Forensic Science International 327 (2021) 110990

Contents lists available at ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Variations in human body water isotope composition across the United States

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ARTICLE INFO

Article history:
Received 4 May 2021
Received in revised form 19 August 2021
Accepted 29 August 2021
Available online 2 September 2021

Keywords:
Stable isotopes
Region of origin
Biogeochemistry
Body Water
Predictive model

ABSTRACT

Accurate human provenancing using stable isotopes depends directly on solid understandings of the geographic and individual factors affecting isotope variability and incorporation into human tissues. Transfer of isotopic, and therefore spatial, information between environmental water and biological tissues is mediated by the isotopic composition of body water. Thus, there is a need to study body water isotope ratios at a population level and over a large isotopic and geographic range. We evaluated oxygen ($\delta^{18}O_{bw}$) and hydrogen ($\delta^{2}H_{bw}$) isotope values of body water from 72 volunteers in 10 different cities across the US, and over a 5–10-day period. We analyzed covariates (e.g., water intake, physical activity, biometrics, gender) that might explain individual stable isotope ratio variations and tested a predictive model that incorporates the δ-values of drinking water, food, and O_2 as well as individual variables to predict the δ-values of body water. The individual variability in body water isotope values overtime (mean 0.3‰ for $\delta^{18}O_{bw}$ and 2.3‰ for $\delta^{2}H_{bw}$) was lower than the intra-city variability (mean 0.9‰ for $\delta^{18}O_{bw}$ and 6.9‰ for $\delta^{2}H_{bw}$). Body water isotope values differed among cities (ANOVA: $\delta^{18}O_{bw}$ $F = 97.2$, $p < 0.001$; $\delta^{2}H_{bw}$ $F = 176.2$, $p < 0.001$). However, significant overlap among some cities with different drinking water was discovered. We detected significant covariation of measured drinking water and human body water isotope values (both isotope systems $R^2 \geq 0.89$, $p < 0.001$) and small but significant effects of the average daily exercise and amount of fluid intake. The differences between measured and model-predicted body water values (mean 0.12 ± 1.2‰ for $\Delta\delta^{18}O$ and −1.2 ± 8.2‰ for $\Delta\delta^{2}H$) were statistically indistinguishable from zero ($\Delta\delta^{18}O$ t = −0.751, $p = 0.45$; $\Delta\delta^{2}H$ t = 1.133, $p = 0.26$). Here we show that community level variation exists in the $\delta^{18}O_{bw}$ and $\delta^{2}H_{bw}$ values and the primary drivers are the regional differences in drinking water isotopes. Consistency of the body water isotope composition over the study period suggests that tissues would incorporate a stable isotope signal over time. The amount of drinking water and physical activity influence body water values, while the variation in the isotopic values of food may contribute to regional level variability, but that still remains to be assessed further. The human body water model provides accurate estimates for measured values, capturing and reproducing the main features of the body water isotope variation across space.

1. Introduction

The stable isotope composition of human tissues records information related to the geographical location of a person at different times throughout life and has been used already in investigations of unidentified human decedents that led to their identification [1–9]. Questions related to place of birth, travel history, timing of movements and agreements in location among people can potentially be addressed by analyzing stable isotope ratios of oxygen and hydrogen (expressed as $\delta^{18}O$ and $\delta^{2}H$, respectively) in various tissues, including hair, fingernails, teeth, bone, blood, and even breath gases [4–6]. Tissue $\delta^{18}O$ and $\delta^{2}H$ values vary spatially echoing known geographic isotope patterns of drinking waters across landscapes [4–7,10–12]. However, the transfer of isotopic and therefore spatial information between external

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https://doi.org/10.1016/j.forsciint.2021.110990
0379-0738/

environmental water and biological tissues is not direct, but rather it is mediated through the isotopic composition of body water [4,11–18].

The $\delta^{18}O$ and $\delta^{2}H$ values of human body water reflect the proportional contributions of different input sources, metabolism, and the effects of water losses [4,16–19]. The body water pool defined as free water in the body, contained in the tissues and cells, is composed of a mixture of consumed drinking water, inspired vapor water, food water (free water contained in food), metabolic water formed from the metabolism of organic molecules, and inspired diatomic oxygen (O_2) used during cellular respiration [4,13–17]. The losses or outputs that influence body water isotope values include liquid water in the form of urine, sweat and fecal water, water vapor loss associated with breathing and evaporation across the skin, and carbon dioxide loss during breathing [4,16,18].

Body water $\delta^{18}O$ and $\delta^{2}H$ values have been shown to correlate primarily with drinking water isotope ratios, but there is individual variability thought to respond to personal differences in total water flux, physical activity, metabolism, dietary preferences and biometrics [4,16,18]. Therefore, accurately predicting isotope values of body water and tissues based on drinking water, and vice versa, requires understanding of these individual effects. Body water isotope values have been directly modeled for humans [18], non-human primates [16] and small mammals [17,20], or modeled as intermediates, sometimes implicitly, of drinking water to tissue isotope transfer in humans [4] and other mammals [13,14]. But to date, no study has reported human body water isotope ratios, or tested model predictions, at a population level and over a large natural isotopic and geographic range. In particular, no study has focused on describing the natural variability of human body water isotope ratios over time, or on which factors affect it.

Here we present data on oxygen ($\delta^{18}O_{bw}$) and hydrogen ($\delta^{2}H_{bw}$) isotope values of human body water collected across the USA. We assess the population variability in water isotope ratios across time and space by measuring the isotopic variation in body water among 72 individuals living in 10 different cities over a 5- to 10-day period. We analyze potential covariates (e.g., amount of water intake, physical activity, biometrics, gender) that might explain individual stable isotope ratio variations. Finally, we test a mechanistic model developed by Podlesak et al. [18] that incorporates the isotope composition of drinking water, food, and O_2 as well as variables such as individual estimates of water flux and energy expenditure to predict the δ-values of human body water.

