPM) in the MEC. The AMPM recall method improves respondent recall of foods and beverages consumed in the previous 24-hour period from midnight to midnight through standardized probes and minimizes bias (Moshfegh et al., 2008). Caffeine intake was dichotomized using the consumption value associated with higher risk of dehydration or hypohydration (< or ≥400mg) (Killer et al., 2014; Silva et al., 2013).

The Global Physical Activity Questionnaire (GPAQ) was used to construct the physical activity variable (T. Armstrong & Bull, 2006). During the home interview, participants were asked using the computer-assisted personal interviewing system to list the total time they spent in the previous week in moderate and vigorous activities from biking or walking, work, and leisure activities. Physical activity was dichotomized based on whether or not the individual met national guidelines of 150 minutes or more per week of moderate or vigorous physical activity (U.S. Department of Health and Human Services, 2008).

To test for diabetes, blood specimens were collected in the MEC for all participants and samples were analyzed for hemoglobin A_1c (HbA_{1C}) in the Fairview Medical Center Laboratory at the University of Minnesota. Adults with HbA_{1C} values of 6.5% or higher or who reported that a doctor told them they ever had diabetes were categorized as having diabetes (The International Expert Committee, 2009; Zelnick et al., 2017). Adults in NHANES provided medication information (if they had taken prescription medications in the last 30 days) through self-report. If they reported yes, they showed the container to the interviewer and the prescriptions were coded by NCHS. The codes for any diuretic medication (loop, thiazide, and potassium-sparing) were identified.

In Bolivia, available covariates were ambient temperature, physical activity level (in phase one), sex, BMI, urine sample time, lactating status, and community residence. Ambient temperature was measured in shade during urine collection with an indoor/outdoor wall thermometer (rounded 0.5°C) (Springfield Precision #90116). In Tanzania, available covariates were sex, BMI, urine sample time, lactating status, and residence camp. No diuretic prescription medications were reported or observed among Tsimane' and Hadza participants.

Statistical analysis

Due to the complex, four-stage sample design of NHANES, analyses were conducted using survey commands with standard errors (SE) estimated by Taylor series linearization following specified analytic survey procedures in Stata 15.0 (College Station, TX) (National Center for Health Statistics, 2015). We used day one dietary sample weights, which adjust for over-sampling, non-response, non-coverage, and day of week, because we controlled for dietary intakes. Weighted descriptive statistics were estimated for the general population and a healthier subpopulation (excluding adults with diabetes and taking diuretics). Scatterplots were generated to illustrate the unadjusted relationship between age and Usg and Uosm separated by sex and lactating status and Pearson's correlations were examined overall. Next, multiple linear regression models were used to test the relationship between age and urine concentration, first only adjusted for time of sample, second controlling for all covariates on the full population, and finally restricted to the healthier subpopulation controlling for confounders. R^2 values were examined among the three models to assess how much of the variability of urine concentration was explained.

Tsimane' and Hadza data were analyzed using robust-clustered SEs to account for multiple observations per individual in the longitudinal data using Stata 15.0 (College Station, TX). Random-effects (RE) panel regression models were constructed to assess the effect of age on Usg adjusting for individual fixed-effects, first only adjusted for time of sample, and second

fully adjusted for all available covariates related to urine concentration as discussed in the covariates section above, including community residence to account for lifestyle differences, time of urine sample, BMI, and sex. Physical activity level and ambient temperature were also adjusted for in wave one of Tsimane' regressions. Differences in within- and between-person Usg variation were tested across samples by age using RE post-estimation chi-square tests. For Tsimane' and Hadza analyses, all regressions and post-estimations were analyzed taking into account the multiple observations per individuals appropriately, thereby not treating each observation as independent, but rather allowing assessment of how urine concentration changes within a person across days and time due to varying environmental and physical conditions.

We re-estimated regression models using the same available covariates across study sites to assess potential residual confounding in Tsimane' and Hadza data. Additionally, we performed sensitivity analyses restricting NHANES, Tsimane', and Hadza data to the subset that provided first morning specimens and re-estimated the regression models with the same covariates as the primary analyses to assess whether results change substantially when including samples from throughout the day.

Sample

Adults aged ≥18 years were included in analyses with the exclusion criteria of pregnancy and renal failure.

In 2007–2008 NHANES, we used a sample of 4,928 adults without missing covariate data after excluding 56 pregnant women and 138 with kidney failure (told by doctor they had weak/failing kidneys). We sequentially excluded 728 adults for diabetes and 275 for diuretic use, leaving n=3,925. In 2009–2012, we used a sample of 10,127 adults after excluding 108 for pregnancy and 280 with kidney failure. We sequentially excluded 1,417 adults for diabetes and 531 for diuretic use, leaving n=8,179.

For Tsimane', 116 non-pregnant adults provided 266 urine samples (2.3/per person). Thirty-three adults participated in round 1 and provided 2 urine samples that day, 107 participated in round 2, and 94 in round 3.

For Hadza, 39 non-pregnant adults provided 160 urine samples (4.1/per person). One had missing covariate data yielding n=38 adults (156 observations).

Results

Sample descriptions and comparisons

Tsimane' and Hadza samples had younger average ages than NHANES (37.9 years vs 37.3 vs 43–46.2, respectively) and lower weights and heights (Table 1). Mean BMI of Tsimane' was 23.7 kg/m^2, with 16.5% overweight (25.0≤ BMI ≤29.9) and 5.6% with obesity (BMI≥30.0). No Hadza adult a had BMI >23.9 kg/m^2. The mean BMI for US adults was 27.8–28.6 kg/m^2 depending on exclusions. Kidney problems, diabetes, and diuretic medication use were not reported among Tsimane' and Hadza samples, while ~21% of U.S. adults had diabetes or diuretic use.

