Isotope Dilution Space Ratio Declines Above the Age of 60, Potentially Impacting Estimates of Total Energy Expenditure by the Doubly Labeled Water Method[1-3, *, ^]

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[3] Abbreviations used: BMI, body mass index; rCO_2, carbon dioxide production rate; DLW, doubly labeled water; FFM, fat free mass; FM, fat mass; k_D, fractional turnover rate of ^2H; k_O, fractional turnover rate of ^{18}O; N_D, isotope dilution space of ^2H; N_O, isotope dilution space of ^{18}O; DSR, isotope dilution space ratio; TBW, total body water; TEE, total energy expenditure.

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Running title: **Isotope dilution space ratio for the doubly labeled water method**

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Abstract

Background: Doubly labeled water is the gold standard method for measuring free-living total energy expenditure (TEE). Measurements using the method are sensitive to the isotope dilution space ratio (DSR). Based on the International Atomic Energy Agency Doubly Labeled Water database with 6,787 measurements, we recently derived an equation based on DSR of 1.036 because it improved the accuracy and precision of the TEE values with indirect calorimetry.

Objectives: Accuracy and precision of the method might be improved if we could identify factors influencing DSR. We evaluated the potential effects of age, sex, race/ethnicity, anthropometry, body composition, fractional turnover rates of the isotopes, body composition, geographical location and elevation on DSR.

Methods: After removing DLW studies with missing study data and DSR outliers (> 2 SDs from mean), we used simple regression analysis to explore the relationships between the continuous variables and analysis of variance to test the relationships between the categorical variables with DSR. Subsequently, we used General Linear Modeling and One-way ANOVA to evaluate the simultaneous effect of age, sex, race, fat-free mass (FFM) and fat mass (FM) on DSR.

Results: Based on 5,124 measurements of subjects aged between 0.02 and 96 y with 65.8% females compiled from studies around the world with diverse race/ethnicity representation and at various elevations, the average DSR was 1.0363 ± 0.011 (mean ± SD). No meaningful physiological effect of any of the continuous and categorical variable on DSR was detected based on simple regression analysis or analysis of variance. General Linear Model analysis revealed no effect of FFM and FM ($P > 0.33$) on DSR, but DSR decreased with age ($P < 0.001$) among those older than 60 years of age regardless of sex. DSR was on average 0.0032 unit lower among the older Asians when compared to the Caucasians, but not among the other races.

Among the Caucasians who were younger than 60 years of age, DSR was not related to FFM and FM (P = 0.73) but affected by both age and sex (P < 0.001). DSR was significantly lower by 0.0032 units among Africans but significantly higher by 0.0033 unit among African Americans when compared to Caucasians (P < 0.001).

Conclusion: Although body composition might in theory be expected to impact DSR, we showed that FFM and FM had no effect on DSR. There was also no impact of sex. However, above the age of 60, DSR declined. Previous estimates of age-related decline in TEE, which used a DSR of 1.036, may have underestimated 5% decrease in TEE at age 90 when compared to updated age-specific DSR values determined in this study. We suggest using the derived equations here to estimate DSR to calculate TEE in subjects aged over 60. Validation studies on older subjects are required to confirm these alternative equations.

Introduction

The doubly labeled water (DLW) method is considered to be the reference method for the measurement of total energy expenditure (TEE) in humans under free-living conditions (1-8) The method has been validated in and applied to small mammals with specific metabolic rates (1-4) which are at least 3-fold higher than those of premature infants and at least 5-fold higher than adults. The dilution spaces of the two isotopes however are not identical and slightly larger than total body water due to exchange with or sequestration of the isotopes in non-aqueous components of the bodies. The proportion of these isotopes entering into non-aqueous components of the bodies has been estimated to be 4.3 % for deuterium (^{2}H) (5) and 0.7% for oxygen-18 (^{18}O) (6).

Error in the estimation of the isotope dilution spaces and hence the isotope dilution space ratio (DSR) as defined as the dilution space of ^{2}H (N_D) divided by the dilution space of ^{18}O (N_O), lead to significant errors in the calculated carbon dioxide production (rCO_2) and TEE calculations (5, 7). The variation in DSR can stem from technical factors such as incomplete reduction of the sample to hydrogen gas during sample preparation, memory effects between samples during isotope ratio measurements, using speciments not attaining the equilibrium values when the plateau method is used to estimate the isotope dilution spaces, or physiological differences. Based on the data from the International Atomic Energy Agency (IAEA) DLW Database, we recently proposed a DSR of 1.036 to be applied to the equation for the calculation of rCO_2 because it produced the most accurate and precise rCO_2 values when applied across 61 individuals from six adult validation studies of the DLW method against indirect calorimetry (8-14). Because DSR depends on the extent of exchange of the isotopes onto non-aqueous components of the body, variations in these components might explain some of the individual to individual difference in DSR. Hence understanding how different factors are related to DSR is useful but the potential effects of age, sex, body mass index (BMI), race/ethnicity, body water content, body composition, turnover rates of the isotopes, as well as the geographical location and elevation of the study sites on DSR have not been previously evaluated in adults. If the predicted DSR can be refined, this may help improve precision of the DLW method. In this paper, using the data available in the IAEA DLW Database, we tested the potential effects of several continuous and categorical variables on DSR.