2. Methods

2.1. Participants and sample collection

Seventy-two adult volunteers (age range 19–56 years of age) from ten cities across the USA were recruited for this study (Table 1). The volunteers were asked to collect one urine sample daily, first thing in the morning, for five consecutive days, with the exception of the volunteers from Salt Lake City, UT where participants collected urine over ten consecutive days. A minimum of four samples needed to be collected to participate in the study. The volunteers were also asked to collect a tap water sample, hereafter referred to as drinking water (dw), from their homes, fill out daily activity logs and answer an initial survey aimed at detecting previous travels, as well as to obtain information on dietary practices, physical activity and biometrics (height and weight). A list of variables obtained from questionnaires and surveys is provided in supplementary information (SI Table 1). Volunteers from the state of Utah collected samples during winter, while all other volunteers collected samples during summer and fall. All procedures involving humans were approved by the University of Utah Institutional Review Board (IRB) under protocol number 00028065.

Urine was collected in sterile 100 ml specimen containers; following collection, the cap and container vial were wrapped with laboratory film (Parafilm®) to prevent evaporation. Volunteers stored samples in a freezer until the last day of collection, when the samples were shipped with frozen cold packs to the University of Utah for analyses. Not all volunteers provided information on all variables, nor all samples; hence the number of samples varied in different analyses. The participants from Salt Lake City did not provide drinking water samples and we used tap water isotope data from a separate study [21]; consequently, we could not directly pair urine to drinking water for each individual from Salt Lake City.

2.2. Stable isotope analyses

We measured the stable hydrogen and oxygen isotope ratios of unfiltered drinking water and of water cryogenically extracted from urine, hereafter referred to as body water (bw), following previous work from our research group [20,22,23]. After extraction, 0.4 ml aliquots of body water were transferred to 1.8-ml crimp-top gas chromatography (GC) vials and sealed until analysis. Body water and drinking water were analyzed by TC-EA-IRMS at the Stable Isotope Ratio Facility for Environmental Research (SIRFER) from the University of Utah using the same procedure outlined in O'Grady et al. [16].

All water samples were analyzed alongside a set of three laboratory reference waters previously calibrated to the Vienna Standard Mean Ocean Water (VSMOW) scale. The oxygen and hydrogen isotope ratios of two primary reference waters (DI and ZE), were − 16.5‰ and − 123‰ for DI and − 0.2‰ and − 0.1‰ for ZE, when calibrated against international standards (GISP, SLAP and VSMOW). As a Quality Control (QC), a third well-characterized water reference was used (values −10.16‰ for $\delta^{18}O$ and −72.5‰ for $\delta^{2}H$). Raw $\delta^{18}O$ and $\delta^{2}H$ values for unknown and QC samples were corrected to the VSMOW scale using a two-point correction with the two primary reference waters. All QC analyses met the required specifications. The acceptable standard deviations for the QC water at SIRFER are

Table 1
Biometrics data for each of the 10 cities. Weight and Height are expressed as average ± standard deviation [maximum - minimum] (sample size).

City	Females: Males	Weight (Kg)	Height (cm)
Austin, TX	1:2	85.7 (1)	175.3 (1)
Uvalde, TX	5:4	70.7 ± 6.8 [78.9–58.9] (6)	171.8 ± 10 [185–157.5] (6)
San Marcos, TX	4:1	66.5 ± 9.7 [76.2–56.7] (3)	173.9 ± 5.8 [179–167.6] (3)
Tallahassee, FL	3:3	71.9 ± 24.4 [113.4–51.3] (5)	171.5 ± 12.2 [190.5–160] (5)
Duluth, MN	2:8	74.8 ± 11.8 [102–58.9] (10)	176.7 ± 7.8 [188–162.5] (10)
West Lafayette, IN	5:2	64.6 ± 10.8 [83.9–53.5] (7)	168.5 ± 9.9 [185.4–160] (7)
Logan, UT	2:2	70.7 ± 16.7 [86.2–47.6] (4)	174.0 ± 14.7 [188–155] (4)
Salt Lake City, UT	5:5	70.9 ± 13.6 [90.7–43.5] (10)	172.8 ± 10 [184–157] (10)
Eugene, OR	4:5	71.5 ± 15.5 [95.3–52.2] (8)	171.7 ± 11.2 [193–160] (8)
Fairbanks, AK	4:5	69.5 ± 15 [104.3–51.2] (9)	171.0 ± 10 [185.4–154.9] (9)

Not all individuals chose to report weight and height.

0.15‰ for $\delta^{18}O$ and 1.1‰ for $\delta^{2}H$. All water samples were analyzed in duplicate with average standard deviation between replicates of 0.07‰ for $\delta^{18}O$ and 0.6 for $\delta^{2}H$.Stable isotope abundances are reported in the standard δ-notation as parts per thousand (‰), where.

$$\delta_{sample} = (R_{sample} / R_{standard} - 1)$$

and R_{sample} and $R_{standard}$ are the molar ratios of the rare to abundant isotope (e.g., $^{2}H/^{1}H$) in the sample and standard, respectively [24]. The international standard for both hydrogen and oxygen stable isotope analysis is VSMOW.

2.3. Statistical analyses

We used parametric correlations and linear regressions (Ordinary Least Squares, OLS) to assess the covariation between $\delta^{2}H$ values and $\delta^{18}O$ values of water samples, and between body water isotope values and drinking water isotope values. We used multiple linear regressions to model the relationship between multiple explanatory variables obtained from participants' samples and surveys (SI Table 1) and the stable isotope values of body water. The independent variables were drinking water isotope values, Body Mass Index (BMI), Body Surface Area (BSA), average daily duration of physical activity, average intensity of physical activity, average daily water intake, average daily fluid intake, vegetarianism, consumption of local food, and large consumption of bottled water. We also included several potential interactions (for example, daily activity duration and intensity of activity, vegetarian and consumption of local food).

The Akaike Information Criterion (AIC) was used to determine which of these fitted statistical models best described the body water isotope data. The AIC provides an approach of selecting which model, from a set of models, is most parsimonious at explaining the data, retaining as much information as possible, but avoiding overparameterization. The AIC was conducted using the function *stepAIC* in the package *MASS* in R [25], which conducts a stepwise model selection by adding (forward direction) or removing (backward direction) variables to the multiple linear regression models. The model selection was conducted both in forward and backward directions. For the AIC approach only complete records of all variables were used (n = 37 participants). Once the models with the lowest AIC values were achieved for body water isotope ratios ($\delta^{18}O_{bw}$ and $\delta^{2}H_{bw}$), they were tested on the entire dataset (n = 72) using multiple linear regressions and correlations.

