Individuality of the plasma sodium concentration

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1Division of Nephrology and Hypertension, Department of Medicine, Oregon Health and Science University, Portland, Oregon; Oregon Health and Science University, Portland, Oregon; 2The Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon; and 3Department of Biostatistics, Brown University School of Medicine, Providence, Rhode Island; 4Division of Pulmonary and Critical Care Medicine, Department of Medicine, Oregon Health and Science University, Portland, Oregon; 5Section of Nephrology, Portland Veterans Affairs Medical Center, Portland, Oregon; 6Department of Biostatistics, Brown University, Providence, Rhode Island; and 7Health Service Research and Development, Portland Veterans Affairs Medical Center, Portland, Oregon

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Zhang Z, Duckart J, Slatore CG, Fu Y, Petrik AF, Thorp ML, Cohen DM. Individuality of the plasma sodium concentration. Am J Physiol Renal Physiol 306: F1534–F1543, 2014. First published April 9, 2014; doi:10.1152/ajprenal.00585.2013.—Older literature has suggested that the plasma sodium concentration is not individual, that it is neither intrinsic to an individual nor reproducible, longitudinally. We recently observed that the plasma sodium concentration is heritable. Because demonstrable heritability requires individuality of the relevant phenotype, we hypothesized that the plasma sodium concentration was substantially individual. In two large health plan-based cohorts, we demonstrated individuality of the plasma sodium concentration over a 10-yr interval; the intraclass correlation coefficient (ICC) averaged 0.4–0.5. The individuality of plasma sodium increased significantly with age. Plasma sodium individuality was equal to or only slightly less than that for plasma glucose but was less than the individuality for creatinine. The individuality of plasma sodium was further confirmed by comparing the Pearson correlation coefficient for within-individual versus between-individual pairs of sodium determinations and via application of the agreement index. Furthermore, the distribution of all sodium determinations for all participants within a population was similar to the distribution for the mean sodium concentration for individuals within that population. Therefore, the near-normal distribution of plasma sodium measurements within a population is likely not attributable to assay-specific factors but rather to genuine and durable biological variability in the osmotic set point. In aggregate, these data strongly support the individuality of the plasma sodium concentration. They further indicate that serial plasma sodium values for any given individual tend to cluster around a patient-specific set point and that these set points vary among individuals.

Human; hyponatremia; osmoregulation; population

Disorders of systemic water balance are reflected in abnormalities of the serum sodium concentration. Hyponatremia is prevalent among the acutely ill (41), among patients undergoing surgery (1), and among the elderly (2, 19). Hyponatremia commonly complicates congestive heart failure and chronic liver disease (11, 16, 24, 40) and is seen in a substantial percentage of patients treated with thiazide diuretics, antidepressants and antipsychotic medications, and other agents (12, 25, 38). Hyponatremia associates with increased mortality (6, 23), and even subtle abnormalities in water balance cause reversible defects in coordination, balance, and cognition (32, 36). Furthermore, hyponatremia can be extremely challenging to treat (12, 22, 44). Therefore, maintenance of water balance is clinically important.

Apart from the extremes of serum sodium concentrations (profound hypo- and hypernatremia), the individuality of this phenotype has received comparatively little attention. Individuality in this context refers to the degree to which a phenotype is reproducible and specific to an individual; for example, adult height is highly individual (varying little over serial determinations), whereas arterial blood pressure is less so. Patients with Mendelian disorders affecting genes encoding key water balance proteins exhibit a serum sodium concentration that is consistently reduced (or elevated) (10, 13, 27, 29, 34, 42). Outside these extremes, it is unclear whether an individual’s plasma sodium concentration is to any extent intrinsic to him or her or whether it fluctuates in a more or less stochastic fashion within the broadly defined normal range of plasma sodium concentrations.

Older literature has referred to a lack of individuality of the plasma sodium concentration (8, 17, 31, 43, 45). Specifically, the intraindividual variation in sodium concentration upon repeated determinations from a single individual was believed to obscure any interindividual variation.