Participants and Methods

Database and study participants

The IAEA DLW Database version 3.1 was used in the analysis. The database consisted of 6,787 DLW measurements from 112 studies carried out in 25 countries with the United States accounting for the majority of the studies. After removing measurements with incomplete data such as age, basic anthropometric measurements, DLW primary outcome variables such as fractional turnover rates of the isotopes and DSR, negative percentage of fat mass, and studies with DSR outliers (>2SD from the mean), we ended up with 5,124 DLW studies. The demographic, physical characteristics, DLW parameters, body composition, geographic locations and study site elevations of the 5,124 DLW studies are summarized in **Table 1**. Across the included measurements, the mean DSR value was 1.0363 (SD = 0.011). Therefore, any DSR values below 1.0114 or above 1.0613 were considered outliers and were excluded from the statistical analyses.

Statistical methods

Initially, simple linear regression analysis and scatter plots were used to evaluate the relationship between DSR and the continuous variables. Analysis of variance and histograms were used to evaluate the relationship between DSR and the categorical variables. Subsequently, we used the GLM to assess the relationships between DSR and multiple variables simultaneously. To avoid generation of many complex interactions with minor effects, we limited the included continuous variables to sex, age, fat-free mass (FFM) and fat mass (FM). We excluded latitude, longitude and altitude. With Caucasians accounting for 4-17 times more data than the other racial groups, GLM analysis including all racial groups in the model would generate artificial outcomes because of the highly unbalanced racial distrituion. Therefore, the GLM analysis was performed initially among Caucasians. The dervived model was then used to predict TEE for other groups and deviations from the model evaluated via one-way ANOVA to determine if the same relationships apply to the other racial groups. All statistical analyses including descriptive statistics, scatter plots and histograms were done using the SPSS Statistics program, version 27 (IBM Corporation, 1 New Orchard Road, Armonk, NY). A P value $\leq$ 0.05 was considered significant.

Results

As shown in **Table 1**, the study population consisted of 3,371 females and 1,753 males aged between 0.02 y and 96 y, most of which (55%) were Caucasians. Study subjects with mixed race/ethnicity were classified as Other whereas those with unknown race/ethnicity were classified as Unknown. These two groups were excluded from the analysis of variance with DSR. The study subjects weighed between 2.6 and 174.1 kg with height between 47 and 204 cm. The median BMI of the study subjects was 24.4 kg/m^2. For the primary DLW outcome variables, the fractional turnover rates of ^{18}O (k_O) and ^{2}H (k_D) were 0.1283 ± 0.046 d^{-1} (mean ±

SD) and 0.1004 ± 0.041 d^{-1}, respectively and the isotope dilution spaces of ^{18}O and ^{2}H were 1745.4 ± 604.8 mol and 1808.5 ± 626.7 mol, respectively. The DSR of the 5,124 study subjects was 1.0363 ± 0.011 (mean ± SD). The percentage of TBW relative to body weight ranged between 21.8% to 74.1% with an average value of 49.1± 8.0% (mean ± SD). The latitudes and longitudes of the study sites reflected the diversity of the study population in 25 countries. In terms of altitude, a single measurement was carried out at an elevation of 7,490 m above sea level with complete data.

Effects of age, anthropometry, body composition, DLW parameters, altitude and geographical locations on DSR by simple regression analysis and scatter plots

The effects of age, anthropometry, BMI, DLW primary outcome parameters, body composition, study locations, and study site elevations on DSR by simple regression analysis were summarized in **Table 2**.

As shown in **Table 2**, age, body weight, height, k_O, k_D, N_O, N_D, total body water (TBW), and FFM had no effect of DSR with *P* values ranged between 0.15 and 0.90. BMI, percentage of TBW, percentage of fat mass (FM), latitude, longitude and altitude all appeared to have a significant effect on DSR with *P* values between <0.001 and 0.03. However, the regression coefficients of these continuous variables were all around 10^{-5} to 10^{-6} suggesting that the significance relationship between these continuous variables and DSR was detected simply because of the large sample size. For example, the BMI coefficient indicated that a one unit increase in BMI was associated with a 6.189×10^{-5} (0.00006189) increase in DSR. Therefore, a 10-unit increase in BMI is associated with a 0.0006189 increase in DSR which is only 0.06 of one DSR standard deviation (0.011). The same argument can be applied to percentage of TBW, percentage of FM, latitude, longitude and altitude. The lack of significant effects of these

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continuous variables on DSR is best illustrated by the scatter plots of DSR as shown in **Figure 1** against age (panel A), BMI (panel B), percentage of TBW (panel C), percentage of FM (panel D), k_O (panel E), latitude (panel F), longitude (panel G) and altitude (panel H). Similar scatter plots (not shown) were observed for body weight, height, TBW, k_O, k_D, N_O, N_D, and FFM.

