# Accuracy of prediction equations for serum osmolarity in frail older people with and without diabetes[1–4]

*Mario Siervo, Diane Bunn, Carla M Prado, and Lee Hooper*

**ABSTRACT**

**Background:** Serum osmolality is an accurate indicator of hydration status in older adults. Glucose, urea, and electrolyte concentrations are used to calculate serum osmolarity, which is an indirect estimate of serum osmolality, but which serum osmolarity equations best predict serum osmolality in the elderly is unclear.

**Objective:** We assessed the agreement of measured serum osmolality with calculated serum osmolarity equations in older people.

**Design:** Serum osmolality was measured by using freezing point depression in a cross-sectional study. Plasma glucose, urea, and electrolytes were analyzed and entered into 38 serum osmolarity-prediction equations. The Bland-Altman method was used to evaluate the agreement and differential bias between measured osmolality and calculated osmolarity. The sensitivity and specificity of the most-promising equations were examined against serum osmolality (reference standard).

**Results:** A total of 186 people living in UK residential care took part in the Dehydration Recognition In our Elders study (66% women; mean ± SD age: 85.8 ± 7.9 y; with a range of cognitive and physical impairments) and were included in analyses. Forty-six percent of participants had impending or current dehydration (serum osmolality ≥295 mmol/kg). Participants with diabetes ($n$ = 33; 18%) had higher glucose ($P < 0.001$) and serum osmolality ($P < 0.01$). Of 38 predictive equations used to calculate osmolarity, 4 equations showed reasonable agreement with measured osmolality. One [calculated osmolarity = 1.86 × ($Na^+$ + $K^+$) + 1.15 × glucose + urea +14; all in mmol/L] was characterized by narrower limits of agreement and the capacity to predict serum osmolality within 2% in >80% of participants, regardless of diabetes or hydration status. The equation's sensitivity (79%) and specificity (89%) for impending dehydration (≥295 mmol/kg) and current dehydration (>300 mmol/kg) (69% and 93%, respectively) were reasonable.

**Conclusions:** The assessment of a panel of equations for the prediction of serum osmolarity led to identification of one formula with a greater diagnostic performance. This equation may be used to predict hydration status in frail older people (as a first-stage screening) or to estimate hydration status in population studies. This trial was registered at the Research Register for Social Care (http://www.researchregister.org.uk) as 122273. *Am J Clin Nutr* 2014;100:867–76.

## INTRODUCTION

Water is a vital component of the human body and accounts for ~60% of its weight (1, 2). The tight regulation of water balance and tonicity seen in humans involves several physiologic functions including thirst, salt-seeking behavior, neuroendocrine, and organ-specific responses. However, these functions tend to work less well in the elderly, and thus, dehydration becomes more common. In the US NHANES III cohort, water-loss dehydration (serum tonicity ≥300 mOsm/L) was shown in 16% of 20–29-y-olds and increased to 28% of 70–90-y-olds (3), and in a study of Californian nursing homes, 31% of residents were dehydrated at least once over 6 mo (4). This high level of dehydration in older people has clinical and public health impacts. Several prospective analyses of older people, which were carefully adjusted for concurrent risk factors, showed that dehydration was associated with increased risk of mortality and disability (5–7). It is important to accurately identify older people with impending or current dehydration to restore euhydration and improve a disability-free life expectancy (8).

In young men and women, plasma or serum osmolality is the only useful marker of static dehydration with a "cut-off of 301 ± 5 mmol/kg" having the best diagnostic accuracy (9). Although, to our knowledge, such rigorous analysis has not been carried out in older people, serum osmolality is likely to be the best indicator. Its advantages include *1*) the use of standardized, objective analytic procedures, *2*) the determination of hydration status by a single measurement, and *3*) no requirement for additional clinical and nutritional information. Serum osmolality is carefully controlled by the body. Increases in serum osmolality associated with dehydration stimulate cellular osmoreceptors that, in turn, stimulate thirst (leading to increased water intake) and vasopressin (or antidiuretic hormone) secretion (reducing urinary water excretion) (10). The key physiologic role of serum osmolality in the maintenance of euhydration provides

[1] From the Human Nutrition Research Centre, Institute for Ageing and Health, Newcastle University, Newcastle on Tyne, United Kingdom (MS); the Norwich Medical School, University of East Anglia, Norwich, United Kingdom (DB and LH); and the Department of Agricultural, Food and Nutritional Sciences, University of Alberta, Edmonton, Canada (CMP).

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[4] Address correspondence to L Hooper, Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, Norfolk NR4 7TJ, United Kingdom. E-mail: l.hooper@uea.ac.uk.

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additional support for its use as a reference standard for the assessment of dehydration in older adults (11–13).

However, in some circumstances, the direct measurement of serum osmolality is not routinely undertaken because of cost implications (eg, in UK hospitals, the measurement of serum osmolality is uncommon). If a valid equation for the calculation of serum osmolarity can be derived from osmotically active determinants (serum sodium, potassium, urea, and glucose) generated from generic blood testing, this equation would improve the likelihood of detecting dehydration in older people. It would also be possible to assess hydration in existing research data sets, in which these determinants are routinely available but serum osmolality is not. Many equations have been used to calculate osmolarity, but it is not known which equation maps best onto measured osmolality in the elderly. Raised serum osmolality may be due to low fluid intake (general hemoconcentration) or poorly controlled diabetes (raised serum glucose) (14), and thus, the accuracy of formulae should not be influenced by hematocrit concentration or diabetes status.

We conducted a validation study of equations for the calculation of serum osmolarity (mapping onto serum osmolality) in older people with and without diabetes. The primary objective was to identify a prediction equation that is not prone to differential bias associated with factors that influence body hydration such as age, body size, or concentrations of particular effective solutes and characterized by good diagnostic accuracy.