US: NHANES

Mean Usg was 1.0166 g/ml (SE=0.0002) for US adults. Urine concentration declined with age for US adults (Figure 1A/1B). When only adjusting for time of urine sample, age was negatively associated with Usg (Beta (B)= −0.0008 g/ml/10yr; SE=0.0001; P<0.0001; Table 2, Model 1) and the model explained approximately 4% of the variation of Usg. When fully adjusted for covariates (Model 2), the results were consistent but 16% of the variation was explained. When excluding adults with diabetes and diuretics, results were again consistent (B= −0.0009 g/ml/10yr; SE=0.0001; P<0.0001; Model 3) and 17% of the variation was explained by the model.

Mean Uosm among US adults was 622.2 mOsm/kg (SE=6.5). When only controlling for time of urine sample, age was negatively associated with Uosm (B= −30.6 mOsm/kg/10yr; SE=2.1; P<0.0001; Table 2, Model 4) with 4% of the variation explained by the model similar to the Usg results. When the model was fully adjusted for covariates, the results were consistent (B= −28.9 mOsm/kg/10yr; SE=2.2; P<0.0001; Model 5) and the variation explained by the model increased to 15%. With additional exclusions, results were consistent (B= −28.1 mOsm/kg/10yr; SE=2.4; P<0.0001; Model 6). Women had consistently lower Usg and Uosm than men, declining over age for both sexes (Figure 1A/1B).

Bolivia: Tsimane’

For Tsimane’, mean Usg was 1.020 g/ml (SD =0.007). The average Usg among adults across the 3 time points in the year when data was collected was highly consistent: 1.020 g/ml (SD =0.008) in Sept-Jan (end of dry into rainy); 1.021 g/ml (SD =0.007) in March-April (end of rainy season); and 1.020 g/ml (SD =0.006) in May-June (dry season), indicating that urine concentration was not affected by season. We analyzed the effect of age on Usg in 6 separate models, for phase 1, phase 2 and 3 combined, and phases 1–3 combined, first only adjusted for time of day and then fully adjusted as described in the statistical methods above (Table 3, Models 1–6). When only controlling for time of urine sample, age was not associated with Usg while the model accounted for 12% of the within-person variance. Fully adjusting for sex, BMI, community residence, physical activity level, and ambient temperature, the results were consistent, indicating no significant relationship between age and Usg (B= −0.00004 g/ml/10yr, SE=0.0004; P=0.94; Model 1) while the within-person R^2 increased to 30% and the between-person R^2 (or the amount of variance between individuals in the panel explained by the model) increased to 58%. In Models 3 and 4, when examining the relationship across days, the direction of the relationship was positive, but not significant (B= 0.00036 g/ml/10yr, SE=0.0002; P=0.08; Model 4) with less of the within- and between-person as well as overall variance (the weighted average of the within- and between R^2) explained by the model.

When all Tsimane’ data was combined, age was again positively but not significantly associated with Usg (B= 0.0003 g/ml/10yr, SE=0.0002; P=0.16; Model 6). The within-person variance when only accounting for age and time of day was 12%, higher than the 5% of the between-person variance explained by the model. The fully adjusted model (6) explained more of the between-person variance than within-person variance. There were no sex differences (Figure 1C) and no significant sex-by-age interaction (results not shown).

Across days and urine samples, younger (18–30 years), middle-aged (31–55y), and older adults (≥56y) did not have different average within-individual variability (0.0044 vs 0.0044 vs 0.0042 g/ml, respectively; chi2=2.29; p=0.32) in Usg (Figure 2).

Tanzania: Hadza

For Hadza, mean Usg was 1.020 g/ml (SD=0.008). When only adjusting for time of urine sample, age was not significantly associated with Usg among Hadza adults (B= −0.0004 g/ml/10yr; SE=0.00004; P=0.21, Table 4, Model 1), though the coefficient was negative and 3% of the within-person variation was explained by the model. The results were consistent when fully adjusting for sex, BMI, time of urine sample, and camp of residence (B=−0.0004 g/ml/10yr; SE=0.00004; P=0.29, Table 4, Model 2), however the within-person variance accounted for by the model decreased to 2% while the between-person variance was 19%. When examining sex differences, Usg did not differ significantly between men and women (Figure 1D). Across sampling periods, younger Hadza (18–30y), middle-aged (31–55y), and older adults (≥56y) did not have different within-individual variability (0.0069 vs 0.0061 vs 0.0062 g/ml, respectively; chi2=3.92; p=0.14), all exhibiting large deltas in Usg across days (Figure 3).

Comparing Usg across sites and sensitivity analysis

We compared results from linear regressions for NHANES excluding adults with diabetes and using diuretics to RE regressions for Tsimane' (pooled sample) and Hadza limiting models to include covariates (BMI, sex, time of urine sample, and location or ethnicity) available across sites. Results were consistent; the effect of age (ten years) was significantly negatively associated with Usg for US adults but not for Tsimane' and Hadza (Figure 4).

When restricting data to first morning urine samples, results were also consistent with primary analyses finding significant age-related decline in Usg (B= −0.0008 g/ml/10yr; SE<0.0001; P<0.0001; n=1,908) and Uosm (B= −22.4 mOsm/kg/10yr; SE=3.3; P<0.0001; n=3,964) among US adults, but not among Tsimane' or Hadza adults. Among Tsimane' 35 samples were analyzed for 30 adults (B= −0.0003 g/ml/10yr; SE=0.0006; P=0.60), while 33 samples were analyzed for 25 Hadza adults who provided urine samples in the morning (B= −0.0004 g/ml/10yr; SE=0.0008; P=0.64).