Effects of sex and race/ethnicity on DSR by analysis of variance and histogram

The differences in DSR values were very minor between males and females (**Table 3**) with an overall value of 1.0363. The relationship again was best illustrated by the histogram as shown in **Figure 2 (panel A)**.

The relationship between DSR and race/ethnicity by analysis of variance was summarized in **Table 4** and illustrated graphically in **Figure 2 (panel B)**. As shown in **Table 4**, the differences in DSR values of the African Americans, Hispanics, Asians, and Africans were not significant when compared to the DSR value of the Caucasians, who comprised the majority of the study population.

Effects of age, sex, race, FFM and FM on DSR by GLM

A scatter plot (**Figure 3 panel A**) between DSR and age among Caucasians showed a drop off in DSR values beginning at age 60 years. Limiting the data to those 60 years of age and older clearly demonstrated the linear relationship between age and DSR (**Figure 3 panel B**). Among those who were 60 years of age and older, a GLM analysis of DSR with age, sex, FFM and FM yielded no significant 2-way interactions ($P = 0.15\text{-}0.78$). Other than age ($P < 0.001$), none of the other variables including sex, FFM and FM had any significant effect ($P = 0.33\text{-}0.72$) on DSR. The analysis showed that among Caucasians who were older than 60 years of age, DSR decreased with age ($DSR = 1.077 – 0.000562 \times Age$) regardless of sex. For example, at age 70, DSR was 1.038, decreased to 1.032 at age 80 and was 1.026 at age 90. Based on the average DLW parameters for people who were 70, 80 and 90 years of age in the database, using an age-adjusted DSR value would reduce TEE for those who were 70 years of age by 13 kcal/d (0.6%) but increased TEE by 37 kcal/d (1.7%) for those who were 80 years of age and by 64 kcal/d (3.7%) among those who were 90 years of age, compared with the unadjusted values. This suggests the earlier detected impact of age above 60 on TEE is partially due to an artefact of assuming a constant DSR in the calculation. Using these figures and the observed decline, we estimate the contribution of this age related DSR effect was 2% of the observed decline in TEE with age.

When we applied the DSR equation dervived from the Caucasians who were 60 years of age and older to individuals of other races in the same age range, only Asians (n = 168) had an average DSR value which was 0.0032 unit lower (P=0.002) than the predicted value for the older Caucasians. Using the age-adjusted DSR values with the offset for the older Asians, TEE would be increased by 58 kcal/d (3.3%) among older Asians when compared to using the average DSR value of 1.0363. The increase was calculated to be 17 kcal/d (0.7%) at age 70, 61 kcal/d (2.8%) at age 80, and 96 kcal/d (6.3%) at age 90. Since the age effect on DSR among older Hispanics, Africans and African Americans was similar to older Caucasians, the effects of the age-adjusted DSR values on TEE are anticipated to be similar to those observed among older Caucasians as mentioned above. When all the older adults including the Asians were combined, using the age-adjusted DSR values, rather than a single value of 1.0363, would lead to a change in TEE by 1.7 kcal/d (0.1%) at age 70, 49 kcal/d (2.3%) at age 80, and 80 kcal/d (5.0%) at age 90.

Among Caucasians who were younger than 60 years of age (**Figure 3, panel C**), a GLM analysis showed that DSR was significantly related to age ($P < 0.001$) just like the older population but the relationship depended on sex (DSR_{Male} = 1.04188 – 0.000139 x age or DSR_{Female} = 1.03665 – 0.00033 x age, *P* < 0.001). Again, neither FFM nor FM had any effect on DSR (*P* = 0.128-0.727). Among the younger Caucasians between 1 and 50 years of age, using the DSR values adjusted for age and sex would lead to an average change in TEE by 25 kcal/d (0.9%) when compared to TEE calculated based on a DSR value of 1.0363.

When the female Caucasian equation was applied to the younger female population in the other racial groups, one-way ANOVA showed that DSR was significantly lower by 0.0026 unit among female Africans (n = 297) but significantly higher by 0.0033 unit among female African Americans (n = 373) when compared to Caucasians (*P* < 0.001). Similar offsets were observed among the younger male Africans (-0.0032, n = 449) and male African Americans (0.0033, n = 496) when compared to Caucasians. When the age-adjusted DSR value along with the race-dependent offsets were applied to the younger Africans and African Americans, TEE was increased on average by 101 kcal/d (4.7%) among Africans and by 32 kcal/d (1.7%) among African Americans when compared to TEE calculated using a single DSR value of 1.0363.