Our anecdotal experiences suggested that even within the normal range, there is a degree of individuality to the plasma sodium concentration. With the advent of electronic medical records and the attendant ease of graphing laboratory values, it was notable that an isolated “low” or “high” plasma sodium concentration, which might otherwise be ignored, often occurred in the context of many near-abnormal values (e.g., Fig. 1A). That is, at least some otherwise well patients, in the absence of overt dysnatremia, appeared to have a sodium concentration “set point” toward either extreme of the normal range (Fig. 1B). We also inferred individuality of the plasma sodium concentration from our recent demonstration of the heritability of the serum sodium concentration across various ethnicities (46) and from a functional genetic polymorphism in a putative water balance gene that associated with the plasma sodium concentration on a population-wide basis (39). Specifically, were there to be no individuality of the plasma sodium concentration, it would not have been possible for us to observe either heritability or genetic association. Individuality needn’t imply heritability of a phenotype; however, demonstration of heritability requires individuality. Therefore, despite earlier published reports to the contrary obtained in small sample sizes, we hypothesized that...
the plasma sodium concentration would exhibit significant individuality when examined on a population-wide basis.

MATERIALS AND METHODS

Cohorts Investigated

Plasma sodium concentration determinations for a recent 10-yr window were retrieved for all cohort members. Filters were applied to reduce the impact of clinical variables that could confound the relationship between plasma sodium concentration and systemic osmoregulation or of disease states that could otherwise independently affect systemic osmolality. To reduce the impact of acute illness (e.g., hypovolemia, systemic infection, etc.), inpatient sodium determinations were excluded. Similarly, for any pair of determinations occurring within 7 calendar days (as might occur with acute illness or in response to an unexpected abnormality in laboratory value), both determinations were excluded. Participants with congestive heart failure, abnormal kidney function, or liver disease were excluded (based on diagnostic codes and/or biochemical laboratory data; see below), as were participants prescribed thiazide-type diuretic medications or antidepressant or antipsychotic medication; these states or circumstances predispose to hyponatremia. Plasma sodium concentrations unaccompanied by simultaneous glucose and creatinine determination were excluded from analysis, as were sodium values corresponding to a subnormal glomerular filtration rate (GFR). Markedly reduced GFR impairs the excretion of dietary water, and hyponatremia is increasingly expected as GFR decreases. Subnormal GFR was defined as estimated GFR of <60 ml·min⁻¹·1.73 m⁻² (calculated using the four-component Modification of Diet in Renal Disease equation using creatinine, age at the time of the sodium test, sex, and race). Plasma sodium determinations accompanied by markedly elevated glucose (>150 mg/dl) were excluded owing to the osmotic depression of sodium concentration; for modestly elevated glucose, plasma sodium was transformed to account for this osmotic effect using the method of Katz (20). Because each cohort reflected data obtained from many different facilities over many years, we do not have specific information on the method used for the determination of plasma sodium concentrations or the dates when any such method may have been modified by one or more of the clinical laboratories.

Veterans Affairs cohort. All data for the Veterans Affairs (VA) cohort were retrieved from the VISN 20 Data Warehouse on March 16, 2012, by the data analyst (J. Duckart). All outpatient plasma sodium, glucose, and creatinine laboratory values were retrieved for the period from January 1, 2000, through December 31, 2010, for all veterans in VISN 20. The initial number of sodium concentration occurrences retrieved was 2,801,958, sodium laboratory determinations that overlapped with a veteran’s diuretic, antidepressant, or antipsychotic prescription were also excluded. sodium laboratory determinations of any veterans with a diagnosis of congestive heart failure within the 10 yr of the study window were excluded. All laboratory values for veterans with a diagnosis of liver disease, hepatitis, or end-stage liver disease were removed, as were value from participants with bilirubin > 2 during the study window. An additional 261,646 sodium records were removed because there was only one sodium value for each of these participants. The maximum number of determinations per participant was 91; participants with >20 separate sodium determinations were combined in a “>20” determinations category, and only the first 21 sodium measurements (chronologically) were included for analysis. For n = 2 determinations of plasma sodium, there were 41,707 participants, whereas there were only 181 participants for n > 20 determinations (the smallest group). The total number of plasma sodium determinations included in the study was 688,611, representing 143,973 participants. The sodium value was then transformed for the corresponding (simultaneously obtained) glucose value to account for the independent osmotic effect of glucose using the following formula of Katz (20) as previously reported: transformed sodium = sodium (in meq/l) + [0.016 × [glucose (in mg/dl) − 100]]. The effect of this transformation was modest because the maximal allowable glucose for this study was 150 mg/dl and the impact on sodium at this glucose level is expected to be <1 meq/l).