Discussion

We found significant age-related declines in urine concentration among two nationally-representative samples of US adults even when excluding adults with diabetes, similar to previous water restriction studies (Lindeman et al., 1985; F. Manz & Wentz, 2003; Rowe et al., 1976). In contrast to the hypothesis of universal decline, older Tsimane' forager-horticulturalists and Hadza hunter-gatherers did not have statistically lower urine concentration or blunted Usg variability. A 0.01 g/ml Usg increase represents a 2.5% body mass change (Cheuvront et al., 2010); several older adults exhibited fluctuations of at least this magnitude across sampling periods (Figures 2 & 3). The anticipated differences between 20 and 70 year-old persons across these populations would be 0.0065 g/ml (US versus Tsimane') and 0.003 g/ml (US versus Hadza). While urine concentration is affected by many

factors, generally people have similar daily hydration rhythms (Perrier et al., 2013). These findings demonstrate statistical variation in age-related declines in urine concentration across populations. Yet as these results are derived from statistical modelling, the lack of statistical significance of urine concentration with age among Tsimane' and Hadza may or may not match the biological significance. Maintaining urine concentration into late adulthood may help prolong kidney health. We next place the results in context and discuss potential mechanisms driving these results.

Ecological conditions vary widely within the US and between the US, Bolivia, and Tanzania. In the US, air conditioning is widely present. In contrast, many Tsimane' and Hadza live their lives outside and use behavioral adaptations, like napping and seeking shade, to reduce heat exposure (J M Hanna & Brown, 1983). Tsimane' and Hadza have higher water needs given their environmental conditions and significantly higher physical activity levels than US adults (Gurven, Jaeggi, Kaplan, & Cummings, 2013; Pontzer et al., 2015; Raichlen et al., 2017; Rosinger, 2015; Rosinger & Tanner, 2015). Seasonality did not affect Usg of Tsimane' and average levels were similar between Tsimane' and Hadza. Living in water-demanding environments may necessitate lifelong kidney adaptations which favor conserving water more efficiently (J M Hanna & Brown, 1983). Ethnic differences in urine concentration exist, such that healthy black adults had more concentrated urine than white adults though creatinine clearance rates were similar indicating that differences were not due to GFR (Bankir, Perucca, & Weinberger, 2007; Michael L. Hancock et al., 2010). Our results, however, indicate that young adults (20-year-olds) in all three populations have similar average Usg levels (~1.020) suggesting urine concentration differences may emerge in later-life.

A key mechanism that may be contributing to sustained ability to concentrate urine is blood pressure. Chronic hypertension can damage kidney tissue, blood vessels, arterioles, glomeruli, and if untreated can lead to CKD. In fact, hypertension can increase the rate of kidney function decline (Lindeman et al., 1984). Despite lifestyle changes, Tsimane' maintain high physical activity levels, and low prevalence of obesity and hypertension (4–5%) (Gurven et al., 2012), which likely has led to some of the healthiest hearts in the world (Kaplan et al., 2017). Similarly, Hadza have low prevalence (13% overall, 26% in 60+) of hypertension (Raichlen et al., 2017). In contrast, 29% of US adults and 63% of 60+ year-olds suffer from hypertension (Fryar, Ostchega, Hales, Zhang, & Kruszon-Moran, 2017). Low weight and high physical activity among Tsimane' and Hadza likely help maintain low blood pressure (Gurven et al., 2012; Raichlen et al., 2017). Differences in blood pressure with aging across populations may be a moderating factor affecting age-related decline in urine concentration.

Variation in regularity of protein intake, may also help explain results. Episodic protein intake may be better for kidney health (Brenner et al., 1982). Brenner (Brenner et al., 1982) proposed that regular high protein intake increases kidney filtration rate and renal blood flow, such that it stays at a sustained work level, analogous to chronic stress or inflammation. Rats with different levels of renal mass who were fed a high protein diet compared to ones on a low protein diet had faster progression of declining kidney function and sclerosis (Hostetter et al., 1986). Low protein intake may help restore kidney function

and slow progression of declining kidney function (Bosch et al., 1983; Hostetter et al., 1986).

US Protein intake is ~86g/day (Ford & Dietz, 2013). In comparison, previous studies using household weekly recall found that Tsimane' protein intake was also ~86g/day (Godoy, Reyes-García, Byron, Leonard, & Vadez, 2005). While Tsimane' consume market foods, including dried meat, with market integration, their protein intake is episodic due to heavy reliance on fishing and hunting, which varies greatly by season and distance to market (Tanner, Rosinger, Leonard, Reyes-García, & Taps Bolivia Study, 2013). Among Hadza, food returns (pooled across residents per camp) suggest high average protein intakes (~160g/day). However, the bulk comes from big hunting returns every one-to-two weeks indicating episodic intake (Wood & Marlowe, 2013). Dietary shifts from episodic protein intake, i.e., every few days, to Western diets with consistent protein intake in the context of energy surplus may lead to reduced ability to concentrate urine later in life. Future research should examine the role of the nutrition transition on urine concentration and risk of CKD.

Limitations

This paper is subject to several limitations. Tsimane' and Hazda sample sizes are small in comparison with NHANES but comparable to laboratory studies, limiting generalizability of findings to their broader populations. Due to remote conditions and locations of the fieldsites, only Usg was collected on Hadza and Tsimane' and other measures of urine concentration, like creatinine clearance, and other markers of renal function were not assessed. Additionally, spot sampling was used and differences in collection time between sites were therefore statistically adjusted accordingly (Perrier et al., 2013). Repeated spot samples provided within- and between-person variation of urine concentration across days to demonstrate urine dilution and concentration was similar between young and older adults during daily living conditions in response to water intake and excretion. However, a sensitivity analysis of first morning specimens to attempt to control for renal function found consistent results with the primary analyses for all three populations. Future studies should collect additional markers of kidney function along with longitudinal data with larger samples of older adults.