Discussion

There has been a long debate on whether a single DSR value should be applied to DLW studies. In 1985, Schoeller *et al* reported a mean DSR value of 1.034 ± 0.016 (15). In a subsequent publication in 1988, Schoeller further suggested that using a fixed relationship of DSR would reduce the coefficient of variation in the rCO_2 and TEE calculations in the DLW method (16). Based on 107 adult studies, Coward reported in 1990 a mean DSR value of 1.034 but a slightly higher DSR value of 1.035 based on 136 infant studies (17). In a validation study against indirect calorimetry based on 12 adult subjects in 1991, Ravussin *et al* reported an average DSR value of 1.049 (10). In 1992, based on studies on 18 obese adults, 13 elderly, 11 young men and 13 young children, Goran *et al* reported an average DSR value of 1.05 and the DSR value was not affected by body composition or age (18). The lack of effect of body composition on DSR in these previous studies is potentially because they were grossly underpowered. The study here based on >5000 measurements however supports these earlier findings. In 1993, based on 161 published measurements, Speakman *et al* recommended the use of a single DSR value of 1.0427 in DLW studies and estimated that approximately 19% of the variability of DSR was accounted for by analytical imprecision in isotopic assays (5). This sentiment was echoed by Coward *et al* (19). In 1994, based on 99 DLW measurements of 85 females and 14 males between 4 and 78 years of age but with isotope ratio measurements all carried out in a single mass spectrometry laboratory, Racette *et al* again reported a DSR value of 1.034 (20). These authors further indicated that the variance in DSR value was due primarily to analytical error in ^{2}H analyses and incomplete isotope equilibration due to timing of sample collection and was not related to age or body fat. Based on 44 studies with sample size ranging between 4 and 136 subjects and from premature infants to older adults, the DSR value was found to range between 1.0006 and 1.056 (21). These authors also attributed the large variance in DSR value was due primarily to sample preparation for ^{2}H analyses.

In a theoretical paper, Matthews *et al* were able to demonstrate that using the average of two isotope dilution spaces rather than a single dilution space value would limit the effect of pool size error in the calculation of TEE and that technical errors imposed significant errors in the measurements of the two isotope dilution spaces (7). Based on 2297 DLW studies on subjects between 0.25 and 89 years of age, Sagayama *et al* reported an average DSR value of 1.0374 and that the DSR value was not affected by age, sex and BMI (22). The lack of effect of BMI on

DSR is in agreement with our finding in this larger dataset. Since the isotope ratio measurements in Sagayama et al were all done in a single mass spectrometry laboratory, these authors further reviewed 103 DLW publications with subjects ranging from 1 to 80 years old and found an average DSR value of 1.036. Because the isotope ratio measurements of these DLW studies were carried out by multiple mass spectrometry laboratories, these authors recommended that a DSR value of 1.036 should be adopted. However, after removing studies with missing study data and DSR outliers in the 2297 DLW studies reported by Sagayama *et al* which are included in the DLW database, we found an average DSR value of 1.0359 which was not statistically different (*P* = 0.13) from the DSR value of 1.0363 calculated from the other DLW studies in the DLW database.

Although DSR was independent of body composition, it did decline with age among Caucasians, Hispanics, African Americans, Asians and Africans who were older than 60 years of age, with no difference between males and females. In a recent study using this DLW database (23), energy expenditure was found to decline with age among older adults at 0.7% per year with energy expenditure among adults in their nineties up to 26% below that of middle-age adults when a single DSR value was used in the calculation of energy expenditure. Based on the present study, we suggest that part of this effect was an artefact of not accounting for the declining DSR with age. However, the age-related decline in energy expenditure after 60 y reported by Pontzer cannot be entirely an artefact of DSR, because using a single DSR value would not be able to account for the 26% decline in energy expenditure among adults in the nineties. Of course, the over and underestimation of energy expenditure reported here using the age- and sex-adjusted and race-dependent offset were calculated using available DLW parameters at each age group.

A limitation of this analysis is sample size diminished substantially among non-Caucasian racial groups. The sample size within each age group also significantly reduced particularly among the non-Caucasian racial groups. For example, there were only three Asians (1 female and 2 males) in their nineties in the database. For the young population, among the 50-y-old, there were only 7 Africans (1 male and 6 females) and 26 African Americans (2 males and 24 females). Among the 10-y-old, there were 10 Africans (4 males and 6 females) and 23 African Americans (7 males and 16 females). There were no 5-y-old Africans and no 1-y-old Africans and African Americans in the database.

Both ^{2}H and ^{18}O isotopes are known to be sequestered or exchanged with the hydrogen and oxygen isotopes on non-aqueous components of FFM or FM. For example, ^{2}H is known to be sequestered into adipose tissues (24), incorporated into cholesterol during *in vivo* cholesterol syntheseis (25), and exchanged with the labile hydrogen atoms on amino acids (7). The ^{18}O isotopes can exchange with exchangeable oxygen atoms in bone carbonate and tissue phosphate (6). However, these isotope exchanges or sequestration have been estimated to be very small, approximately 4% for ^{2}H and 0.7% for ^{18}O (16), totally insignificant when compare to FFM or FM. Therefore, the lack of effect of FFM and FM on DSR is not surprising.