Kaiser cohort. Data for the Kaiser cohort were extracted from Healthconnect. Plasma sodium concentrations were obtained for patients who were Kaiser Northwest members between January 1, 2001, and December 31, 2010. Patients were included if they were over 18 yr of age or had two or more outpatient plasma sodium measurements >7 days apart or if two or more of the sodium determinations were accompanied (same day) by measurements of glucose and creatinine. Exclusions were as described above. Also, patients with ICD-9 codes for congestive heart failure (428.0, 428.9, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.91, 404.93, 429.4A, 429.9B, 429.9A, and 428.1) and liver disease (456.0–456.21, 571.2, 571.4, 571.5, 571.6, and 572.2–572.8) were excluded. The final data set represented 89,973 sodium determinations from 30,216 participants. All included sodium concentrations were transformed to account for the independent osmotic effect of the simultaneous glucose measurement using the formula of Katz (20) as described above. For n > 8 determinations, only the first nine sodium determinations (chronologically) were included in the final data set. Of note, when these Kaiser data were initially examined as raw data (i.e., in the absence of exclusion for high glucose or for low GFR and without transforming sodium for glucose), substantial individuality of the plasma sodium concentration was again seen.

This study was approved by the Institutional Review Board (IRB) of the Portland VA Medical Center, the IRB of Kaiser Permanente Northwest, and/or by the IRBs of the institutions of the investigators for each study or were deemed exempt under Code of Federal Regulations [Title 45 - Public Welfare, Department of Health and Human Services, Part 46 - Protection of Human Participants, and Paragraph 46.101(b)(4)], i.e., Exemption 4].

Fig. 1. The concept of individuality of the plasma sodium concentration ([sodium]). A: distribution of plasma [sodium] among hypothetical subjects 1–5 showing individuality (i.e., within-individual “relatedness”) of [sodium], particularly among subjects 2 and 3. B: actual distribution of plasma [sodium] determinations in one study participant as a function of relative time [in days (d)] spanning nearly a decade. The laboratory-reported normal range for plasma [sodium] during this interval is shown by the gray shading.
Individuality of Plasma Sodium Concentrations in Two Large Cohorts

We sought to determine the individuality of the plasma sodium concentration in two large cohorts derived from health plan databases: the VISN 20 Data Warehouse computerized medical record system and the patient population of Kaiser Permanente Northwest. Data obtained in the setting of hyperglycemia or an abnormal GFR were excluded, as were inpatient data. In addition, an effort was made to exclude patients with clinical diagnoses, medications, or laboratory abnormalities likely to independently impact water balance (see MATERIALS AND METHODS). In the VA-based cohort, there were 143,973 individuals with two or more plasma sodium determinations obtained at least 1 wk apart and not subject to exclusion (Table 1). The ICC calculation was then used to determine individuality of the plasma sodium concentration. The ICC describes how closely values drawn from a group resemble each other; in this instance, each study participant is a “group” and the plasma sodium concentrations obtained over the course of the study interval for that one individual constitute the “values” for that group (21). Data were stratified on the number of sodium measurements per individual participant that had been obtained over the 10-yr interval; this can help in the detection of cryptic confounders. For example, one could hypothesize that there were important biological differences between participants undergoing (i.e., requiring) several dozen plasma sodium concentration determinations versus those receiving two or three measurements (see MATERIALS AND METHODS). Therefore, the ICC was calculated for all participants with \( n = 2 \) sodium measurements over the study interval, separately for \( n = 3 \) determinations, and so on.