Additionally, differences existed in covariates across sites which may lead to omitted variable bias. NHANES has information on more covariates associated with urine concentration, including dietary and water consumption data, which were lacking for Tsimane' and Hadza. Physical activity data was collected on Tsimane' for round 1, which did not modify the relationship with age but did increase the percent variance of Usg explained by the model. Previous work demonstrated Tsimane' have higher water intake and higher activity levels than Americans (Gurven et al., 2013; Rosinger, 2015; Rosinger & Tanner, 2015). In US and Hadza samples, ambient temperature was not recorded while among Tsimane' temperature was associated with Usg and may help explain why the R^2 was higher among Tsimane' models than Hadza models (Rosinger, 2015). While sensitivity analyses restricting covariates to those available across sites found consistent results, residual confounding may exist. In autarkic societies, some uncertainty about age exists, especially among older adults, due to lack of birth certificates issued at birth for the older

generation. Results from a panel study among Tsimane' demonstrated that 17% of adults over the age of 21 admitted not knowing their exact age and provided a best-guess estimate (Rosinger & Godoy, 2016). We used long-term field records to supplement participant responses to address this issue among Tsimane' and Hadza, but potential differential error between these sites and the US for the measurement of age exists. Finally, participants were not deprived of water to simulate maximal urine concentrating ability; therefore, this study does not present maximal urine concentration. Future studies should conduct water restriction challenges in naturalistic settings.

In conclusion, while kidney function decline occurs at different rates across populations (Rowe et al., 1976), results from this comparative study provide evidence for potential sustained urine concentration variability with aging. Our results finding statistical variation in urine concentration across populations are consistent with other studies in small-scale societies investigating age-related declines in physiological processes and function (Campbell et al., 2006a; Ellison et al., 2002; Gurven et al., 2012; Raichlen et al., 2017). Our results suggest that the universal decline in urine concentrating ability may be linked with lifestyle shifts toward lower activity levels and Western diets. Results should be confirmed with additional kidney function markers. Without ability to conserve water via urine concentration, dehydration risk is greater, increasing vulnerability of heat stroke and CKD (Rolls & Phillips, 1990). Lifestyle changes, including reducing protein intake, increasing physical activity, and reducing sodium to reduce blood pressure, may help mitigate kidney decline. More work is needed to examine variation in kidney physiology outside industrialized populations.

Acknowledgements:

We thank Dr. Tomas Huanca, Esther Conde, CBIDSI, Dino Nate, Dr. Katerine Arias, and Dr. Kelly Ochs Rosinger for help with data collection. We also thank the Grand Tsimane' Consejo and all participants associated with this study.

Grant sponsorship: This work was supported by funding from the Wenner-Gren Foundation #8718 (AR), National Science Foundation #1341161 (AR), NSF-BCS-0850815 (HP), NSF-BCS 1440867 (DAR), NSF-BCS 1440841 (HP), NSF-BCS 1440671 (BMW), and National Institutes of Health NIH R01 DK41707 (JS).

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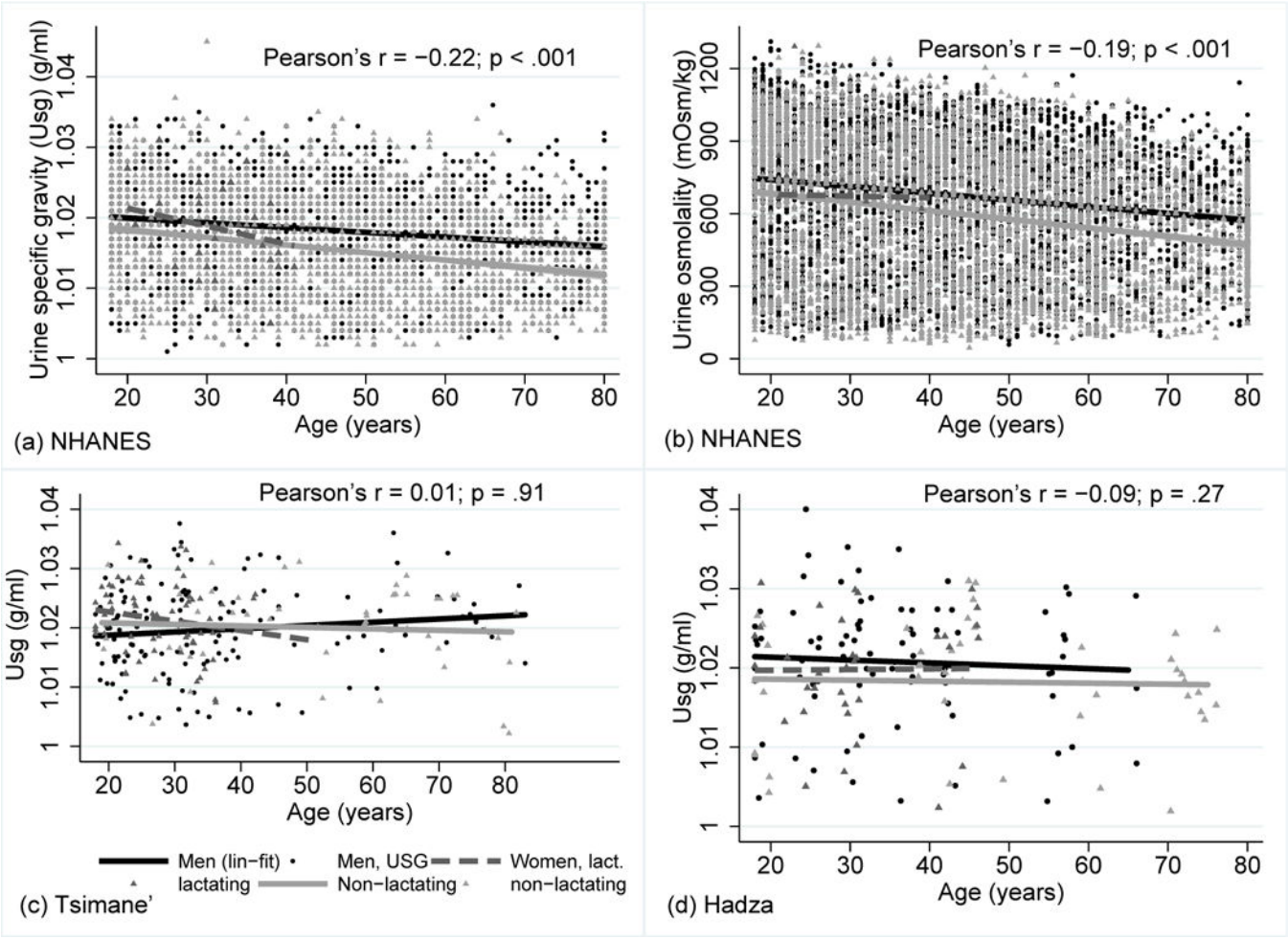