## SUBJECTS AND METHODS

The Dehydration Recognition In our Elders (DRIE)[5] study was a cohort study approved by the National Research Ethics Service Committee London–East Research Ethics committee (11/LO/1997; full ethical approval granted 25 January 2012), and all study procedures were in accordance with the ethical standards of the Helsinki Declaration. *See* Online Supplementary text files and DRIE Letters under "Supplemental data" in the online issue and the DRIE website (15) for the full study protocol, including measurement details, methods for the assessment of capacity, and other study documentation. Baseline recruitment of 198 participants began in April 2012 and was completed in August 2013, and this publication uses baseline (cross-sectional) data. Men and women aged ≥65 y who were living in residential care (residential care homes, nursing homes, specialist dementia care homes, and mixed homes) in Norfolk and Suffolk, United Kingdom, were recruited. Participants were excluded if they had been diagnosed with renal failure or heart failure, were in receipt of palliative care, had illnesses that suggested they were unlikely to survive <3 mo, had a care home manager who reported that the resident did not wish to participate, or was too anxious or unwell for researchers to approach. Each participant signed informed written consent if they were willing to participate and able to answer several questions about the study. Participants who were willing to take part but unable to answer the questions (and, thus, unable to provide informed consent) were included when their designated consultee (a relative or close friend) provided a written declaration that they thought the participant would have chosen to take part if they still had the capacity to do so (*see* Online Supplementary text files under "Supplemental data" in the online issue for a full description).

### Data collection

Study interviews were scheduled for times when participants were available and varied from 0800 to 2000. In summary, nonfasting venous blood samples were collected from an antecubital vein or, when necessary, from the back of the hand after participants had rested ≥5 min in a sitting (or occasionally lying) position. If a blood sample was not obtained after the second attempt, the procedure was abandoned, and the participant was excluded. The interview continued with measurements of anthropometric measures, body composition, physical function, potential signs of dehydration (including skin turgor, capillary refill, mouth examination, sitting and standing blood pressure, and urine testing) and standardized questionnaires that were used to assess health status and cognitive capability, including the Mini-Mental State Examination (MMSE). The MMSE is scored from 0 to 30, with lower scores indicating greater cognitive impairment (16, 17). Body weight was measured with participants wearing light clothes to the nearest 0.1 kg by using care-home scales. Height was obtained from care-home records or estimated from the ulnar length when necessary (18). BMI (in kg/m$^2$) was calculated (weight divided by height squared).

Data on age at interview, sex, comorbidities (including diabetes), and current medication use were obtained from care-home records. The Barthel index is a measure of physical function (19, 20) that has potential scores from 0 to 100, with 100 representing best functional status. The Barthel Index was completed for each participant, with questions answered by a senior member of the care staff. Diabetes information was double checked so that people identified as having diabetes were compared with participants shown to have raised serum glucose or taking any diabetic medication. No additional potential participants with diabetes were identified in this way.

Blood samples were collected by using a needle and syringe, transferred to collection tubes that were immediately inverted several times, and placed in a temperature-controlled box (without heating or cooling and protected from outside-temperature extremes) and driven to the Department of Laboratory Medicine, Norfolk and Norwich University Hospitals Trust (Norfolk, United Kingdom), delivered within 4 h of collection, and samples were analyzed immediately. The laboratory is fully accredited with the Clinical Pathology Accreditation (UK) Ltd, has daily internal quality control run along with calibrators, and is judged fortnightly against its peers (external quality control). Serum osmolality (measured by the assessment of depression of the freezing point; model 2020; Advance Instruments) was assessed in all samples. This model has a repeatability (±SD) ±3 ± 1 mmol/kg in the 0–400-mmol region. The laboratory CV for analysis of serum osmolality (at all amounts) was 0.9%. When sufficient blood was collected, we also assessed serum urea (by using urease; Abbott Architect), serum creatinine (by using the eenzymatic method; Abbott Architect), serum sodium and potassium (by using ion-selective electrode diluted; Abbott Architect), hemoglobin (Instrument Sysmex XN), and blood

[5] Abbreviations used: DRIE, Dehydration Recognition In our Elders; eGFR, estimated glomerular filtration rate; MMSE, Mini-Mental State Examination.

glucose (by using hexokinase/glucose 6-phosphate dehydrogenase; Abbott Architect). The estimated glomerular filtration rate (eGFR) was calculated by using the Cockcroft-Gault formula. The classification of hydration status was based on measured serum osmolality. Participants were categorized as being normally hydrated (serum osmolality from 275 to <295 mmol/kg), having impending dehydration (serum osmolality: 295–300 mmol/kg), or current dehydration (serum osmolality >300 mmol/kg) (9, 12).

### Predictive equations

Fazekas et al (21) collected 36 different equations used to determine serum osmolarity). The equations involved summing multiples of serum sodium, potassium, glucose, and urea and, occasionally, ionized calcium, magnesium, lactate, and bicarbonate. Because sodium, potassium, glucose, and urea are regularly measured in older people who have blood tests, our study has focused on the 33 equations that only included these factors [with the omission of 3 equations discussed by Fazekas et al (21) that included ionized calcium or lactate because these test results are not routinely available (22–24)]. Fazekas et al (21) chose to multiply the results of several equations by 0.985 because they were reported in milliosmoles per liter (25–27); however, this method was unlikely to have been the original authors' intention, and thus, we ran the equations with and without this multiplication. In addition, we evaluated the predictive accuracy of widely used simple formulae for plasma osmolality (28) and tonicity (6) as well as the use of the aggregate method proposed by Wells et al (29). This latter approach was based on the assumption that osmolarity prediction equations are independent of one another, and these independent predictions can be aggregated. Under these conditions, the error will not be correlated across predictions but will, rather, be randomly distributed across them and, hence, tend to cancel out, which increases the accuracy of the serum osmolarity aggregate prediction. *See* Supplemental Table 1 under "Supplemental data" in the online issue for all resulting 38 equations analyzed in this study.

### Terminology and units

Measured osmolality was assessed in milliosmoles per kilogram or millimoles per kilogram (molal units), whereas calculated osmolarity was in milliosmoles per liter or millimoles per liter (molar units), which made the terminology when we compared the 2 measurements complex. Some authors of equations used herein have converted constituent units of millimoles per liter into millimoles per kilogram (by dividing by 0.933) before carrying out a regression, and thus, the input of units of millimoles per liter generates an output in millimoles per kilogram (30). This method means that some equations used in this study produced outputs in milliosmoles per liter or millimoles per liter, and some equations used in this study produced outputs in milliosmoles per kilogram or millimoles per kilogram, which would allow the osmolar gap to be expressed in millimoles (31). For clarity within this article, all equations were written by using International System of Units unit conversions, referred to as calculated osmolarity, and expressed in millimoles per liter. Measured osmolality is reported herein as millimoles per kilogram, although the units provided by our laboratory were milliosmoles per kilogram. Because we were aiming for the equivalence of osmolarity and osmolality whereby we have equations for which measured osmolality and calculated osmolarity were added or subtracted, units have been given as millimoles.