Conclusion

In conclusion, DSR was affected by age, sex, and race/ethnicity with no effect of FFM and FM. Using the age- and sex-adjusted DSR values along with the race-dependent offsets led to an average increase of TEE by 52 kcal/d (2.4%) when compared to TEE calculated using the average DSR value of 1.0363. When compared to the actual average TEE values at each age group between 20 and 90 years of age, the overestimation of 52 kcal/d amounted to an average deviation of 2.1 ± 0.5% of the average measured TEE value. Among the infants and children under 10 years of age, TEE increased by 4.2 ± 1.9% of the average measured TEE value. This is anticipated because of the much lower absolute TEE values among the infants and children. With the minimal effect on the absolute TEE values due to effects of age, sex and race on the DSR value, we recommend that the DSR value of 1.036 as proposed in our earlier report (26) be universally adopted to all DLW studies among study participants who are under 60 years of age to minimize potential errors in rCO_2 and TEE calculations associated with errors introduced by using other unvalidated DSR values, sample preparation and analysis. For DLW studies among study participants who are older than 60 years of age, the DSR values should be adjusted as shown in this study to optimize the accuracy of the TEE measurements. However, additional DLW studies on the elderly are needed to confirm the age effect on DSR values.

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TABLE 1 Demographic, physical characteristics, DLW parameters, body composition, study locations, and study elevations of the 5,124 participants in the IAEA DLW Database. The data excluded studies with missing and unphysiological data.[1]

	n (%)	Mean	SD	Median	Minimum	Maximum
Age, y		42.0	25.0	41.0	0.02	96.0
Sex						
Male	1,753 (34.2)					
Female	3,371 (65.8)					
Race/ethnicity						
White	2,816 (55.0)					
African American	692 (13.5)					
Hispanic	201 (3.9)					
Asian	278 (5.4)					
African	399 (7.8)					
Other	174 (3.4)					
Unknown	564 (11.0)					
Weight, kg		65.8	24.8	67.4	2.6	174.1
Height, cm		158.0	25.1	163.9	47.0	204.0
BMI, kg/m^2		25.0	6.4	24.4	10.9	57.1
k_O, d^{-1}		0.1283	0.0460	0.1182	0.0525	0.5779
k_D, d^{-1}		0.1004	0.0407	0.0915	0.0367	0.5324
N_O, mol		1745.4	604.8	1759.5	80.5	4037.7

N_D, mol	1808.5	626.7	1824.0	84.5	4110.6
DSR	1.0363	0.0110	1.0364	1.0114	1.0613
TBW, mol	1731.9	600.1	1,747.2	80.4	3971.6
TBW, %	49.1	8.0	48.7	21.8	74.1
FFM, kg	42.6	14.8	43.0	2.0	97.7
FM, %	33.0	10.8	33.6	0.4	70.1
Latitude, deg of arc	35.5	16.3	38.6	-34.0	63.8
Longitude, deg of arc	-56.4	58.8	-77.1	-123.1	135.8
Altitude, m	184	339	97	0	7490

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[1] BMI, body mass index; DLW, doubly labeled water; FFM, fat free mass; FM, fat mass; k_D, fractional turnover rate of ^{2}H; k_O, fractional turnover rate of ^{18}O; IAEA, International Atomic Energy Agency; N_D, isotope dilution space of ^{2}H; N_O, isotope dilution space of ^{18}O; DSR, isotope dilution space ratio; TBW, total body water.

TABLE 2 Effects of age, anthropometry, BMI, DLW primary outcome parameters, body composition, study locations, and study elevations on the isotope dilution space ratio (DSR) by simple regression analysis.[1]

Variables	Coefficient	*P*
Age, y	-6.977×10^{-6}	0.26
Weight, kg	8.986×10^{-6}	0.15
Height, cm	-2.032×10^{-6}	0.74
BMI, kg/m^2	6.189×10^{-5}	0.01
k_O, d^{-1}	0	0.90
k_D, d^{-1}	-0.002	0.52
N_O, mol	-3.793×10^{-7}	0.14
N_D, mol	1.773×10^{-7}	0.47
TBW, mol	-9.877×10^{-8}	0.70
TBW, %	-6.989×10^{-5}	<0.001
FFM, kg	-3.839×10^{-6}	0.71
FM, %	5.116×10^{-5}	<0.001
Latitude, deg of arc	2.288×10^{-5}	0.02
Longitude, deg of arc	-5.676×10^{-6}	0.03
Altitude, m	1.271×10^{-6}	0.01

[1] BMI, body mass index; FFM, fat free mass; FM, fat mass; k_D, fractional turnover rate of ^2H; k_O, fractional turnover rate of ^{18}O; N_D, isotope dilution space of ^2H; N_O, isotope dilution space of ^{18}O; TBW, total body water.