2.4. Mechanistic, predictive model

We used a process-based mechanistic model aimed at predicting the isotopic composition of human body water at steady state (at equilibrium with local drinking water). The model equations were built on the basis of models previously published by our research group [4,16,18,20]. The equations of the model are presented in Supplementary Information (document "*HBWM equations*"). Basically, the model incorporates variables such as drinking water isotope values (‰), gender (female, male), weight (kg), height (cm), physical activity (minutes*intensity), Fluid Intake (liters), Relative Humidity (average RH for the month of collection for each city), and ambient temperature (°C). Fluid intake was included using the average daily amount of fluid intake reported by each individual. Physical activity was estimated by the amount of time and the exercise intensity (scale from 1 to 5) reported by each participant per day; we created a physical activity variable by multiplying the average activity duration by the average intensity. Ambient temperature was set to 20 °C for all participants assuming that modern humans spent most of their time indoor at a constant temperature. Other fixed parameters with equal values for all individuals, such as fractionation values, are presented in the SI document "*HBWM equations*".

The main difference with previous body water models is related to the contribution of food $\delta^{18}O$ and $\delta^{2}H$ values. Previous body water models have used a fix value, assuming that all food across the US is non-local to a consumer [18], have modeled the food values assuming a linear relationship with local drinking water [18] or have directly measured the isotope values of dry food in a study involving non-human primates [16]. However, for modern humans it is difficult to determine what proportion of the consumed food is local versus imported from other regions, and even if this proportion was known, there are not enough data to evaluate the possible isotope ratios of all local and non-local food items. Recognizing these unknowns, we assumed the following: 1) during the spring and summer months, there is a link between local tap water and food isotope ratios (i.e., part of the local signal should have a connection to local water, due to local food production and consumption), and 2) during winter (specifically for Utah), production and consumption of local food is minimal and the majority of consumed food is imported from other regions in the U.S [26]. Therefore, for samples obtained in spring and summer, we used empirical data collected across the US that links the isotope values of some common foods to a consumer's drinking water isotope values from Chesson et al. [27]. Particularly for our modeling exercise, we used the linear relationship found for beef and purchase location across the U.S., in which the isotopes of beef available for purchasing in a supermarket are related to the isotope values of local (to the consumer) tap water [27], as follows:

$$\delta^{18}O_{beef} = 0.17 \times \delta^{18}O_{local\ tap\ water} + 14{\cdot}8‰,$$

$$\delta^{2}H_{beef} = 0.19 \times \delta^{2}H_{local\ tap\ water} - 115‰.$$

For samples collected in winter we did not use these equations, but rather we used fixed isotope values for the food, $\delta^{18}O_{food}$ = 26‰ and $\delta^{2}H_{food}$ = −115‰, following Ehleringer et al. [4] and Podlesak et al. [18] whom assumed an isotopically homogeneous 'continental supermarket' diet.

3. Results

3.1. Individual variability

The individual variability in body water (bw) isotope values (estimated as the standard deviation of each participant's isotope values over the collection period) was lower than the intra-city variability (estimated as the standard deviation of individual means) for all cities (Table 2, Supplementary Information Fig. 1–10). The average standard deviations for all individuals were 0.3‰ for $\delta^{18}O_{bw}$ and 2.3‰ for $\delta^{2}H_{bw}$ values. The average intra-city standard deviations were 0.9‰ for $\delta^{18}O_{bw}$ and 6.9‰ for $\delta^{2}H_{bw}$. The average isotopic ranges for all individuals were 0.8‰ for $\delta^{18}O_{bw}$ and 3.3‰ for $\delta^{2}H_{bw}$ values. The maximum isotopic ranges were 3.4‰ for $\delta^{18}O_{bw}$ and 22.3‰ for $\delta^{2}H_{bw}$ values; both maximum values corresponded to the same individual (BW12) from Duluth, MN. The average and maximum isotopic differences between two consecutive sampling days were 0.4‰ and 3.2‰ for $\delta^{18}O_{bw}$ and 2.3‰ and 21‰ for $\delta^{2}H_{bw}$; in both cases these maximum differences were associated with individual BW12.

Since body water isotope values showed little variation over time, we calculated an isotopic average for each individual and used those values for the rest of the work. We did not exclude any apparent outlier (such as collection day 4 for BW12) as all samples passed SIRFER QC tests.

Table 2
Isotope ratios and isotopic variability for each city and average SD for each city.

	Body Water average ± SD		Individual BW average of SD		Drinking Water average ± SD	
City	$\delta^{18}O_{bw}$	$\delta^{2}H_{bw}$	$\delta^{18}O_{bw}$	$\delta^{2}H_{bw}$	$\delta^{18}O_{dw}$	$\delta^{2}H_{dw}$
Austin, TX (3)	-2.3 ± 1.6[a]	-21.5 ± 14.8[d]	± 0.4	± 3.5	0.5 ± 0.2	0.2 ± 2.0
Uvalde, TX (9)	-2.0 ± 0.8[a]	-16.5 ± 5.2[d]	± 0.2	± 1.5	-4.0 ± 0.4[f]	-24.3 ± 1.7[h]
San Marcos, TX (5)	-2.6 ± 0.7[a]	-22.9 ± 7.5[d]	± 0.2	± 1.1	-3.6 ± 0.7[f,g]	-19.8 ± 3.8[h]
Tallahassee, FL (6)	-1.8 ± 0.6[a]	-12.7 ± 4.6[d]	± 0.2	± 1.2	-2.6 ± 0.7[g]	-12.5 ± 3.6
Duluth, MN (10)	-5.1 ± 0.8[b]	-52.5 ± 4.0	± 0.7	± 3.3	-9.0 ± 0.8	-69.6 ± 4.5
West Lafayette, IN (7)	-4.2 ± 0.9[b]	-36.2 ± 6.2	± 0.2	± 1.6	-7.0 ± 0.3	-43.9 ± 2.1
Logan, UT (4)	-8.3 ± 0.4[c]	-85.0 ± 2.3[e]	± 0.3	± 1.9	-17.5 ± 0.1	-127.2 ± 0.3
Salt Lake City, UT (10)	-8.5 ± 0.9[c]	-85.2 ± 8.4[e]	± 0.5	± 2.7	-15.9 ± 0.3	-120.0 ± 2.0
Eugene, OR (9)	-6.5 ± 0.9	-64.0 ± 6.1	± 0.3	± 1.8	-12.3 ± 0.1	-86.9 ± 1.2
Fairbanks, AK (9)	-11.6 ± 1.2	-112.8 ± 8.6	± 0.4	± 3.4	-19.8 ± 0.6	-155.1 ± 5.0