### Statistical analysis

The cohort study was powered to allow the development of a diagnostic decision tree to identify dehydration, and thus, the study size was not directly related to the current analysis. The *t* test for independent samples was used to compare participants stratified by diabetes status, whereas the chi-square test was used to detect differences in the frequency of accurate predictive estimates in participants stratified by diabetes and hydration status. An ANOVA was used to examine differences in the predictive accuracy between participants stratified by sex and diabetes status. The difference ($\Delta$; measured osmolality in mmol/kg minus calculated osmolarity in mmol/L) was expressed $\pm 2$ SDs and deemed accurate if the mean fell between $-1$ and +1 mmol. The number of participants with calculated osmolarity values within $\pm 2\%$ of measured osmolality was also calculated. The paired *t* test was used to determine the statistically significant differences between the measured osmolality and calculated osmolarity. The Bland-Altman method was used to evaluate the agreement of absolute (mmol) and relative (%) differences between measured osmolality and calculated osmolality (32). Pearson's correlation was used to assess the association of $\Delta$ with age, BMI, and biochemical variables (serum hemoglobin, $Na^+$, $K^+$, glucose, urea, and eGFR). Hydration status on the basis of calculated osmolarity was plotted in $2 \times 2$ tables against measured osmolality. These tables were used to calculate sensitivity, specificity, a positive predictive value, a negative predictive value, and other diagnostic criteria. All statistical analyses were carried out with PASW 19 for Windows software (Polar Engineering and Consulting, formerly known as SPSS). Significance was set at $P < 0.05$.

## RESULTS

The DRIE study took place in 56 care homes and included 1816 residents of whom 1077 residents were deemed ineligible by care-home managers. Of the 739 potentially eligible residents approached by the researchers, 374 residents told us they were not interested, whereas 365 residents wanted to take part, and 256 residents provided their own or consultee consent. We initiated research interviews with 232 individuals (*see* **Figure 1** for additional details), obtained serum osmolality for 198 individuals plus serum sodium, potassium, and urea data for 186 individuals, of whom 172 also had random serum glucose measurements. Of the 186 participants, 33 (18%) had diabetes, and 35 (19%) had current dehydration (serum osmolality >300 mmol/kg), an additional 50 (27%) had impending dehydration (serum osmolality: 295–300 mmol/kg), 94 (51%) were normally hydrated (serum osmolality from 275 to <295 mmol/kg), and 7 (4%) had serum osmolality <275 mmol/kg. Of 186 participants, 122 (66%) were women, the mean (±SD) age was 85.8 ± 7.9 y (range: 65.7–105.5 y), and mean (±SD) BMI was 25.8 ± 5.5 (range: 15.5–42.2). The mean (±SD) MMSE score was

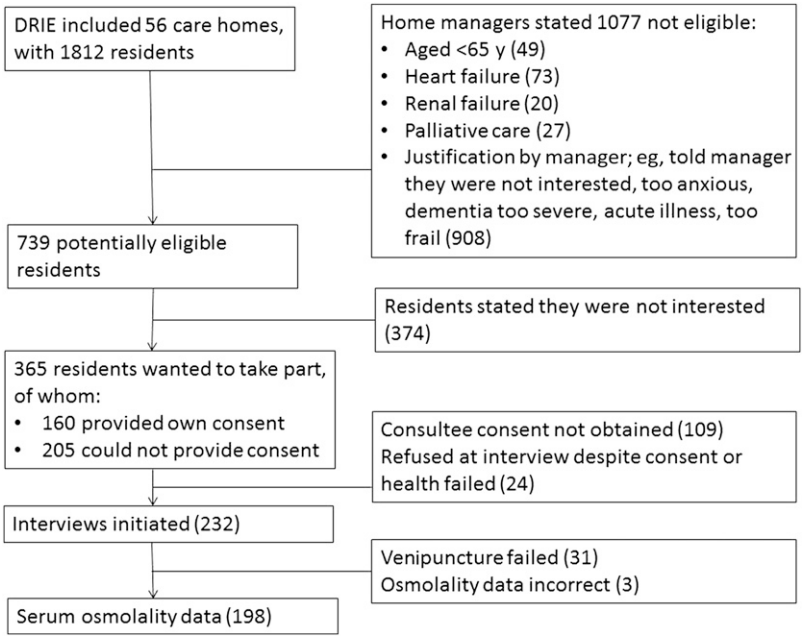


**FIGURE 1.** Flowchart for inclusion of care home residents into DRIE. DRIE, Dehydration Recognition In our Elders.

21.8 ± 5.7 (range: 0–30), and mean (±SD) Barthel index was 66.6 ± 26.4 (range: 0–100).

These characteristics did not differ between participants with and without diabetes (**Table 1**). Participants with diabetes did differ from those without diabetes in having higher serum osmolality, sodium, urea, and glucose concentrations and lower hemoglobin but similar serum potassium, creatinine, and eGFR on average. Serum osmolality was significantly positively correlated with serum $Na^+$ ($r = 0.73$, $P < 0.001$), urea ($r = 0.47$, $P < 0.001$), creatinine ($r = 0.30$, $P < 0.001$), and glucose ($r = 0.36$, $P < 0.001$) but not with serum potassium (*see* Supplementary Table 2, online supplementary material under "Supplemental data" in the online issue. )

### Assessment of absolute bias (paired *t* test)

Analyses were conducted in the whole sample (of $n = 186$ for equations that did not include glucose, and $n = 172$ for equations that involved serum glucose measures) and after stratification by diabetes status. Equations were characterized by a wide range of predictive bias from 31 to −27 mmol. Four equations (Equations *24*, *26*, *32*, and *33*) had no significant differences between