TABLE 3. Analysis of variance between DSR and sex.[1]

Sex	**n**	**DSR (mean ± SD)**	**95% CI**	***P***
Female	3,371	1.0362 ± 0.0111	1.0359 – 1.0366	0.72
Male	1,753	1.0363 ± 0.0109	1.0358 – 1.0369	
Total	5,124	1.0363 ± 0.011		

[1] DSR, isotope dilution space ratio.

Figure legends

Figure 1. Scatter plots of isotope dilution space ratio (DSR) against age (panel A), body mass index (BMI, panel B), percentage of total body water (%TBW, panel C), percentage of fat mass (%FM, panel D), fractional turnover rates of ^{18}O (k_O, panel E)), latitude (panel F), longitude (panel G) and altitude (panel H). The dotted line in each figure panel represented the mean DSR value of 1.0363.

Figure 2. Histograms of isotope dilution space ratio (DSR) versus sex (panel A) and race/ethnicity (panel B). The dashed lines represented the mean DSR value of 1.0363.

Figure 3. Scatter plots of isotope dilution space ratio (DSR) versus age among Caucasians. Panel A represents data from all Caucasians regardless of age. Panel B represents data from Caucasians who were 60 years of age and older. Panel C represents data from Caucasians who were younger than 60 years of age. The solid upside down triangles in each panel denote the data from females where as the open circles denote the data from males. The dotted lines in each panel represent the regression lines for the females and the solid lines represent the regression lines for the males.

FIGURE 1.