Table 1. Demographic information for the two cohorts

<table>
<thead>
<tr>
<th></th>
<th>Veterans Affairs Cohort</th>
<th>Kaiser Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>143,973</td>
<td>30,216</td>
</tr>
<tr>
<td>Number of sodium determinations</td>
<td>688,611</td>
<td>89,973</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7.2%</td>
<td>51.2%</td>
</tr>
<tr>
<td>Male</td>
<td>92.8%</td>
<td>48.8%</td>
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<tr>
<td>Race/ethnicity</td>
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<tr>
<td>White (Caucasian)</td>
<td>70.1%</td>
<td>85.6%</td>
</tr>
<tr>
<td>African-American</td>
<td>5.6%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Asian</td>
<td>1.0%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Unknown</td>
<td>20.9%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Other</td>
<td>2.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Age (means ± SD), yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>72.2%</td>
<td>77.1%</td>
</tr>
<tr>
<td>&gt;65</td>
<td>27.8%</td>
<td>22.9%</td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Means ± SD for cohort</td>
<td>139.3 ± 2.7</td>
<td>139.8 ± 2.6</td>
</tr>
<tr>
<td>Means ± SD for participant’s mean value</td>
<td>139.3 ± 2.0</td>
<td>139.8 ± 2.0</td>
</tr>
</tbody>
</table>

Shown are baseline demographic data for the two cohorts investigated. The Veterans Affairs cohort represents data from Jan 1, 2000, through December 31, 2010, for all veterans in Veterans Integrated Service Network 20 (VISN20); the Kaiser cohort represents the cohort of Kaiser Permanente Northwest enrollees for this same period, encompassing the Portland, OR, metropolitan area, including parts of southwest Washington. The VISN20 includes the states of Alaska, Washington, Oregon, most of the state of Idaho, and one county each in Montana and California.
For the VA cohort, and considering all participants, the ICC was ~0.42 and varied relatively little as a function of the number of sodium determinations (Fig. 2A). The confidence interval increased with increasing number of determinations, reflecting fewer participants per stratum.

The Kaiser population exhibited a more balanced sex ratio than the VA patient population. We tested this second major cohort for corroboration and extension of our data from the VA cohort. In the Kaiser cohort, there were 30,216 individuals with two or more recorded plasma sodium concentrations not subject to exclusion (Table 1). These data were again “binned” by the number of determinations, from \( n = 2 \) to \( n > 8 \). (For \( n > 8 \), only the first 9 sodium determinations were used for the ICC calculation.) Similar to the VA cohort, the overall ICC for the Kaiser cohort (Fig. 2B) ranged from 0.38 (0.37–0.40) to 0.51 (0.46–0.56). Together, these data establish that there is substantial individuality to the plasma sodium concentration.

**Effect of Sex on the ICC for Sodium Concentration**

We have previously observed differences in heritability (and in genetic association on sodium concentration) among men and women (39, 46). We hypothesized that differences in the individuality of sodium concentration could account for these observed effects. That is, were individuality less in one sex, that could account for a lower heritability estimate because a single point determination of plasma sodium was used in our investigations of heritability unrelated to this study. Note that the present investigation does not address heritability; the relationship of any participant to any other was not ascertained. The ICC was significantly lower among women than men for two to seven sodium determinations; at a higher number of determinations, there were too few female participants to draw inferences (i.e., confidence intervals were too large; Fig. 3A). In the Kaiser cohort, the ICC among women exceeded that of men at three, four, and greater than eight sodium determinations (Fig. 3B). Therefore, firm conclusions about the role of sex in individuality of the sodium concentration cannot be drawn from these data.

**Effect of Race on the ICC for Sodium Concentration**

In our earlier investigations unrelated to this study, the heritability of sodium concentration among African-Americans generally exceeded that among Caucasians (46). Although there is likely a genetic or environmental basis for this distinction, it is conceivable that greater individuality of the sodium concentration may create the appearance of increased heritability. The individuality of the plasma sodium concentration is the subject of the present investigation. Greater individuality of this phenotype would lead to increased accuracy of any single determination of sodium concentration, thereby reducing noise.
in a heritability signal for a given population size. However, we observed in the VA cohort that individuality of the sodium concentration among African-Americans was less than that for Caucasians (Fig. 4A). At higher numbers of sodium determinations, the confidence intervals were too large to permit inferences to be drawn. In the Kaiser cohort, the number of African-American participants was too small to permit detection of a difference of this magnitude (Fig. 4B).