**TABLE 1**
Descriptive characteristics of participants stratified by diabetes status[1]

| | All | Without diabetes | With diabetes | *P* |
|---|---|---|---|---|
| *n* | 186 | 153 | 33 | — |
| Age (y) | 85.8 ± 7.9[2] | 85.8 ± 8.0 | 85.5 ± 7.5 | 0.85 |
| Sex [*n* (%) F] | 122 (66) | 104 (68) | 18 (55) | 0.16 |
| Weight (kg) | 69.0 ± 17.2 | 67.4 ± 16.7 | 76.3 ± 17.6 | 0.007 |
| Height (cm) | 163.1 ± 10.4 | 162.0 ± 10.2 | 168.1 ± 9.7 | 0.002 |
| BMI (kg/m$^2$) | 25.8 ± 5.5 | 25.5 ± 5.4 | 27.0 ± 6.0 | 0.17 |
| MMSE[3] | 21.8 ± 5.7 | 21.6 ± 5.9 | 22.5 ± 4.8 | 0.43 |
| Barthel index | 66.6 ± 26.4 | 66.9 ± 26.9 | 65.3 ± 3.9 | 0.74 |
| Serum osmolality (mmol/kg) | 292.1 ± 9.3 | 291.3 ± 9.1 | 295.9 ± 9.5 | 0.01 |
| Sodium (mmol/L) | 137.5 ± 3.7 | 137.7 ± 3.7 | 136.2 ± 3.6 | 0.03 |
| Potassium (mmol/L) | 4.2 ± 0.4 | 4.2 ± 0.4 | 4.2 ± 0.3 | 0.36 |
| Urea (mmol/L) | 6.9 ± 2.6 | 6.7 ± 2.4 | 8.2 ± 3.1 | 0.003 |
| Creatinine ($\mu$mol/L) | 89.4 ± 35.2 | 87.4 ± 34.3 | 98.7 ± 38.2 | 0.09 |
| Glucose (mmol/L)[4] | 6.9 ± 3.1 | 5.9 ± 1.5 | 11.0 ± 4.8 | <0.001 |
| eGFR (mL · min$^{-1}$ · 1.73 m$^{-2}$) | 63.8 ± 18.8 | 64.5 ± 18.4 | 60.5 ± 20.4 | 0.26 |
| Hemoglobin (g/dL) | 12.4 ± 1.4 | 12.5 ± 1.4 | 11.9 ± 1.5 | 0.02 |

[1] *P* values were determined by using a *t* test for independent samples (continuous variables) and chi-square test (categorical variables) to compare participants categorized according to diabetes status. eGFR, estimated glomerular filtration rate; MMSE, Mini-Mental State Examination.

[2] Mean ± SD (all such values).

[3] MMSE scores were available in 179 participants.

[4] Glucose measurements were available in 172 participants.

the measured osmolality and calculated osmolarity, and the predictive bias was between −1 and 1 mmol. Of these equations, only Equation *32* showed no significant difference between measured osmolality and calculated osmolarity for the full sample and for both subgroups (with and without diabetes) (**Table 2**).

### Bland-Altman analysis

The accuracy of the 4 selected equations was evaluated by using a Bland-Altman analysis (**Figure 2**, A–D). Equation *32* was characterized by the greatest agreement with the measured osmolality. Specifically, Equation *32* (Figure 2C) had narrower limits of agreement (±7.4) than those of the other 3 equations (Figure 2, A, B, and D) and the bias was not associated with increasing values of osmolality.

### Predictive and diagnostic accuracy

We assessed the number of individual predictions (calculated osmolarity) that fell within ±2% of the measured osmolality for each of the 4 equations and stratified by diabetes status and hydration status. Again, Equation *32* out-performed the other 3 equations by consistently predicting >80% of osmolality values

**TABLE 2**
Difference between measured plasma osmolality and calculated osmolarity (measured serum osmolality minus calculated osmolarity) in all participants and stratified by diabetes status[1]