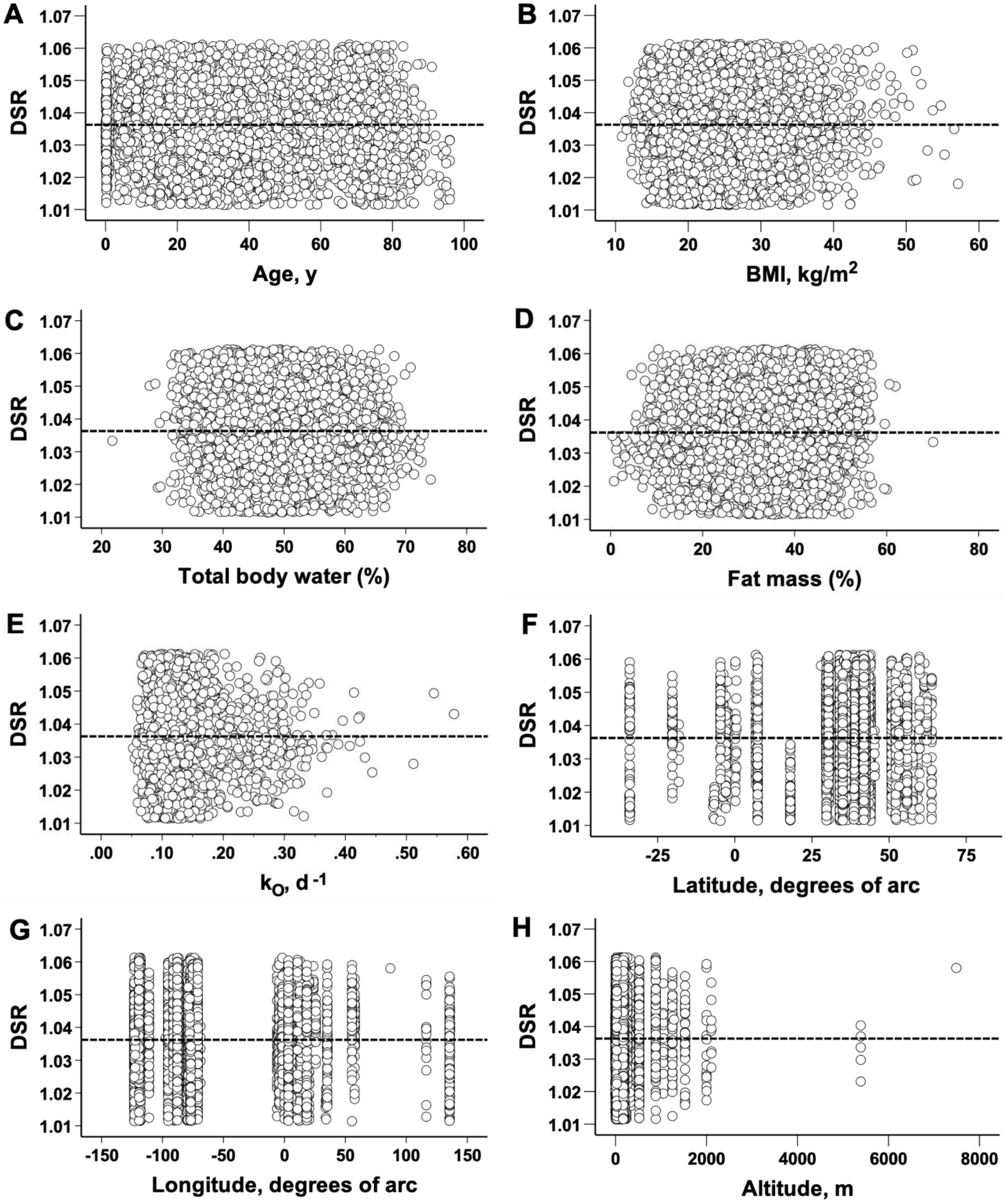

A
DSR
1.07
1.06
1.05
1.04
1.03
1.02
1.01
0
20
40
60
80
100
Age, y
B
DSR
1.07
1.06
1.05
1.04
1.03
1.02
1.01
10
20
30
40
50
60
BMI, kg/m^2
C
DSR
1.07
1.06
1.05
1.04
1.03
1.02
1.01
20
30
40
50
60
70
80
Total body water (%)
D
DSR
1.07
1.06
1.05
1.04
1.03
1.02
1.01
0
20
40
60
80
Fat mass (%)
E
DSR
1.07
1.06
1.05
1.04
1.03
1.02
1.01
.00
.10
.20
.30
.40
.50
.60
k_O, d^{-1}
F
DSR
1.07
1.06
1.05
1.04
1.03
1.02
1.01
-25
0
25
50
75
Latitude, degrees of arc
G
DSR
1.07
1.06
1.05
1.04
1.03
1.02
1.01
-150
-100
-50
0
50
100
150
Longitude, degrees of arc
H
DSR
1.07
1.06
1.05
1.04
1.03
1.02
1.01
0
2000
4000
6000
8000
Altitude, m

FIGURE 2.