Effect of Age on the ICC for Sodium Concentration

We previously detected association of a functional variant in the osmoregulatory transient receptor potential V4 (TRPV4) gene in two elderly populations (39); therefore, we sought an age-dependent effect on the ICC for sodium concentration. In both the VA and Kaiser populations, the ICC was higher among participants aged 65 yr and older relative to those younger than 65 yr old (Fig. 5, A and B), with a difference of ~0.1 ICC units. In both cohorts, after stratification by decade, there was a relatively steep relationship between age and the ICC, with the greatest individuality of sodium concentration evident among the oldest participants (Fig. 6). The ICC more than doubled with age, increasing from 0.23 (0.21–0.26) for the VA cohort and 0.21 (0.09–0.32) for the Kaiser cohort at the youngest decade to 0.54 (0.52–0.55) and 0.46 (0.42–0.50), respectively, at the oldest decade.

Determining the ICC for Other Laboratory Data-Based Phenotypes

To help put the sodium ICC data in a biological context, it was compared with data for two other laboratory values. From a clinical perspective, glucose and creatinine are intuitively “intrinsic.” Although plasma glucose varies considerably within an individual, patients in practice segregate along a spectrum of low to high average glucose. This principle underlies the utility of measuring glycated hemoglobin (i.e., hemoglobin A1c) as a surrogate for glycemic control (15), even among nondiabetic patients (4). Creatinine is expected to be highly intrinsic or individual; in the absence of progressive kidney disease or gross changes in muscle mass, creatinine remains relatively constant. Therefore, the ICC on these variables can help frame the individuality of the sodium concentration. In the VA cohort, the ICC for glucose was slightly less than that for the sodium concentration (~0.37; Fig. 7) and decreased further as the number of determinations increased. In the Kaiser cohort, glucose was more individual than in the VA cohort, with an ICC of ~0.57. The ICC for creatinine was highest of all the phenotypes in both cohorts (Fig. 7). Among the VA participants, it ranged from 0.62 (0.59–0.64) to 0.68 (0.67–0.68), whereas among the Kaiser participants, it ranged from 0.76 (0.73–0.78) to 0.80 (0.77–0.82). Therefore, the
The plasma sodium concentration receives little attention in clinical care until or unless it is abnormal. Anecdotally, we have frequently encountered the belief that the plasma sodium concentration varies stochastically and conveys little meaning in the absence of an overtly abnormal value. Our overarching hypothesis was that water balance (i.e., plasma sodium concentration) is genetically determined, heritable, and to a significant extent intrinsic or individual. That is, although one’s sodium concentration fluctuates, it does so around an intrinsic set point that differs among individuals.

Part of the bias against the utility of the plasma sodium concentration (in the absence of overt abnormality) may stem from investigations comparing within- and between-individual correlations of plasma sodium concentration, we also sought to compare the distribution of all sodium determinations for all participants to the distribution of the mean plasma sodium concentration (i.e., a single mean value per participant) within each cohort. It was hypothesized that the per-participant histogram would be similar to the all-values histogram. That is, much of the dispersion in the distribution of the all-values histogram can be attributed to true biological variation between participants and not simply to assay imprecision or intraindividual variability. Although the SD was less for the per-participant data than for all sodium determinations considered in aggregate (Table 1), the distribution histograms were similar (Fig. 10). Importantly, a left-sided tail (consistent with hyponatremia) was evident in both populations and was retained in the per-participant mean data.