The number of participants for each city is presented between parentheses next to the city and state names. Mean isotope values ± SD with the same superscript (a, b, c, d, e, f, g or h) are not statistically different from each other after an ANOVA and Tukey HSD test at $\alpha = 0.05$. The *individual BW average of SD* (Standard Deviation) for each city was estimated as the arithmetic mean of the individual's SD through time. The number of Drinking Water samples equals the number of participants in all cases except in Salt Lake City (n = 25). Drinking water data for Salt Lake City, UT were collected separately from the body water samples in this study. All values reported in VSMOW and ‰.

3.2. Geographic variation

Body water isotope values differed among cities (ANOVA: for $\delta^{18}O$ values $F = 97.2$, $p < 0.001$; for $\delta^{2}H$ values $F = 176.2$, $p < 0.001$; Table 2). *Post hoc* Tukey HSD tests revealed that Austin, Uvalde, San Marcos and Tallahassee were statistically indistinguishable from each other (at a significance level $\alpha = 0.05$) for both $\delta^{18}O$ and $\delta^{2}H$ values, and that Logan and Salt Lake City were also statistically indistinguishable from each other for both isotope systems (Table 2). Duluth and West Lafayette $\delta^{18}O$ values were indistinguishable from each other (at $\alpha = 0.05$) (Table 2).

Drinking water also differed among cities (ANOVA: for $\delta^{18}O$ values $F = 1050$, $p < 0.001$; for $\delta^{2}H$ values $F = 1735$, $p < 0.001$; Table 2). Tukey HSD tests showed that Uvalde and San Marcos were indistinguishable from each other for $\delta^{18}O$ and $\delta^{2}H$ values, while Tallahassee and San Marcos were indistinguishable for $\delta^{18}O$ values (at a significance level $\alpha = 0.05$).

The measured drinking water (dw) and body water (bw) $\delta^{2}H$ values were positively correlated to the correspondent $\delta^{18}O$ values of drinking water and body water. The OLS linear regressions and coefficients of determination (R^2) for drinking water and body water were: Fig. 1.

$$\delta^{2}H_{dw} = 7{\cdot}96 \times \delta^{18}O_{dw} + 6{\cdot}64‰,\ R^2 = 0.99\ (p < 0.001,\ n = 72), \quad (1)$$

$$\delta^{2}H_{bw} = 10{\cdot}12 \times \delta^{18}O_{bw} + 2{\cdot}83‰,\ R^2 = 0.98\ (p < 0.001,\ n = 72,\ \text{Fig}{\cdot}1){\cdot} \quad (2)$$

We detected significant strong covariation of measured drinking water and measured human body water isotope values for each element (Fig. 2a and b), with the following linear regression slopes and intercepts, and coefficients of determination:

$$\delta^{18}O_{bw} = 0.50 \times \delta^{18}O_{dw} - 0.68‰,\ R^2 = 0.89\ (p < 0.001,\ n = 72), \quad (3)$$

$$\delta^{2}H_{bw} = 0.65 \times \delta^{2}H_{dw} - 6{\cdot}81‰,\ R^2 = 0.94\ (p < 0.001,\ n = 72){\cdot} \quad (4)$$

3.3. Individual and geographic influences on body water

The model with the lowest AIC for $\delta^{18}O_{bw}$ values incorporated $\delta^{18}O_{dw}$ values, body surface area (BSA), average daily activity, average fluid intake and intake of local food. The model with the lowest AIC for $\delta^{2}H_{bw}$ values incorporated $\delta^{2}H_{dw}$ values, BSA, average daily activity, and intake of local food. These two linear models were tested using the entire dataset (n = 72), resulting in the following multiple linear regression equations and multiple correlations:

$$\delta^{18}O_{bw} = 0.48 \times \delta^{18}O_{dw} - 0.36 \times [\text{Fluid Intake}] - 0.12‰,\ R^2 = 0.91\ (p < 0.001,\ n = 72), \quad (5)$$

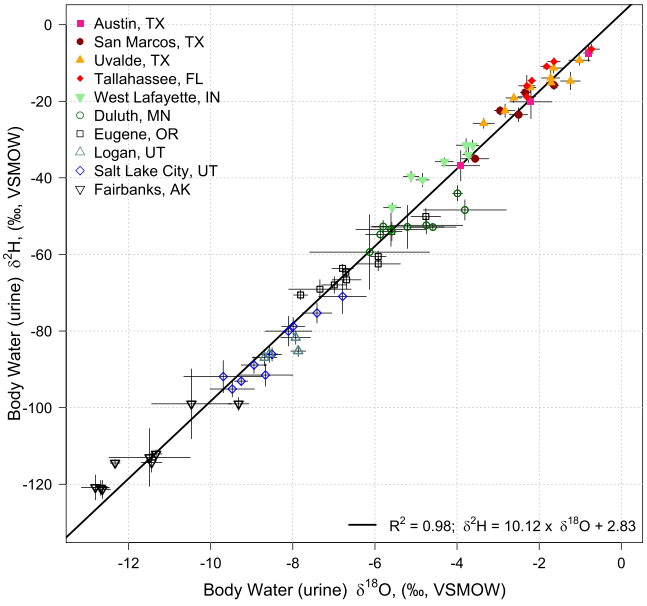

Fig. 1. Average body water $\delta^{2}H$ and $\delta^{18}O$ values for all participants, grouped by city. Error bars in the measured values correspond to 1 x SD of the 5 (10 for Salt Lake City) consecutive sampling days.

$$\delta^{2}H_{bw} = 0.64 \times \delta^{2}H_{dw} - 0.03 \times [\text{Daily Activity}] - 6{\cdot}85‰,\ R^2 = 0{\cdot}95\ (p < 0.001,\ n = 72){\cdot} \quad (6)$$

All least-square β coefficients were significantly different from zero, with the exception of β_0 (−0.12‰) for the model of $\delta^{18}O$ values.