Figure 1:

Pooled linear fit of hydration biomarkers and age among men and lactating and non-lactating women in 3 sites. (a) urine specific gravity (Usg) in US; and (b) urine osmolality in US; (c) Usg among Tsimane'; and (d) Usg among Hadza.

Notes: Pearson's r is presented for sample as a whole, averaged across men, non-lactating women, and lactating women. Results for US come from NHANES and exclude adults with diabetes and on diuretic medications.

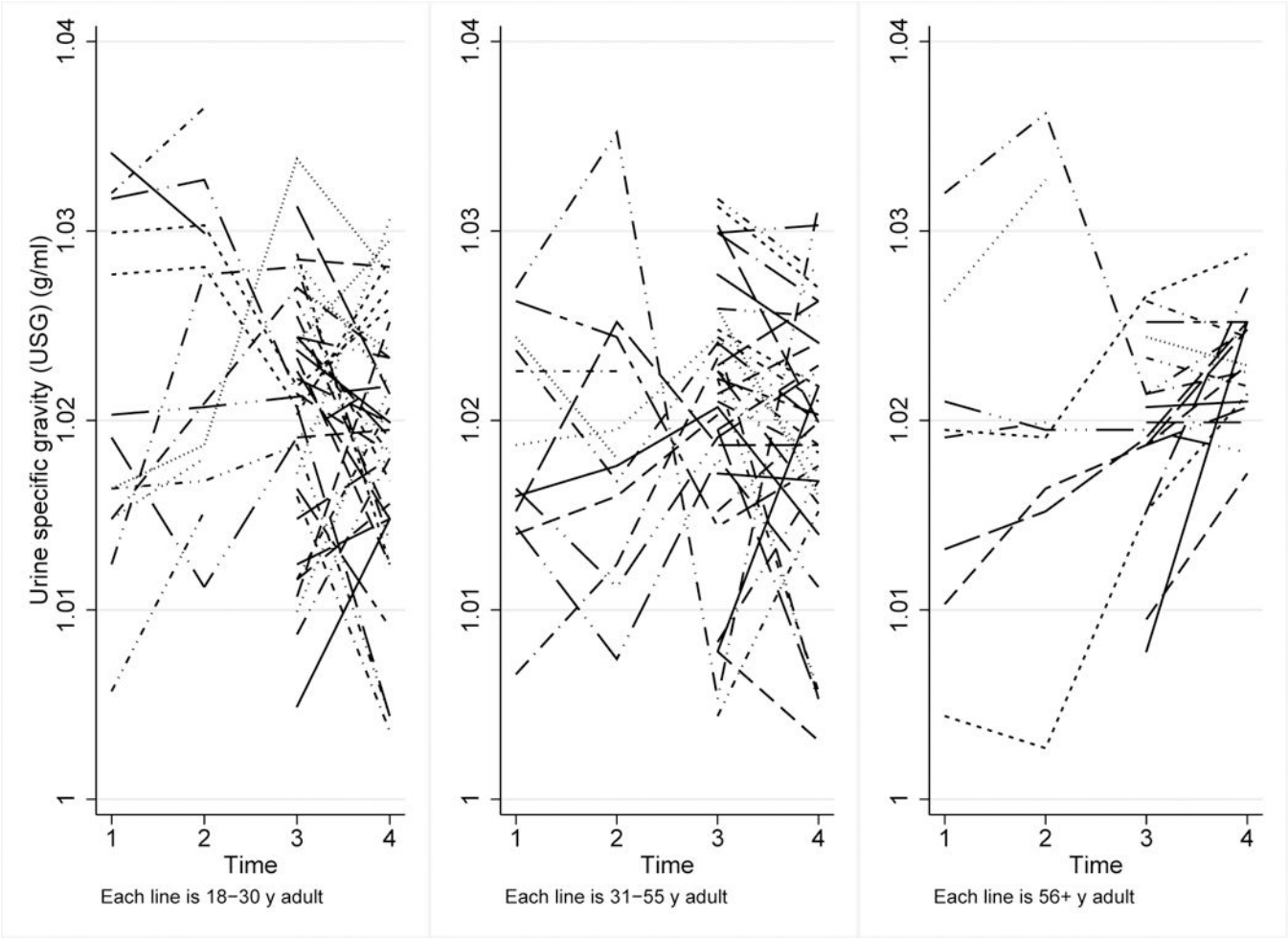

Figure 2:

Longitudinal comparison of variation in urine specific gravity among non-pregnant Tsimane' young (18–30 years), middle aged (31–55 years), and older (56+ years) adults across sampling periods.