DISCUSSION

An additional approach was undertaken to reinforce the concept of within-individual relatedness of the sodium concentration. For all participants in each cohort, scatterplots were generated using the first sodium concentration (chronologically) for a given participant in each cohort versus the second determination for that same participant (Fig. 8, A and C). Note that this approach uses a subset of the data used for the ICC procedure (above) and is expected to less fully capture the totality of within- and between-individual correlation. The Pearson $r$ for these within-individual comparisons was 0.454 for the VA cohort and 0.429 for the Kaiser cohort (Fig. 8, A and C), reflecting substantial individuality of this phenotype. In addition, these Pearson $r$ values are numerically consistent with the ICC values calculated above. Next, the between-individual correlation of the first sodium determination was calculated for each cohort (see MATERIALS AND METHODS). In contrast to the within-individual comparison, there was no between-individual correlation of plasma sodium concentration in either cohort (Pearson $r = -0.004$ for each cohort; Fig. 8, B and D). These data further support the within-individual relatedness—the individuality—of the plasma sodium concentration.

A third, and complementary, approach was used to further establish individuality of the plasma sodium concentration. One of us (Z. Zhang) recently described the agreement index, a novel computational method for assessing within-group relative to between-group variability that is less sensitive to the effects of outlier data (51). An agreement index of 0.5 indicates the absence of correlation, and an index of 1.0 indicates perfect correlation. As was the case for the ICC, the agreement index for sodium was substantial (~0.75) and increased with increasing participant age (Fig. 9). The agreement index for glucose was similar to (VA cohort) or slightly higher than (Kaiser cohort) that for sodium, whereas the agreement index for creatinine was higher in both populations (Fig. 9). These data served to further corroborate the ICC and Pearson $r$ data.

Separate from investigations comparing within- and between-individual correlations of plasma sodium concentration, we also sought to compare the distribution of all sodium determinations for all participants to the distribution of the mean plasma sodium concentration (i.e., a single mean value per participant) within each cohort. It was hypothesized that the per-participant histogram would be similar to the all-values histogram. That is, much of the dispersion in the distribution of the all-values histogram can be attributed to true biological variation between participants and not simply to assay imprecision or intraindividual variability. Although the SD was less for the per-participant data than for all sodium determinations considered in aggregate (Table 1), the distribution histograms were similar (Fig. 10). Importantly, a left-sided tail (consistent with hyponatremia) was evident in both populations and was retained in the per-participant mean data.

Correlating Within-Individual First and Second Sodium Determinations

Fig. 6. ICCs for transformed plasma [sodium] after stratification on age by decade in the VA and Kaiser cohorts. Decades are defined as participant age (in yr) at the time of first plasma sodium determination.

Fig. 7. ICCs for plasma creatinine and glucose concentrations in the VA and Kaiser cohorts. These data were obtained to place the sodium data for ICCs in a clinical context. ICCs for glucose either approximated (VA cohort) or modestly exceeded that for sodium (Kaiser cohort), depending on the cohort. The ICC for creatinine exceeded those for sodium and glucose.

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DISCUSSION

The plasma sodium concentration receives little attention in clinical care until or unless it is abnormal. Anecdotally, we have frequently encountered the belief that the plasma sodium concentration varies stochastically and conveys little meaning in the absence of an overtly abnormal value. Our overarching hypothesis was that water balance (i.e., plasma sodium concentration) is genetically determined, heritable, and to a significant extent intrinsic or individual. That is, although one’s sodium concentration fluctuates, it does so around an intrinsic set point that differs among individuals.

Part of the bias against the utility of the plasma sodium concentration (in the absence of overt abnormality) may stem
from older literature describing a lack of individuality (8, 17, 31, 43, 45). Specifically, the intraindividual variation of plasma sodium was believed to obscure any interindividual variation (8, 17, 31, 43). However, even some of these early reports recognized that intraindividual variations diminished once the analytic variance was subtracted (8, 47–49). These findings suggest that older (and less reliable) methods of measuring plasma sodium concentration may have obscured the individuality of the sodium concentration. In addition, Zerbe et al. (50) showed that the acute vasopressin response to a hypertonic infusion was more closely correlated in seven monozygotic twin pairs than it was in six dizygotic twin pairs.