3.4. Modeled (predicted) values

We were able to model predict body water isotope values for 59 individuals. Thirteen participants did not report the information necessary to include them in the modeling exercise. Fig. 3a and b present a comparison of measured (meas.) and predicted (pred.) values for oxygen and hydrogen isotope values, respectively. The linear regression and coefficient of determinations were:

$$\delta^{18}O_{meas} = 0.99 \times \delta^{18}O_{pred} + 0.06‰,\ R^2 = 0.86\ (p < 0.001,\ n = 59), \quad (7)$$

$$\delta^{2}H_{meas} = 1{\cdot}02 \times \delta^{2}H_{pred} - 0.15‰,\ R^2 = 0.94\ (p < 0.001,\ n = 59), \quad (8)$$

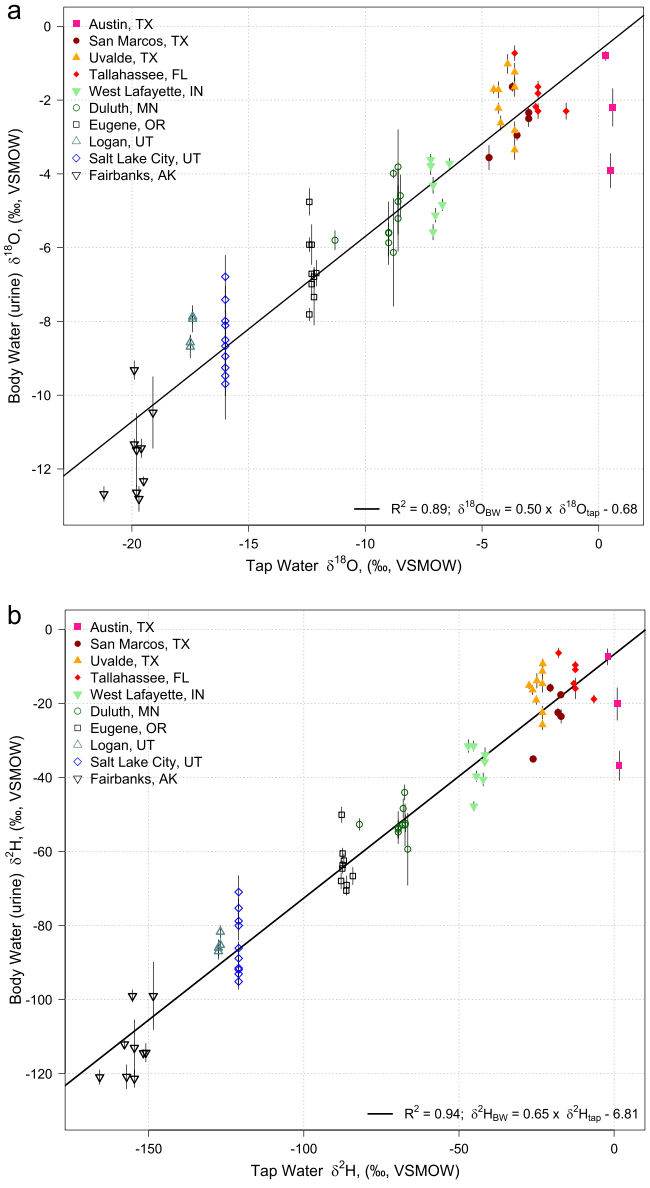

Fig. 2. a Measured body water $\delta^{18}O$ values against measured drinking (tap) water $\delta^{18}O$ values. Drinking water data for Salt Lake City, UT were collected separately from the body water samples in this study, therefore no variability is present on the x axis. b: Measured body water $\delta^{2}H$ values against measured drinking (tap) water $\delta^{2}H$ values. Drinking water data for Salt Lake City, UT were collected separately from the body water samples in this study, therefore no variability is present on the x axis.

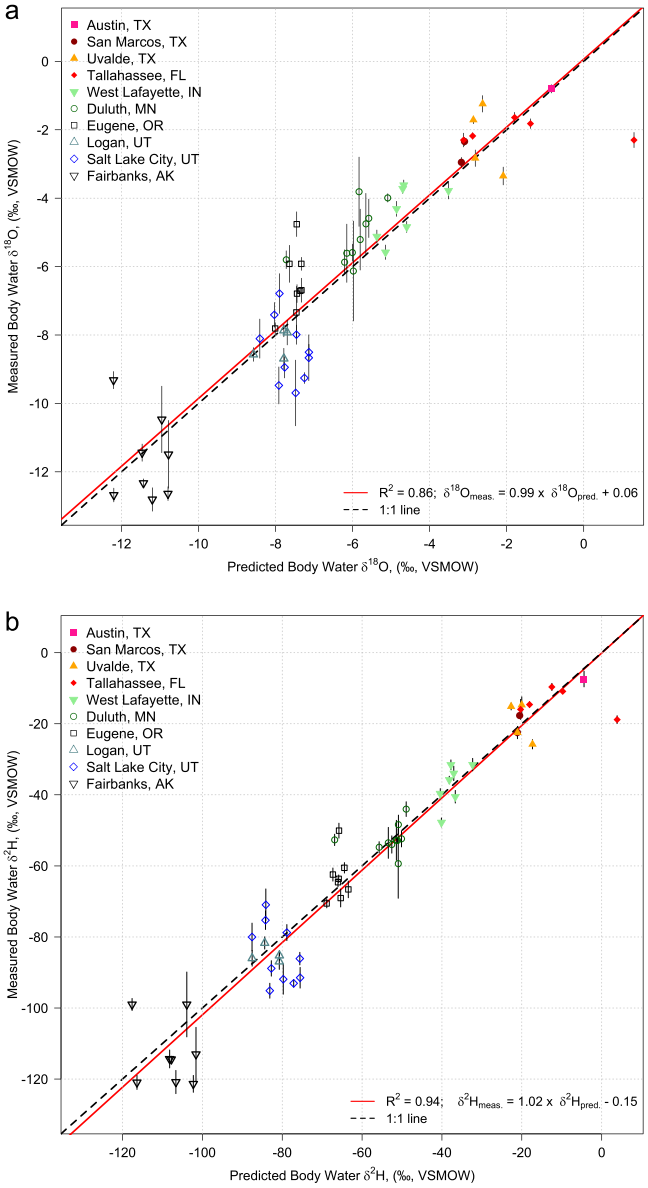

Fig. 3. (a) Measured versus predicted (modeled) Body Water $\delta^{18}O$ values. Error bars in the measured values correspond to 1 x SD of the 5 (10 for Salt Lake City) consecutive samples. N = 59. The OLS regression line is presented in a solid red line, and the 1:1 line in a dashed line. (b) Measured versus predicted (modeled) $\delta^{2}H$ values of human body water. Error bars in the measured values correspond to 1 x SD of the 5 (10 for Salt Lake City) consecutive sampling days. N = 59. The OLS regression line is presented in a solid red line, and the 1:1 line in a dashed line. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the resulting slopes and intercepts were not significantly different from 1 and zero, respectively.