Notes: (a) n = 52 (n=110 observations) Mean ± SD = 1.020 ± 0.007 g/ml; Within-subjects variability = 0.0044 g/ml; between-subjects variability 0.0056 g/ml. (b) n= 47 (103 observations) Mean 1.020 ± 0.007 g/ml; Within-subjects variability = 0.0044 g/ml; between-subjects variability 0.0064 g/ml. (c) n = 21 (53 observations) Mean 1.021 ± 0.006 g/ml; Within-subjects variability = 0.0042 g/ml; between-subjects variability 0.0045 g/ml. chi2 = 2.42; p = 0.30 for difference in variation across age-groups. Each line represents a participant.

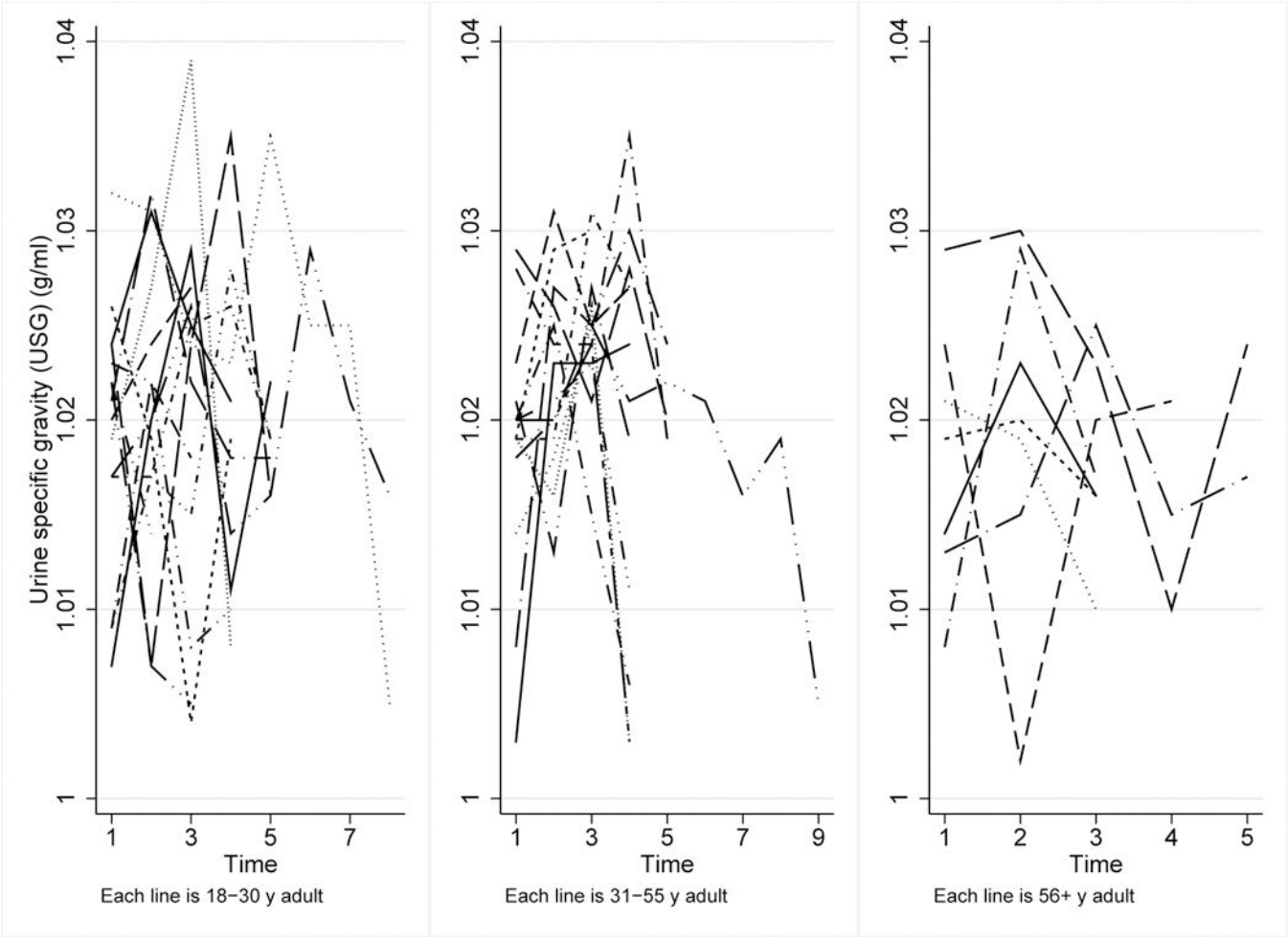

Figure 3:

Longitudinal comparison of variation in urine specific gravity among non-pregnant Hadza young (18–30 years), middle aged (31–55 years), and older adults (56+ years) across sampling periods.

Notes: (a) n = 16 (n=69 observations) Mean ± SD = 1.020 ± 0.008 g/ml; Within-subjects variability = 0.0069 g/ml; between-subjects variability 0.0052 g/ml. (b) n= 15 (64 observations) Mean 1.021 ± 0.007 g/ml; Within-subjects variability = 0.0061 g/ml; between-subjects variability 0.0053 g/ml. (c) n = 8 (27 observations) Mean 1.018 ± 0.007 g/ml; Within-subjects variability = 0.0062 g/ml; between-subjects variability 0.0055 g/ml. chi2 = 3.92; p = 0.14 for difference in variation across age-groups. Each line represents a participant.