| | Δ (measured serum osmolality in mmol/kg minus calculated osmolarity in mmol/L) | | |
|---|---|---|---|
| Equation no. (reference) | All ($n$ = 186) | No diabetes ($n$ = 153) | Diabetes ($n$ = 33) |
| | | *mmol* | |
| Equation *1* (33)[2] | 30.9 ± 8.6[c] | 30.6 ± 8.8[c] | 32.3 ± 8.8[c] |
| Equation *2* (33) | −4.0 ± 14.0[c] | −5.6 ± 11.6[c] | 3.0 ± 15.6[a] |
| Equation *3* (34)[2] | 25.9 ± 8.6[c] | 25.5 ± 8.6[c] | 27.5 ± 8.2[c] |
| Equation *4* (25, 35)[2] | −1.7 ± 8.2[c] | −2.0 ± 8.2[c] | −0.2 ± 7.4 |
| Equation *5* (36) | 17.1 ± 12.6[c] | 15.7 ± 10.4[c] | 23.4 ± 14.4[c] |
| Equation *6* (37)[2] | 6.7 ± 8.8[c] | 6.3 ± 8.8[c] | 8.4 ± 8.2[c] |
| Equation *7* (38) | 10.1 ± 12.6[c] | 8.7 ± 10.4[c] | 16.4 ± 14.4[c] |
| Equation *8* (39) | 7.1 ± 12.6[c] | 5.7 ± 10.4[c] | 13.4 ± 14.4[c] |
| Equation *9* (40)[2] | 10.2 ± 10.0[c] | 9.6 ± 9.8[c] | 12.6 ± 10.0[c] |
| Equation *10* (41) | 3.3 ± 12.8[c] | 2.0 ± 10.4[c] | 9.8 ± 14.4[c] |
| Equation *11* (42)[2] | 6.9 ± 8.8[c] | 6.5 ± 8.8[c] | 8.7 ± 8.4[c] |
| Equation *12* (25)[2] | −2.6 ± 8.2[c] | −2.3 ± 8.2[c] | −4.3 ± 7.4[c] |
| Equation *13* (43)[2] | 20.9 ± 8.6[c] | 20.5 ± 8.6[c] | 22.5 ± 8.2[c] |
| Equation *14* (44)[2] | 7.6 ± 9.0[c] | 7.1 ± 8.8[c] | 9.8 ± 8.4[c] |
| Equation *15* (44) | 13.6 ± 11.2[c] | 12.4 ± 9.4[c] | 19.3 ± 12.6[c] |
| Equation *16* (45)[2] | 5.9 ± 8.6[c] | 5.6 ± 8.6[c] | 7.3 ± 8.2[c] |
| Equation *17* (46)[2] | 12.4 ± 8.0[c] | 12.0 ± 8.2[c] | 13.9 ± 7.4[c] |
| Equation *18* (47)[2] | 18.7 ± 8.6[c] | 18.4 ± 8.6[c] | 20.3 ± 8.0[c] |
| Equation *19* (48)[2] | 16.9 ± 8.6[c] | 16.5 ± 8.6[c] | 18.5 ± 8.2[c] |
| Equation *20* (48)[2] | 13.4 ± 8.0[c] | 13.2 ± 8.0[c] | 14.3 ± 7.2[c] |
| Equation *21* (49)[2] | −1.4 ± 8.2[c] | −1.8 ± 8.2[c] | 0.1 ± 7.6 |
| Equation *22* (50)[2] | 4.2 ± 7.6[c] | 4.1 ± 7.6[c] | 4.7 ± 6.8[c] |
| Equation *23* (50)[2] | 4.5 ± 7.4[c] | 4.4 ± 7.6[c] | 5.3 ± 6.6[c] |
| Equation *24* (51)[2,3] | –0.4 ± 9.0 | –0.8 ± 8.8[a] | 1.8 ± 8.4[a] |
| Equation *25* (26)[2] | 24.7 ± 8.4[c] | 24.5 ± 8.6[c] | 26.0 ± 7.8[c] |
| Equation *25a* (26)[2] | 28.7 ± 8.4[c] | 28.4 ± 8.4[c] | 30.0 ± 7.9[c] |
| Equation *26* (52)[2,3] | –0.9 ± 10.0 | –0.5 ± 9.8 | –2.5 ± 10.6[a] |
| Equation *27* (27)[2] | −32.0 ± 8.2[c] | −32.2 ± 8.2[c] | −31.0 ± 7.4[c] |
| Equation *27a* (27)[2] | −27.1 ± 8.0[c] | −27.3 ± 8.2[c] | −26.1 ± 7.2[c] |
| Equation *28* (53)[2] | 7.3 ± 8.6[c] | 6.9 ± 8.6[c] | 8.9 ± 8.2[c] |
| Equation *29* (53)[2] | 7.4 ± 8.0[c] | 7.0 ± 8.2[c] | 8.9 ± 7.4[c] |
| Equation *30* (54)[2] | 14.5 ± 7.4[c] | 14.4 ± 7.6[c] | 15.3 ± 6.6[c] |
| Equation *31* (30)[2] | 2.1 ± 8.0[c] | 2.0 ± 8.2[c] | 2.6 ± 7.6[c] |
| Equation *32* (30)[2,3] | –0.4 ± 7.4 | –0.4 ± 7.6 | –0.3 ± 7.0 |
| Equation *33* (55)[2,3] | –0.5 ± 8.2 | –0.8 ± 8.2[a] | 0.5 ± 7.4 |
| Equation *34* (28)[2] | 5.2 ± 7.4[c] | 5.4 ± 7.6[c] | 4.3 ± 6.6[c] |
| Equation *35* (tonicity) (6)[2] | 1.7 ± 9.6[c] | −1.2 ± 9.7[c] | 4.0 ± 9.4[c] |
| Equation *36* (29) | 7.4 ± 8.6[c] | −6.9 ± 8.4[c] | 9.6 ± 8.0[c] |

[1] All values are means ± 2 SDs. References for Equations *1–33* were taken from Fazekas et al (21). [a]$P < 0.05$; [c]$P < 0.001$. The paired $t$ test was used to determine the significance of differences between measured osmolality and calculated osmolarity.

[2] Equation includes glucose concentrations, and therefore, calculations were based on a final sample of 172 participants (all other calculations were based on 186 participants).

[3] One of the equations with the best performance.