We used the ICC to assess intraindividual variability in plasma sodium concentration, obtained via repeated plasma sodium determinations over weeks to years, relative to the interindividual variability of this same phenotype. The ICC is often used to demonstrate reproducibility of a physical measurement to validate a new clinical test (28, 37). We considered it the most comprehensive means of assessing the individuality of the sodium concentration across all sex, race, and age groups examined. These data confirm substantial individuality of the sodium concentration across all populations. These data confirm substantial individuality of the sodium concentration across all population groups examined. The individuality of sodium approached or even exceeded that of glucose, which is readily appreciated to be intrinsic in clinical practice. Unsurprisingly, it was less individual than creatinine; even small changes in a patient’s creatinine prompt an investigation for reversible causes of kidney dysfunction.

The ICC data were corroborated with Pearson r values of (chronological) first and second sodium concentration measurements for all participants in both cohorts. Although this

Fig. 8. Scatterplots depicting within-individual and between-individual correlation of plasma [sodium] in the VA and Kaiser cohorts. For within-individual correlation (A and C), the first sodium determination (chronologically) for an individual (x-axis) was plotted against the second sodium determination for that same individual (y-axis); therefore, there as many data points as there are study participants (n = 143,973 for the VA cohort and n = 30,216 for the Kaiser cohort). For n ≥ 2 sodium determinations, only the first and second sodium determinations were used for this analysis; therefore, it was less comprehensive than the ICC calculation. The Pearson correlation coefficient r calculated for these data was 0.454 for the VA cohort and 0.429 for the Kaiser cohort, indicating significant within-individual relatedness of [sodium]. This was also reflected in the relative proximity of data points to the depicted identity lines in A and C. For comparison purposes, the between-individual correlation for plasma [sodium] was also determined (B and D) by first dividing each cohort in half (creating subcohort A-half and subcohort B-half) by study-specific participant identification numbers. The first sodium determination for the first participant in the subcohort A-half of each cohort was plotted against the first sodium determination for the first participant in the subcohort B-half of the cohort. This process was repeated for the first sodium determination for each nth participant in the subcohort A-half versus the nth participant in the subcohort B-half; therefore, the number of data points in B and D is half the number of data points in A and C, respectively. r values for these between-individual data revealed no correlation (r = -0.004 for each cohort), indicating no relatedness of [sodium] between participants.
The individuality of the plasma sodium concentration was lower among African-American patients than among Caucasians patients in at least one of these cohorts (numbers were too small in the Kaiser cohort). We have previously observed a stronger heritability of sodium concentration among African-Americans than among Caucasians (46). Although the present study does not address heritability, it has implications for the interpretation of our earlier heritability data on this phenotype. Individuality needn’t imply heritability; for example, oligodactyly (fewer than five fingers on an extremity, and a highly individual, i.e., persisting, phenotype) can occur in the setting of a heritable syndrome or via traumatic amputation. However, individuality of a phenotype is a prerequisite for demonstrating heritability; a randomly fluctuating phenotype in one generation cannot be correlated with a randomly fluctuating phenotype in another generation. It is unlikely, therefore, that the higher heritability among African-Americans (46) is an artifact of greater individuality of the sodium concentration in this population, because the latter was not observed in the present study.

The biological explanation for the lower individuality of the sodium concentration among African Americans is of interest. It is possible that there were unmeasured confounders disproportionately affecting African-American participants, despite our efforts to exclude use of medications commonly associated with dysnatremia and disease states known to impair systemic water handling and osmoregulation. It is not expected that dietary intake of hypotonic fluids, either acutely or chronically, will affect intraindividual variability in the plasma sodium concentration. Excess water consumption rapidly inhibits central vasopressin release, leading to a prompt water diuresis. This mechanism becomes less reliable with age (33); however, the racial difference observed was most prominent in the earlier decades (data not shown).