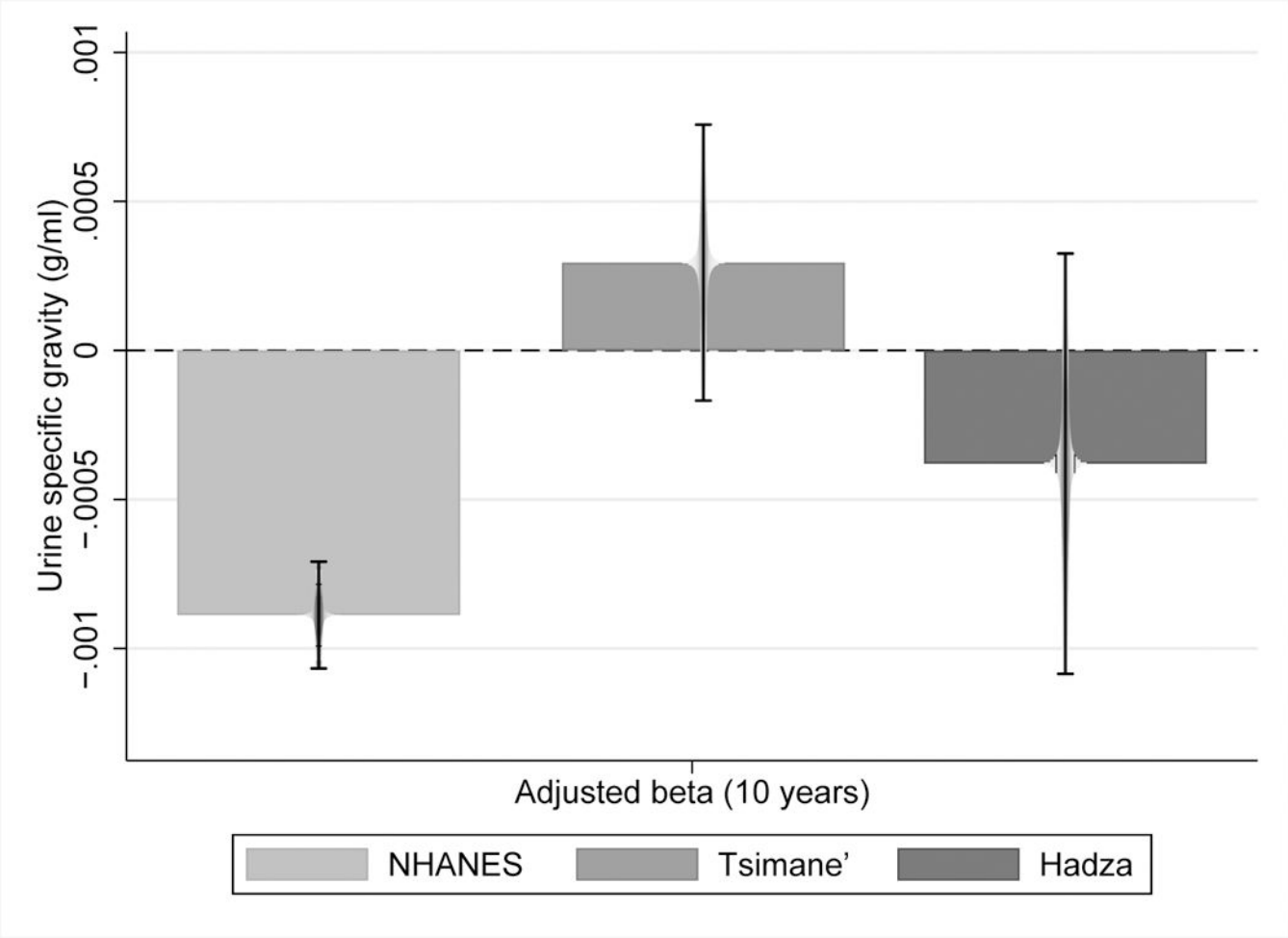

Figure 4:

Adjusted regression coefficients of the effect of age (10 years) and 95% confidence interval on urine specific gravity from NHANES, Tsimane', and Hadza adults.

Notes: NHANES multiple linear regression using survey commands; Tsimane' and Hadza models use random effects multiple linear regression and robust standard errors adjusted for individual effects. All models adjusted for age, sex, time of exam, BMI, and residence/race/ethnicity.

Table 1:

Sample characteristics of non-pregnant adults (aged 18 and over) without kidney failure from the US[1] without[2] and with[3] exclusions for diabetes and diuretic use, Tsimane' (Bolivia), and Hadza (Tanzania).