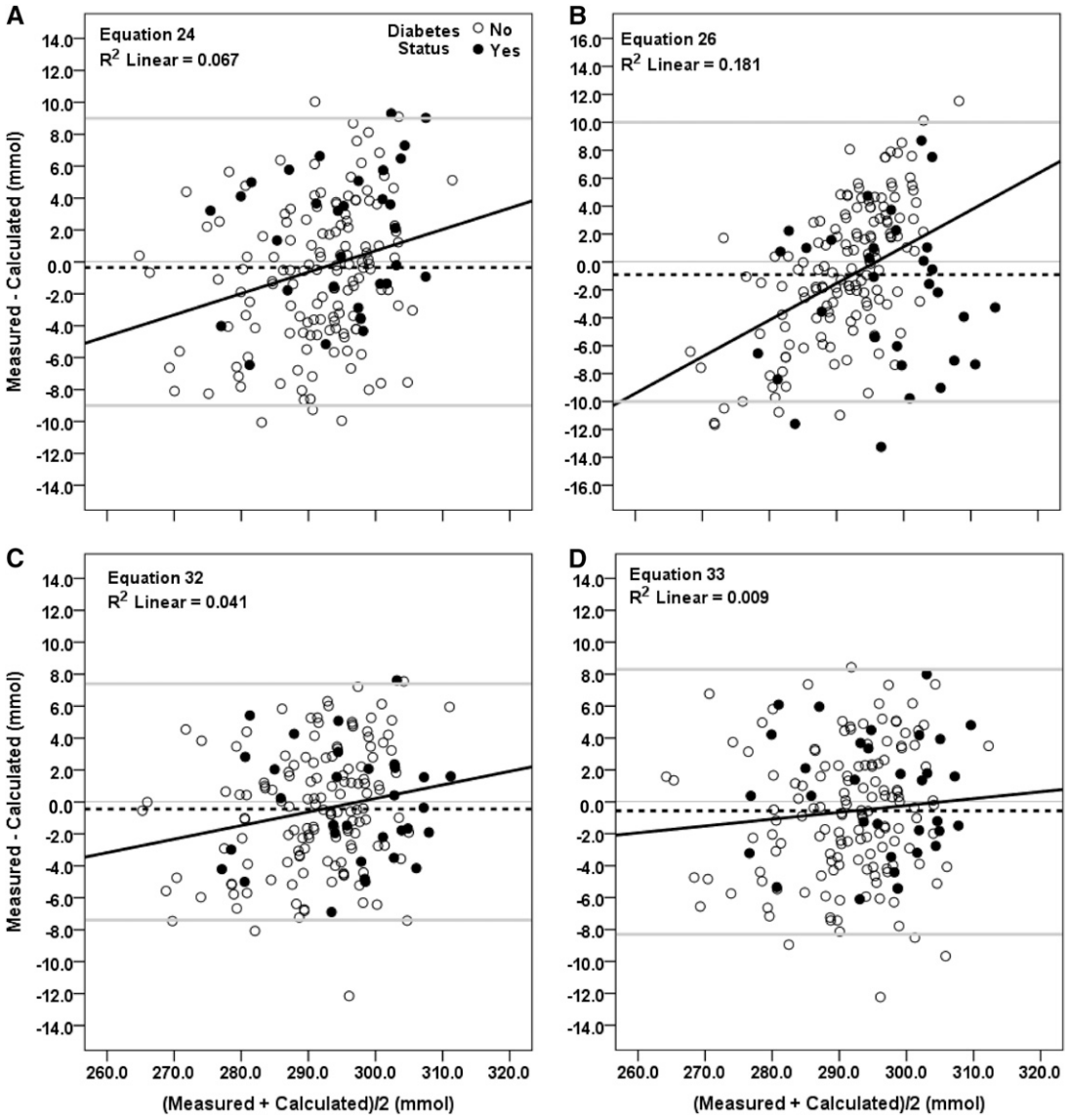


**FIGURE 2.** Bland-Altman plots describing the agreement between measured osmolality and predicted osmolarity by using 4 different equations [Equations *24* (A), *26* (B), *32* (C), and *33* (D)] characterized by the lowest $\Delta$ values (Table 1). Scatter plots have been stratified by diabetes status. A regression line has been fitted to identify the presence of differential bias with increasing osmolality. Solid lines denote limits of agreement ($\pm$2 SDs). Dotted lines denote average differences between measured and predicted values.

within the $\pm$2% margin across diabetic (**Figure 3**A) and hydration (Figure 3B) subgroups. The Bland-Altman analysis of the percentage distribution of the measurement bias confirmed the better agreement of Equation *32* (see Supplementary Figure S1C under "Supplemental data" in the online issue) that the other 3 equations (*see* Supplementary Figures S1A, S1B, and S1D under "Supplemental data" in the online issue). Additional analyses showed that the absolute bias of Equation *32* was not influenced by sex (because differences between the measured osmolality and predicted osmolarity were not significantly different in men and women; **Figure 4**).

### Diagnostic accuracy

The diagnostic accuracy of the 4 equations in the identification of participants with current and impending dehydration and euhydration as assessed by serum osmolality was assessed (*see* Supplementary Table 3 under "Supplemental data" in the online issue). The sensitivity of Equation *32* in the identification of participants with current dehydration (>300 mmol/L) was modest (64%), whereas its specificity was high (93%). Positive and negative likelihood ratios were 8.85 and 0.39, respectively, with a diagnostic OR of 22.6. The diagnostic accuracy of the equation improved for impending dehydration (295–300 mmol/L) as sensitivity and specificity were 79% and 89% respectively, and positive and negative likelihood ratios were 7.53 and 0.23, respectively, with a diagnostic OR of 32.4. If the calculated serum osmolarity were to be used as a screening tool for current dehydration in this population, it would be important not to miss cases of current dehydration, and thus, a high sensitivity would be crucial. Because an additional assessment in people shown to be at risk is simple (by measuring serum osmolality), a lower specificity would be acceptable. We examined the diagnostic accuracy of different calculated osmolarity cutoffs in screening for current dehydration (measured serum osmolality >300 mmol/kg)