We did not observe a consistent sex-specific effect in our stratified data on sodium individuality. In contrast, in our heritability study, differential heritability in men versus women was seen across some races and/or ethnicities (46). As was the case for race-specific data, these findings suggest that the

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**Fig. 9.** Agreement index for plasma sodium, glucose, and creatinine in the VA and Kaiser cohorts as a function of participant age (by decade, expressed in yr). The range for the agreement index was 0.5–1.0, where 0.5 represents no agreement/correlation and 1.0 represents perfect agreement/correlation within each class (e.g., for data from each participant; see text). Plots for [sodium] use dashed connecting lines for greater visibility.

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**Fig. 10.** Histograms showing the distribution of all transformed sodium determinations for the entire cohort (all sodium) and of the per-participant average sodium values (all participants) for the VA (A) and Kaiser (B) cohorts. The all sodiums data include all individual plasma sodium determinations for all participants in the cohort; the all participants data include a single value for each participant, where that value is the mean of all plasma sodium determinations for that patient. The y-axis depicts density, the fraction of values represented by each bar (total = 1.00, or 100%); the x-axis is plasma [sodium] in 1-meq/l intervals. The distribution of average [sodium] for each participant is similar to the distribution for all sodium determinations. A left-sided (hyponatremic) tail was evident in both distributions and in both cohorts.
sex-specific differences in the heritability of sodium concentration are not caused by differences in the individuality of the phenotype.

Apart from the clear demonstration of the individuality of the sodium concentration, the most striking finding to emerge from these data is the progressive increase in sodium individuality with advancing age. We do not have an explanation for this phenomenon, and it is perhaps counterintuitive; it could be argued that disease processes impacting water balance (kidney or liver disease or heart failure) disproportionately affect older patients. Similarly, the use of medications affecting water balance (e.g., diuretics and antidepressant-type medications) generally increases with age. Although we made every effort to exclude these confounders, it remains possible that disproportionately more cases of latent or subclinical pathology affected elderly participants. The elderly have increased vasopressin release in response to hypertonicity (18), and this may suggest tighter resultant osmoregulation, perhaps consistent with our data; however, there is likely decreased vasopressin efficacy at the level of the tubule (for a review, see Ref. 5), such that the net effect is less and not more nimble osmoregulation with aging. Reduced tubular responsiveness to vasopressin has been attributed in part to reduced GFR and/or medication effects (9). Consequently, there is reduced free water clearance in the healthy elderly relative to younger controls, leading to a more pronounced and more durable reduction in systemic osmolality in response to water loading (7). With aging comes a reduction in thirst (30) and total body water (relative to body mass) (3, 14) as well as a decrease in maximal urinary concentrating ability (for a review, see Ref. 35); all would seem to favor reduced and not enhanced individuality of the sodium concentration with aging. It is conceivable that unmeasured confounders could account for this process; however, the clear age-dependent increase in sodium individuality was consistent in magnitude across both cohorts and at all decades examined.

These data convincingly demonstrate individuality of the plasma sodium concentration across two large healthy population-based cohorts. Therefore, even in the absence of dysnatremia, the plasma sodium concentration provides specific information about an individual’s chronic water balance. Within a population, there is a near-normal distribution of the plasma sodium concentration (e.g., Refs. 39 and 46), and this interindividual dispersion is relatively preserved when a per-participant mean sodium concentration is calculated from multiple determinations over time (Fig. 10). We suggest that this relationship supports differing individual set points for human osmostats across a large healthy population, consistent with limited earlier data (50). Importantly, we cannot fully exclude the possibility that there are set point-independent phenomena maintaining individual plasma osmolality at levels reproducibly departing from the population mean over long periods of time. It is conceivable that the force of an individual’s dietary habits or occupational limitations vis-à-vis water access, intake, or loss entrenches this individuality; however, this latter explanation subordinates the role of the osmostat in regulating water balance at the individual level to a perhaps implausible degree. In aggregate, the phenomenon of individuality, coupled with our demonstration of dispersion among individual-specific plasma sodium means, suggests that human osmostats are not tuned to a single set point; rather, it is likely that each individual chronically defends a particular tonicity, generally within the normal “range.” How zealously one’s systemic osmoregulatory mechanisms defend that set point, in terms of chronically promoting water intake and/or facilitating water excretion, may also vary on an individual basis and across racial/ethnic lines.

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