	US[1,2] 2007–2008	US[1,3] 2007–2008	US[1,2] 2009–2012	US[1,3] 2009–2012	Bolivia Tsimane'	Tanzania Hadza
	Mean or % (SE)	Mean or % (SE)	Mean or % (SE)	Mean or % (SE)	Mean or % (SD)	Mean or % (SD)
n (observations)	4,928	3,925	10,127	8,179	116 (266)	38 (156)
Age (yrs)	45.3 (0.5)	43.0 (0.5)	46.1 (0.5)	43.6 (0.6)	37.9 (17.9)	37.4 (15.6)
Sex (% male)	51.6 (0.9)	51.3 (1.0)	49.6 (0.6)	49.0 (0.6)	54.5	51.9
Race/Hispanic origin[4]						
NH white (%)	69.4 (3.7)	70.1 (3.5)	67.8 (2.6)	68.5 (2.6)	--	
NH black (%)	11.7 (2.1)	10.7 (2.0)	11.4 (1.3)	10.6 (1.2)	--	
Hispanic (%)	13.6 (2.1)	13.9 (2.1)	13.9 (1.9)	14.0 (1.9)	--	
Height (cm)	169.0 (0.2)	169.3 (0.3)	169.2 (0.2)	169.5 (0.2)	158.0 (7.2)	152.5 (9.8)
BMI (kg/m^2)	28.4 (0.2)	27.8 (0.2)	28.6 (0.1)	27.8 (0.1)	23.7 (2.9)	20.3 (1.7)
Weight (kg)	81.5 (0.6)	80.1 (0.6)	82.0 (0.3)	80.2 (0.3)	59.4 (8.7)	47.3 (7.2)
Urine specific gravity (g/ml)	1.0166 (0.0002)	1.0165 (0.0002)	--	--	1.0202 (0.007)	1.020 (0.008)
Urine osmolality (mOsm/kg)	--	--	617.7 (5.8)	622.2 (6.5)	--	--
Hypohydration[3] (%)	32.4 (1.3)	32.7 (1.4)	25.3 (0.7)	26.9 (0.8)	52.3	50.6
Physical activity (% ≥ 150 mins/wk)	24.1 (1.5)	25.7 (1.6)	20.3 (0.8)	22.2 (0.9)	--	--
Total water intake (ml)	3,010 (58)	3,030 (68)	3,118 (38)	3,139 (37)	--	--
Caffeine intake (% ≥ 400 mg)	11.9 (1.1)	12.2 (1.1)	11.0 (0.8)	10.9 (0.9)	--	--
Alcohol intake (g)	10.2 (0.8)	10.9 (0.9)	11.8 (0.6)	12.6 (0.6)	--	--
Protein intake (g)	81.5 (1.2)	82.6 (1.2)	84.2 (0.6)	85.2 (0.6)	--	--

[1] Data are from NHANES.

[2] Not excluding adults with diabetes or diuretic use.

[3] Excluding adults with diabetes or diuretic use.

[4] Race/Hispanic origin "other" category is included in total sample, but is not shown.

[5] Defined as >1.020 g/ml for Usg and >800 mOsm/kg for urine osmolality.

Table 2:

Linear regressions testing relationship between age and urine specific gravity and urine osmolality among non-pregnant US adults aged 18 and over.

	Usg[1,2] (g/ml)	**Usg[1,3] (g/ml)**	**Usg[1,3,4] (g/ml)**	**Uosm[1,2] (mOsm/kg)**	**Uosm[1,3] (mOsm/kg)**	**Uosm[1,3,4] (mOsm/kg)**
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**
Age (10 yrs)	−0.0008***	−0.0008***	−0.0009***	−30.6***	−28.9***	−28.1***
	(0.0001)	(0.0001)	(0.0001)	(2.1)	(2.2)	(2.4)
Observations	4,928	4,928	3,925	10,127	10,127	8,179
R^2	0.04	0.16	0.17	0.04	0.15	0.15

Standard errors in parentheses

*** p<0.001

** p<0.01

* p<0.05

[1] Data are from NHANES

[2] Adjusted for time of urine sample

[3] Adjusted for sex, Race/Hispanic origin, BMI, total water intake, alcohol intake, protein intake, high caffeine intake, meeting physical activity guidelines, lactation, and time of exam.

[4] Excluding adults with diabetes or diuretic use.

Table 3:

Random-effects linear regressions testing relationship between age and urine specific gravity (Usg) among Tsimane' adults aged 18 and over.

	Tsimane[1,2] Sept–Dec 2013 Usg (g/ml)	Tsimane[1,3] Sept–Dec 2013 Usg (g/ml)	Tsimane[2,4] Mar–June 2014 Usg (g/ml)	Tsimane[4,5] Mar–June 2014 Usg (g/ml)	Tsimane[2] data pooled Usg (g/ml)	Tsimane[5] data pooled Usg (g/ml)
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**
Age (10 yrs)	−0.0005	−0.00004	0.0003	0.00036	0.0002	0.00028
	(0.0007)	(0.0007)	(0.0002)	(0.0002)	(0.0003)	(0.0002)
Observations	65	65	201	201	266	266
n	33	33	112	112	116	116
Within-person R^2	0.12	0.30	0.10	0.20	0.12	0.25
Between-person R^2	0.28	0.58	0.02	0.30	0.05	0.32
Overall R^2	0.25	0.54	0.04	0.28	0.07	0.31

Standard errors in parentheses; constant omitted

*** p<0.001

** p<0.01

* p<0.05

[1] 2 observations per person in same day.

[2] Adjusted for time of urine sample.

[3] Adjusted for sex, BMI, time of urine sample, community of residence, physical activity level (low, medium, high) and ambient temperature.

[4] Observations from separate days.

[5] Adjusted for sex, BMI, time of urine sample, community, and ambient temperature.

Table 4:

Random-effects linear regressions testing relationship between age and urine specific gravity (Usg) among Hadza adults aged 18 and over.

	Hadza data[1,2] 2010–2015 Usg (g/ml)	Hadza data[1,3] 2010–2015 Usg (g/ml)
	Model 1	**Model 2**
Age (10 years)	−0.00044	−0.00038
	(0.00035)	(0.00036)
Observations	160	156
n	39	38
Within-person R^2	0.03	0.02
Between-person R^2	0.004	0.19
Overall R^2	0.01	0.04

Standard errors in parentheses; constant omitted

*** p<0.001,

** p<0.01,

* p<0.05

[1] Observations from separate days.

[2] Adjusted for time of urine sample.

[3] Adjusted for sex, BMI, time of urine sample, and camp of residence.