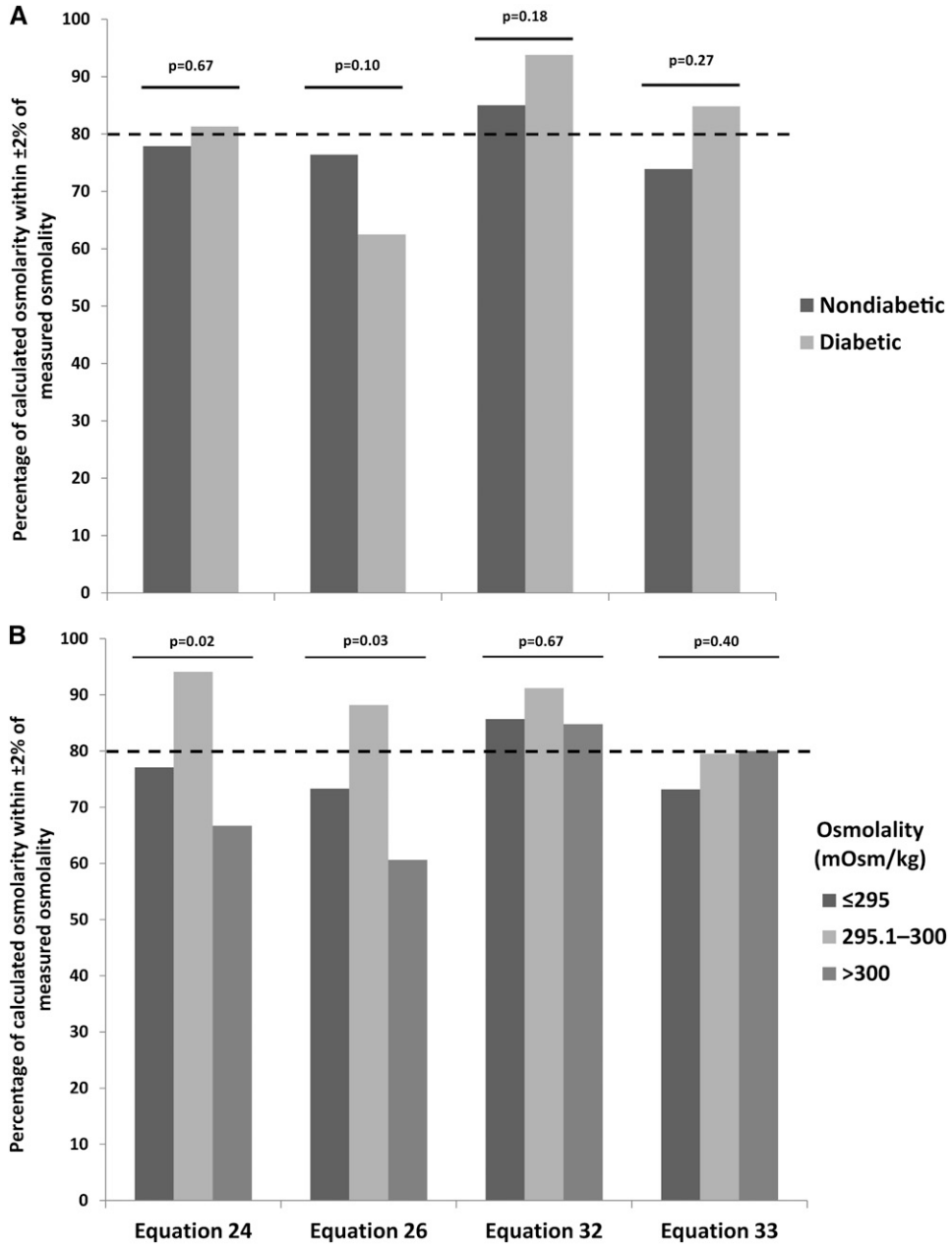


**FIGURE 3.** Predictive accuracy of 4 equations evaluated by calculating the percentage of predicted osmolarity values within ±2% of measured osmolality in participants stratified by diabetes status (A) and degree of dehydration (B). The chi-square test was used to evaluate differences between participants with and without diabetes (A) and participants who were hydrated, had impending dehydration, or current dehydration (B) in the percentage of accurate predictions for Equations *24*, *26*, *32*, and *33*).

and suggested that a calculated osmolarity finding >296 mmol/L had high sensitivity (97%) while retaining reasonable specificity (76%) with a diagnostic OR of 99 (**Table 3**).

### Sensitivity analyses

We analyzed the presence of a differential bias by assessing the correlation of an absolute bias ($\Delta$; measured − calculated) with factors associated with hydration including age, BMI, electrolytes ($Na^+$ and $K^+$), glucose, urea, creatinine, eGFR, urea:creatinine, hemoglobin, MMSE, and Barthel index. Equation *32* suggested the least differential bias because low-order correlations were shown only with $K^+$ ($r = -0.28$, $P < 0.001$) and MMSE scores ($r = 0.21$, $P < 0.01$) (*see* Supplementary Table 4 under "Supplemental data" in the online issue).

## DISCUSSION

The equation for calculated serum osmolarity developed by Khajuria and Krahn (30) [$1.86 \times (Na^+ + K^+) + 1.15 \times$ glucose + urea + 14, where all components were measured in mmol/L] was best able to predict measured serum osmolality in frail older people with and without diabetes. We did not detect evidence for a differential bias related to the influence of factors associated

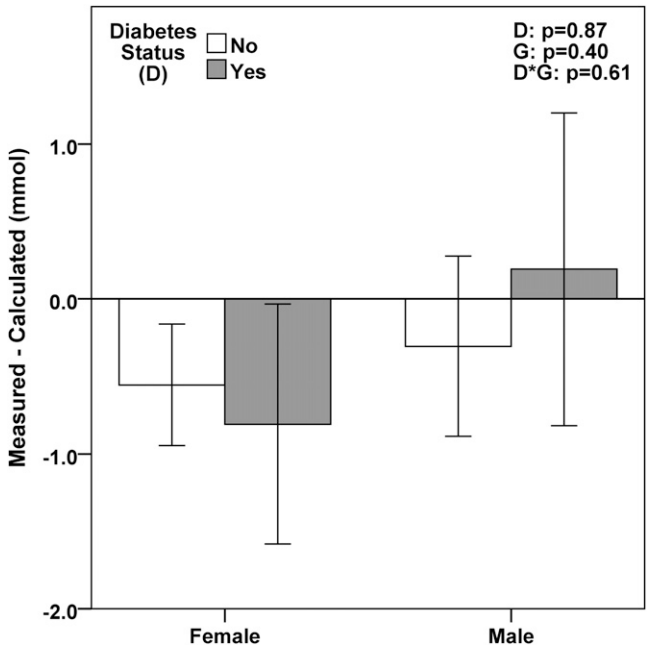


**FIGURE 4.** Mean (±1 SEM) accuracy of Equation *32* in participants stratified by sex and diabetes status. A factorial ANOVA was used to evaluate whether G and D status had an interactive effect on the accuracy of Equation *32*. G*D = interaction term. $n$ = 172. D, diabetes; G, sex.

with hydration such as age, BMI, sodium, urea, and glucose. The equation's sensitivity (79%) and specificity (89%) for impending dehydration (≥295 mmol/kg) and current dehydration (>300 mmol/kg) (69% and 93%, respectively) were reasonable.

Some limitations of our analyses need to be considered in the interpretation of these results. These results are specific to frail older people living in residential care and, thus, should be extrapolated only with care. However, the high prevalence and prognostic value of dehydration in older participants (in this population, 19% of participants had current dehydration, and an additional 27% of participants had impending dehydration) attribute a high clinical relevance to this analysis. The application of the equation in older people living in the community, those with heart or renal failure, and those at end of life may or may not be not appropriate but needs to be tested. However, the population was heterogeneous for sociodemographic characteristics and health-related conditions, which increased the variability of measured serum osmolality and allowed a more-sensitive analysis of the diagnostic accuracy of predictive equations. The cross-sectional study design was a minor limitation of the analysis because it did not attempt to establish the causality of associations between hydration and health factors, but we specifically focused on the evaluation of agreement between measured serum osmolality and calculated serum osmolarity.