The differences between measured and predicted body water isotope values ($\Delta\delta$) ranged from −3.6–2.9‰ for $\Delta\delta^{18}O$ and from −22.7–18.6‰ for $\Delta\delta^{2}H$ values (Fig. 4). In both cases the largest difference belonged to the same individual (BW49) from Tallahassee, Florida. The mean differences were 0.12 ± 1.2‰ for $\Delta\delta^{18}O$ and −1.2 ± 8.2‰ for $\Delta\delta^{2}H$, and resulted statistically indistinguishable from zero (Paired *t*-tests: $\Delta\delta^{18}O$ t = −0.751, df = 58, $p = 0.45$; $\Delta\delta^{2}H$ t = 1.133, df = 58, $p = 0.26$). These differences were positively correlated with the residuals ($\delta^{18}O_{res}$ and $\delta^{2}H_{res}$) from the Linear Regressions between drinking water and measured body water extracted from Eqs. 3 and 4: $\Delta\delta^{18}O = 0.77 * \delta^{18}O_{res} + 0.13‰$ ($R^2 = 0.38$, $p < 0.005$), and $\Delta\delta^{2}H = 1.03 * \delta^{2}H_{res} - 0.66‰$ ($R^2 = 0.67$, $p < 0.005$; Fig. 5). These differences were also positively, although weakly, correlated with body water $\delta^{18}O$ and $\delta^{2}H$ values ($R^2 = 0.12$, $p = 0.005$ and $R^2 = 0.10$, $p = 0.014$ for $\delta^{18}O$ and $\delta^{2}H$ respectively). No other significant correlations were detected between the calculated differences and any measured variables.

4. Discussion

Accurate and precise assignment of human remains to a region of origin using oxygen and hydrogen isotope markers depends on several factors; an important one is the natural variability of human body water. The isotopic composition of body water mediates the transfer of isotopic information between external drinking water and tissues [4,12,16–18]. Therefore, there is a need to understand human body water isotope variability if we are to understand the isotope information recorded in the tissues. In a forensic context we

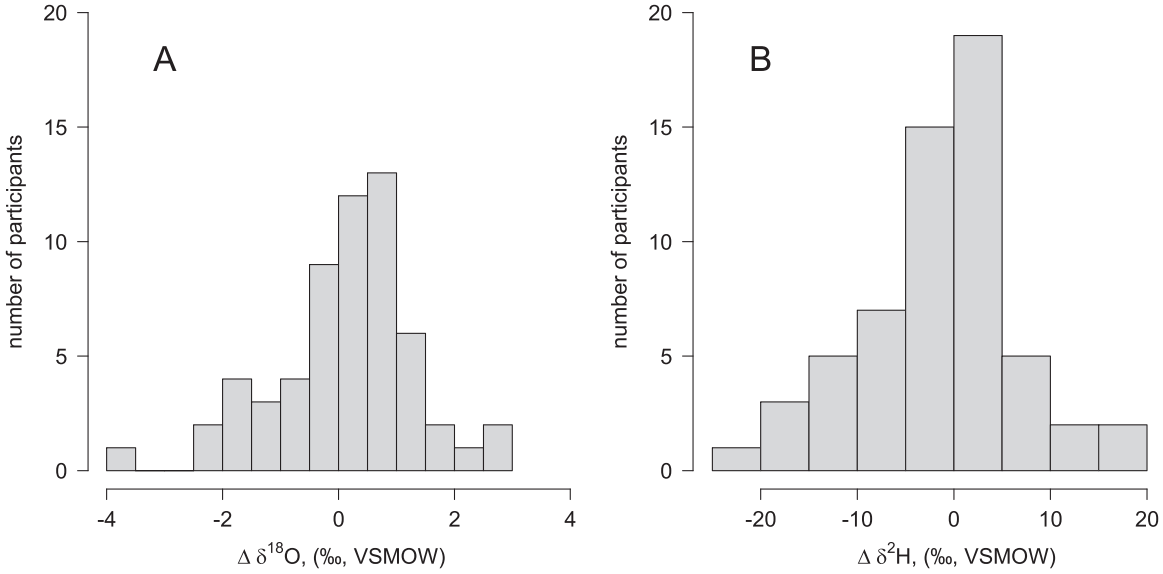

Fig. 4. Histograms of differences between measured and predicted body water isotope values ($\Delta\delta$) for 59 individuals.

need to be able to respond the question: Which factors influence human body water change that could mask a travel or deviates a person from the expected isotope value of a local sample?

4.1. Isotope variation

The data presented here represent the largest evaluation to date of the natural abundance of stable isotopes (oxygen and hydrogen) in human body water (BW) at a population level and across a large geographic and isotopic range. The study was designed to assess the natural variability of BW stable isotopes across a short period of time in healthy people that had not traveled recently. Therefore, the study aimed at capturing the isotopic variation imparted by everyday activities and individual choices.