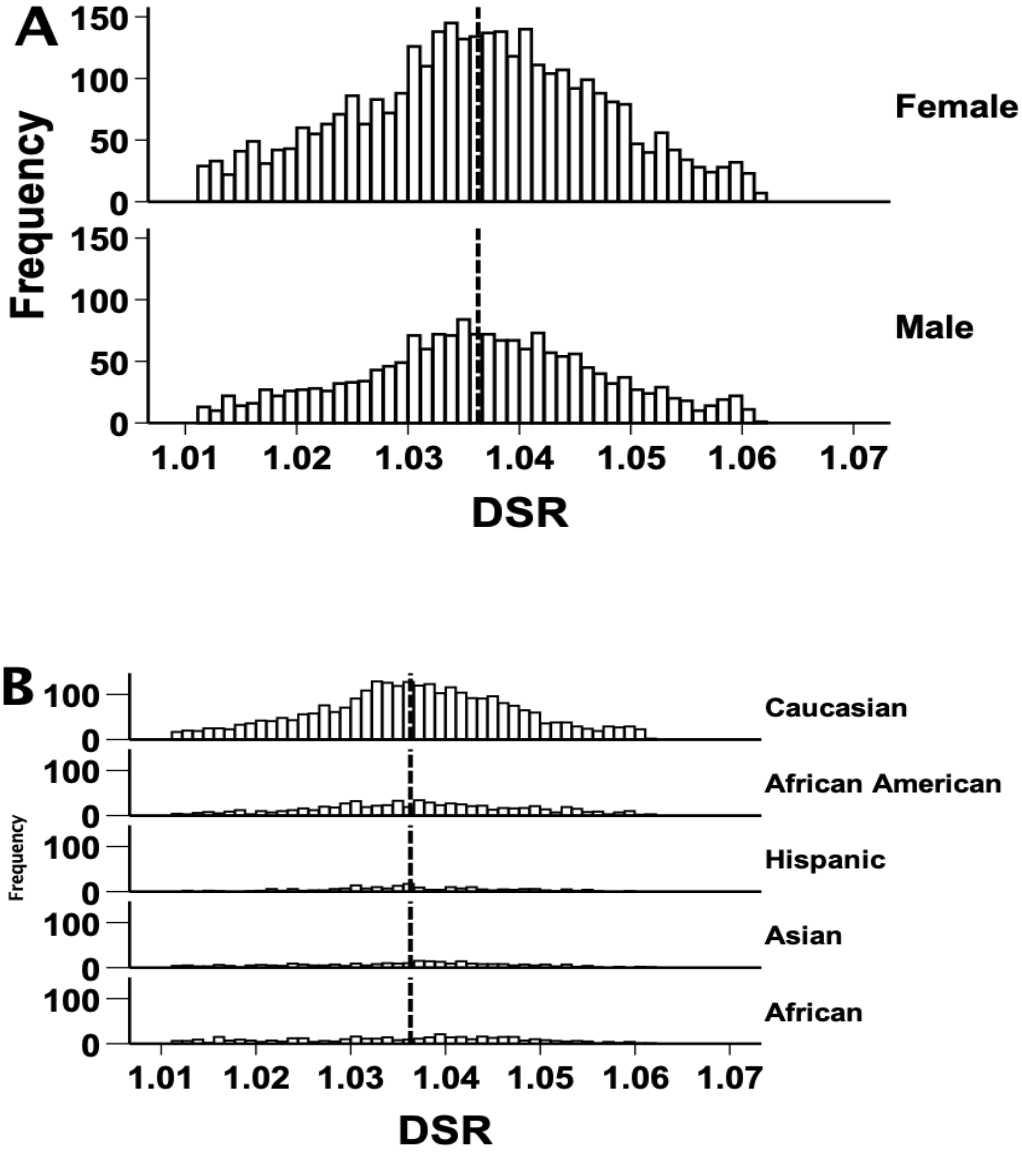
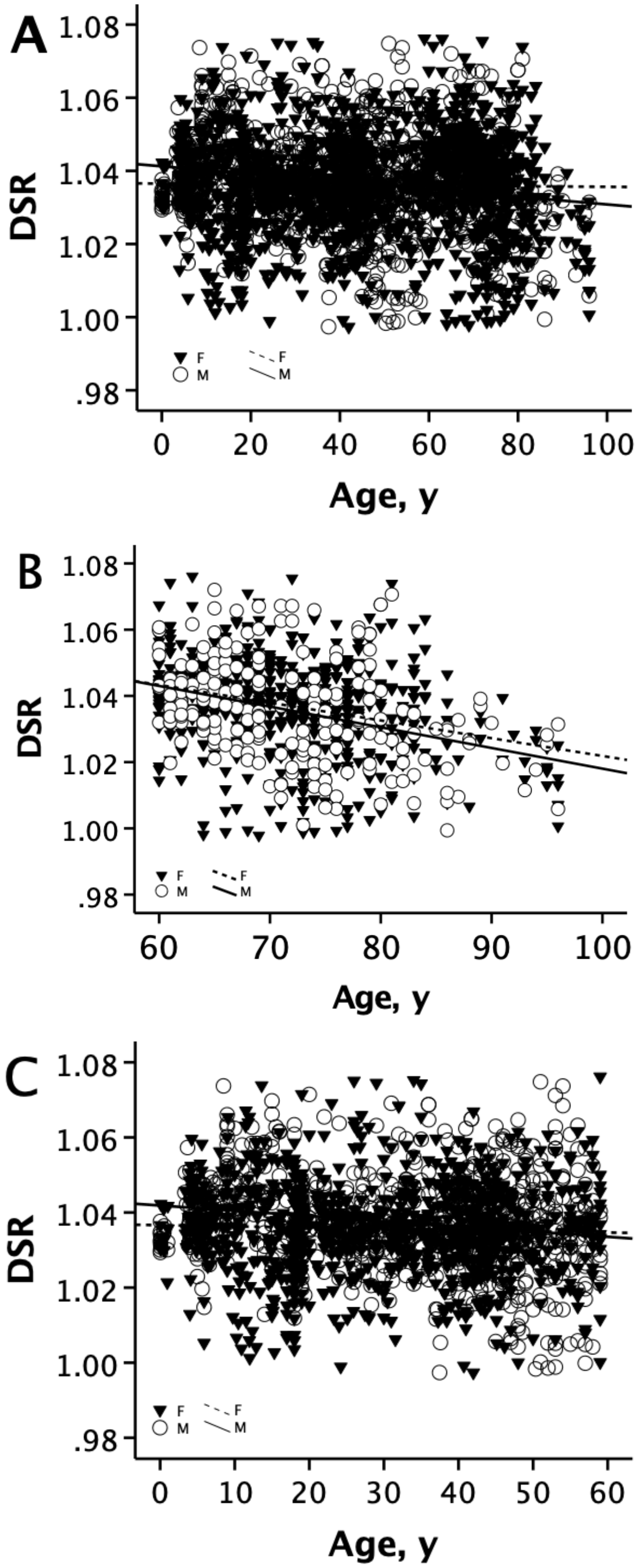

A
150
100
50
0
Frequency
Female
150
100
50
0
Male
1.01
1.02
1.03
1.04
1.05
1.06
1.07
DSR
B
100
0
Caucasian
100
0
African American
Frequency
100
0
Hispanic
100
0
Asian
100
0
African
1.01
1.02
1.03
1.04
1.05
1.06
1.07
DSR

FIGURE 3


A
1.08
1.06
1.04
1.02
1.00
.98
DSR
0
20
40
60
80
100
Age, y
F
M
F
M
B
1.08
1.06
1.04
1.02
1.00
.98
DSR
60
70
80
90
100
Age, y
F
M
F
M
C
1.08
1.06
1.04
1.02
1.00
.98
DSR
0
10
20
30
40
50
60
Age, y
F
M
F
M