A scrutiny of the variables included in Equation *32* revealed the inclusion of main solutes that contribute to serum osmolality (Na+, K+, glucose, and urea); other equations included the same variables in equations, and main differences were coefficients. An external validation of predictive equations is important to establish their accuracy and is affected by the rigor of the study design, measurement protocols, and representativeness of the population included in the validation sample. The validation of Equation *32* was conducted in a sample of frail older people living in residential care with a variety of chronic health problems and a wide range of cognitive and physical limitations. Our analysis framework included the presence of important variables such as age and BMI, but it was not clear whether the results would be generalizable to older people who live independently. Analytically, we were unable to run duplicate assessments of serum osmolality (our reference standard), which may have reduced the accuracy of our hydration-status assessment.

Our Equation *32* was developed by Khajuria and Krahn (30) to minimize the osmolar gap (the difference between serum osmolality and osmolarity) with a view to using any emerging osmolar gap to quantify alcohol intake. In our study, we did not formally assess recent alcohol intake, but no participants were inebriated or smelled of alcohol at the study visit. Alcohol intake is low in UK care homes, many participants discussed drinking favorite alcoholic beverages when visiting family and friends, and some participants kept 1 or 2 bottles of alcoholic drinks to offer visitors, but only 2 men appeared to drink regularly (one man drank 1 pint beer or cider/d; the other man drank 0.5 pints of beer or cider/d). Khajuria and Krahn (30) investigated the predictive capacity of coefficients for glucose, which may explain the good performance of this equation in our population and the maintenance of accuracy in both diabetic and nondiabetic patients.

There has been evidence that dehydration is associated with increased risk of mortality and poorer functional status in older populations (5–7). In one study, 561 nondisabled Americans aged ≥70 y were recruited. Having dehydration (tonicity >300 mOsm/L) at baseline, compared with euhydration (normal

**TABLE 3**
Diagnostic characteristics of different serum osmolarity cutoffs by using Equation *32* to use in screening for current dehydration (measured serum osmolality >300 mmol/kg)[1]

| Serum osmolarity cutoffs for Equation *32* | Sensitivity | Specificity | PV+ | PV− | LR+ | LR− | DOR | Pretest probability | Posttest probability given T+ | Posttest probability given T− |
|---|---|---|---|---|---|---|---|---|---|---|
| >300 mmol/L | 0.64 | 0.93 | 0.68 | 0.91 | 8.85 | 0.39 | 22.58 | 0.19 | 0.68 | 0.09 |
| >299 mmol/L | 0.79 | 0.91 | 0.68 | 0.95 | 9.13 | 0.23 | 39.31 | 0.19 | 0.68 | 0.05 |
| >298 mmol/L | 0.82 | 0.89 | 0.64 | 0.95 | 7.58 | 0.20 | 37.2 | 0.19 | 0.64 | 0.05 |
| >297 mmol/L | 0.88 | 0.81 | 0.53 | 0.97 | 4.70 | 0.15 | 31.51 | 0.19 | 0.53 | 0.03 |
| >296 mmol/L | 0.97 | 0.76 | 0.48 | 0.99 | 3.96 | 0.04 | 98.82 | 0.19 | 0.48 | 0.01 |
| >295 mmol/L | 0.97 | 0.73 | 0.46 | 0.99 | 3.55 | 0.04 | 85.05 | 0.19 | 0.46 | 0.01 |

[1] DOR, diagnostic OR; LR−, negative likelihood ratio; LR+, positive likelihood ratio; PV−, negative predictive value; PV+, positive predictive value; T−, negative test; T+, positive test.

tonicity: 285–294 mOsm/L) was associated with doubled risk of 4-y disability (RR: 2.1; 95% CI: 1.2, 3.6) and a 40% increase in risk of 8-y mortality (RR: 1.4; 95% CI: 1.0, 1.9) (6). Because one of the reasons for increased tonicity and increased disability and mortality may be uncontrolled diabetes, analyses were repeated by omitting participants with raised glucose. These analyses also suggested an 80% increase in risk of 4-y disability and 50% increased risk of 8-y mortality in individuals with dehydration at baseline; however, associations were no longer significant [RR: 1.8 ( 95% CI: 0.8, 3.9) for disability; RR: 1.5 (95% CI: 0.9, 2.3) for mortality in normoglycemics] because of the smaller sample size. Analyses were controlled for age, sex, race, weight, smoking, activity, plasma urea and creatinine, cognitive impairment, depression, and chronic disease (6). These data suggested, but did not prove conclusively, that it is important to identify older people with impending or current dehydration so that we can improve their hydration and help to prevent long-term functional and physical deficits (8). Equations for calculated tonicity (Equation *35*) used in this study (6) mapped quite well onto serum osmolality with a difference ($\pm 2$ SDs) between measured serum osmolality and calculated tonicity of $1.7 \pm 9.6$ but performed better in people without than with diabetes (Table 2).

Additional validations in other populations are needed, but a screening tool for dehydration on the basis of an equation that calculates serum osmolarity and involves routine clinical biochemical variables could have a significant impact in the preliminary assessment and correction of current dehydration in older participants. If this formula is validated in additional elderly populations, serum osmolarity calculated according to our Equation *32* could be automatically calculated on pathology laboratory reports for individuals aged $\geq$65 y, providing an opportunistic method for the assessment of hydration status. A calculated serum osmolarity reading $>$296 mmol/L could equate to a high suspicion of dehydration [as defined by a measured serum osmolality $>$300 mmol/kg (9, 12)] and could usefully lead to serum osmolality testing to confirm hydration status unless clearly because of raised serum glucose (in which case, diabetic control needs to be established).

In conclusion, this comprehensive analysis of equations for the calculation of serum osmolarity identified one equation with a superior diagnostic accuracy in older participants. The equation, with the use of routine biochemical variables, needs to be confirmed in free-living populations but can be recommended as a valid substitute for the direct measurement of serum osmolality in existing data sets and could usefully be used to screen for current dehydration in clinical situations.

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The authors' responsibilities were as follows—LH: was the guarantor of this work, had full access to all study data, and took responsibility for the integrity of the data and accuracy of the data analysis; LH and DB: designed the DRIE study, recruited participants, and collected data; MS and LH: conceived the analysis discussed within this article and wrote the first draft of the manuscript; MS, CMP, and LH: carried out analyses; and all authors: edited the manuscript and agreed on the final content of the manuscript. None of the authors had a conflict of interest.

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