It was reassuring that individual variability in $\delta^{18}O$ and $\delta^{2}H$ values were small, and always smaller than the intra-city variability. This indicated that over short time periods with similar routine activities the isotopic composition of body water remained stable, suggesting a steady isotope signal being incorporated into biological tissues. For most individuals no temporal changes in isotope values were detected. However, a few participants exhibited BW trends overtime (e.g., BW10, BW39 and BW57; see SI Figures). These individuals may have traveled recently or changed behavior (e.g., changes in physical activity or diet) not recorded appropriately in their reports. For example, BW10 (Salt Lake City, UT) reported traveling to Hawaii for seven days in the past year prior to the start of the study; unfortunately, the participant did not report when the travel took place, hence we don't know how many weeks before body water collection this took place. According to O'Brien and Wooller [12], body water isotope values continue to change

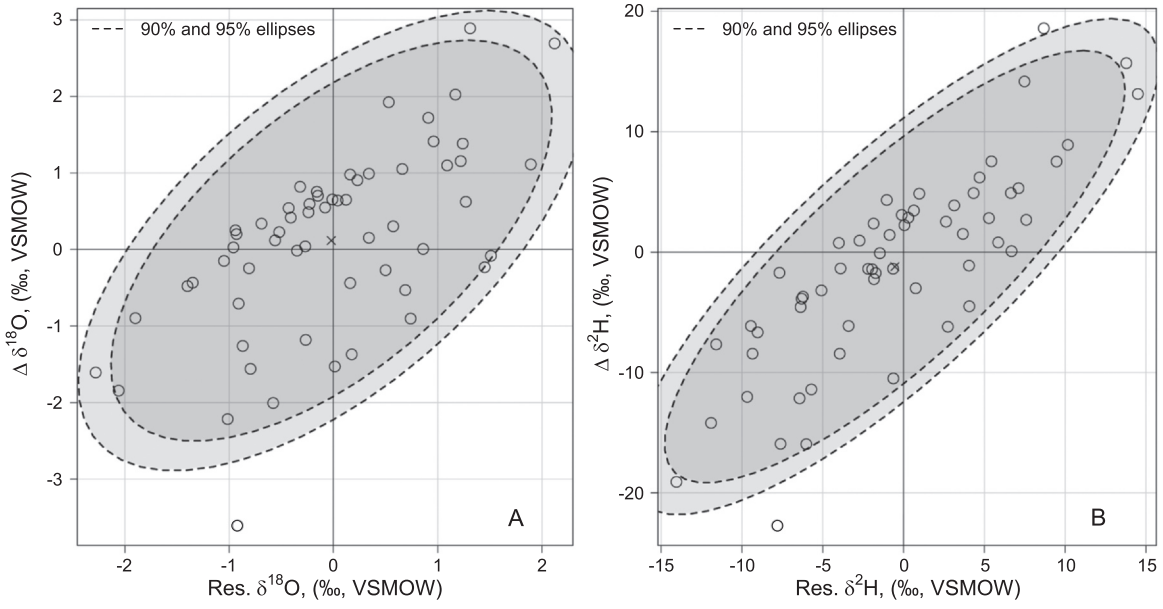

Fig. 5. Covariation of differences between measured and predicted body water isotope values ($\Delta\delta$) and linear regression residuals from Eqs. 3 and 4 for $\delta^{2}H$ and $\delta^{18}O$ values, respectively. $\Delta\delta^{18}O = 0.77 * \delta^{18}O_{res} + 0.13‰$ ($R^2 = 0.38$, $p < 0.005$); $\Delta\delta^{2}H = 1.03 * \delta^{2}H_{res} - 0.66‰$ ($R^2 = 0.67$, $p < 0.005$).

for more than three weeks following a travel. So, for BW10 or any of the other volunteer participants, unreported travels within the recent past could have been influencing water isotope values for several weeks after returning home, particularly if the travel was to a place with significantly different isotope ratios from their place of residence (*e.g.*, Hawaii versus Utah).

As expected, we found that water isotopes values respond primarily to drinking water values with strong correlations, demonstrating that as drinking water varies with geography so does the body water isotopic composition [4,11–15,18]. Although drinking water imparts this primary isotope signature (in this study we estimated that 50% of O and 65% of H signal in body water comes from tap water), not all individuals within a city have the same isotope values despite having the same or very similar tap water isotope values. This is also reflected in the much greater isotopic variation of body water within a city than the variation found in drinking water within the same cities (Table 2). Therefore, within the realm of isotope values expected for a city or municipality, individuals are characterized by isotope values imparted by variables other than drinking water δ-values. In a few cases, individuals deviated significantly from the mean expected for a city (OLS residuals of more than 2‰ for $\delta^{18}O$ and 15‰ for $\delta^{2}H$ were found). Here, we were able to capture a small influence of physical activity and amount of fluid intake on the body water isotope values; note the small, although significant, increase of the coefficients of determination (R^2) in Eqs. (5) and (6) from the simplest regression model including only drinking water isotope values [Eqs. (3) and (4)]. Importantly, all β coefficients of the multiple regressions resulted significantly different from zero (except β_0 for $\delta^{18}O$), suggesting that if drinking water values were kept constant BW values would change according to the significant β factors; for example, if $\delta^{18}O_{dw}$ is kept constant then for each one unit change in fluid intake, $\delta^{18}O_{bw}$ values would decrease 0.36‰, until it reaches the body water values [20].

Although the model with lowest AIC score suggested that average daily activity, average fluid intake, body surface area and intake of local food were important variables in determining body water isotope values, only the first two variables appeared statistically significant. Increased physical activity has a direct influence in the increase of metabolism and therefore in the production of metabolic water, O_2 and CO_2 turnover, and higher perspiration rates, as well as expected increases in fluid intake and food consumption. Therefore, and as detected here, there must be an influence of physical activity on body water isotope values. The amount of fluid intake directly impacts body water. Very large drinking water flux results in body water values resembling drinking water values closely, with extreme cases reaching equal values [20]; this is basically because large inputs of drinking water proportionally dominate all other possible O and H isotope inputs (diet, water vapor, diatomic O_2, etc.). On the contrary, when drinking water flux is reduced, proportionally other sources will become more important in determining the body water isotope signal and they will deviate significantly from water values, likely towards higher values [20]. Even if fluid intake in the form of direct tap water consumption is not particularly large, most bottled drinks (bottled water, soda, chain beer) consumed in the US have local or regional isotope signal [28–30]. Thus, the total fluid intake would have an average regional isotope signal.

Surprisingly, we did not detect an influence of diet on body water values. O'Brien and Wooller [12] suggested that dietary differences might confound geographical interpretation of body water isotope values due to differences in $\delta^{2}H$ and $\delta^{18}O$ values among different food types, particularly between vegetarians and non-vegetarians. We did not quantify the amount of food being consumed, although we did classify (by self-identification) individuals as vegans, vegetarians, or omnivores, and whether or not they bought local food. However, none of these variables showed up as having a statistically significant influence in the individual's isotope values.

One consequence of high inter-individual variation within cities, is that in some regions there was isotopic overlap among cities. We see this pattern primarily in cities within the same state (e.g., Logan and Salt Lake City in Utah; Austin, Uvalde and San Marcos in Texas) and therefore geographically close (e.g., an intercity distance of 225 km between Austin-Uvalde). Therefore, detecting differences between nearby cities might not be feasible.

The unexplained variability found in body water values might be associated with underreported or misreported variables. This could be due to the difficulty of self-quantifying daily activities, such as intensity of physical activity or the extent of fluid consumption. Accurate assessments of physical activity in people living their everyday life are not easy [31,32]. Self-reports of sedentary behavior and exercise are prone to have high interindividual variation [33]; particularly quantifying exercise intensity is problematic due to the differences in the preference for and tolerance of high intensity exercise among people [34–36]. Similarly, estimating fluid intake is challenging as well, with frequency questionnaires and self-reports riddled with biases [37–40]. Therefore, because in our study each participant decided how to estimate the volume of fluid consumed, this could introduce error in the variables used.

4.2. Mechanistic model

This study is the first use of a large dataset to model the natural abundance of human body water isotope ratios. We did not conduct a model parameterization as that was not the aim of the study, rather we applied an already built model [18], to predict body water isotope values, under the primary assumption that all volunteer participants were at an isotopic steady state with local water, and that they accurately reported the information on the required variables. The model was able to capture the total measured isotopic ranges and, with a few exceptions, the model-predicted values were very close to the measured values for each individual; on average they were not statistically distinguishable from each other. The regression lines of the synthetic data against measured values produced slopes and intercepts not significantly different from the 1:1 lines; suggesting that over these large isotope ranges the model is able to predict the true measured value.

The model was not able to reproduce the large deviations found in some participants. Individuals with large measured-predicted differences ($\Delta\delta^{18}O$, $\Delta\delta^{2}H$) tended to have large residuals ($\delta^{18}O_{res}$, $\delta^{2}H_{res}$) as well, suggesting that the reported magnitude of the variables associated with those individuals are not sufficient to produce such isotope values given their drinking water values. It is perhaps in these cases where one can suspect that misreporting of variables (recent travels, amount of fluid intake, physical activity or health conditions) could have a major impact on the results. However, we have no indication that drastic misreporting could have taken place, as the magnitudes of reported variables were similar among individuals. The potential for recent travels was discussed above.

Two of the main assumptions used in the model, perhaps the most significant that are still very difficult to assess, are potential variations in the isotope values of food and food water, both significant inputs to the body water pool. We assumed that during summer collections food values (e.g., vegetables and fruits) would be linked to the local water signal, while during winter collections this might not be the case if fresh foods were imported. There are not many datasets of hydrogen and oxygen isotope values of food available in the US, even fewer linking food and local water isotope ratios. We used the Chesson et al. [27] regression model to link locally available food (ground beef) to local drinking water. Chesson and colleagues [27] show that $\delta^{2}H$ and $\delta^{18}O$ values of ground beef bought in supermarkets were correlated with tap water values, but they also show that no other correlation was significant between food items (bread and potatoes from supermarkets, and hamburger

patty, hamburger bun and French fries from fast food restaurants) and tap water at a city level across the US. Similarly, O'Brien and Wooller [12]detected large and overlapping O and H isotopic ranges in food purchased in supermarkets as distant as Alaska and New York. Furthermore, the authors detected that animal protein had lower isotope values than fruits, vegetables and refined sugars [12]. A similar pattern was found by Chesson and collaborators with animal protein $\delta^{18}O$ values being, on average, lower than hamburger buns and potatoes (French fries) bought at fast food restaurants and bread and potatoes bought at supermarkets, while animal protein $\delta^{2}H$ values were, on average, lower than bread and hamburger buns [27,41]. Given these factors, we conclude that individual dietary choices could explain the intra-city variability and extreme deviations of some individuals seen in the data. A better relationship between food isotope values and geography would improve this mechanistic model.

5. Conclusion

Tissues normally used for human provenancing (teeth, bone, hair, fingernails) acquire their oxygen and hydrogen isotope values from several sources and body pools. Understanding and predicting body water, one of the most important pools, is of uttermost importance. Here we show that community level variation exists in the hydrogen and oxygen stable isotope ratios of body water. The primary drivers are the regional differences in drinking water isotope values. Consistency of the body water isotope composition over the study period suggests that tissues would incorporate a relatively stable isotope signal over time. The amount of drinking water and physical activity influence body water values. The variation in the isotopic values of food (and food water) may contribute to community level variability in body water, but that still remains to be assessed further. While the human body water model used here provides good estimates for measured values, capturing and reproducing the main features of the body water isotope variation across space, some large differences between predicted and measured values remain unexplained. Future research includes further defining the impact that isotopic variation in food and food water has on body water isotope values, by directly measuring food isotope composition.

Our research advances the understanding of human isotope variation across large geographic areas and within communities, thus, aiding in evaluating the potential use of stable isotopes to predict the region of origin of people as well as the capacity to differentiate a migrant isotope value from local signal. We hope this study provides the basis for the incorporation of the presented body water model as an intermediate step in the prediction of the isotopic composition of hard tissues or directly for the prediction of body water or breath water $\delta^{18}O$ and $\delta^{2}H$ values.

CRediT authorship contribution statement

Luciano O Valenzuela: Data curation, Methodology, Formal analysis, Investigation, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Shannon P. O'Grady:** Data curation, Methodology, Formal analysis, Investigation, Writing – review & editing. **James R Ehleringer:** Conceptualization, Funding acquisition, Methodology, Formal analysis, Project administration, Supervision, Writing – review & editing.

Declaration of Interest

The authors declare no conflicts of interests.

Acknowledgments

We acknowledge body water study volunteers for their participation and C. Cook, J. Barnette, L. Enright, and B. Erkkila in the Ehleringer Lab for laboratory assistance.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.forsciint.2021.110990.

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